UNIVERSIDAD AUTÓNOMA
DEL ESTADO DE MÉXICO
Facultad de Química

Tesis

para obtener el Grado de

Doctor en Ciencias Químicas

Estudio y Desarrollo de Nuevos Métodos de Obtención de 1,2,3-Triazoles a través de Cicloadiciones (3+2) Azida-Enolato y su Aplicación en la Síntesis de Análogos Nucleosídicos y del Miconazol

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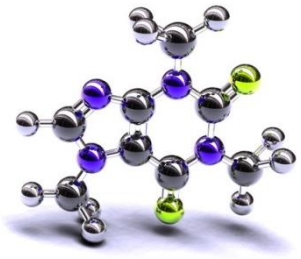

Agosto 2017
TOLUCA – ESTADO DE MÉXICO

La imaginación es más importante que el conocimiento

Albert Einstein

A mi bella **ESPOSA**, la única responsable del porqué y para quien se ha hecho todo esto, solo tú conociste los sentimientos más íntimos de todo este esfuerzo. Gracias por tu apoyo incondicional.

A mi **MADRE**, mujer virtuosa, siempre imponente en mi vida, pues tus grandes méritos me han alcanzado, EL ETERNO tenga siempre memoria de ti.

Todos los resultados que se encuentran en el presente escrito han sido publicados en revistas científicas internacionales arbitradas.

Dichos resultados están representados por 6 artículos publicados. Para fines meramente prácticos, cada uno de estos trabajos se referirán desde este momento y de manera arbitraria como **Proyecto 1**, **Proyecto 2**, **Proyecto 3**, **Proyecto 4**, **Proyecto 5** y **Proyecto 6**.

En el **Anexo 1** se adjuntan cada uno de estos trabajos en sus versiones publicadas por las editoriales correspondientes.

Cabe mencionar que cada uno de los compuestos sintetizados fueron identificados por Resonancia Magnética Nuclear (^{1}**H** y ^{13}**C**), espectrometría de masas de baja resolución (**MS**) y/o alta resolución (**HRMS**). Sin embargo las copias de dichos análisis **no se adjuntan en este trabajo** ya que pueden consultarse directamente en los sitios/ligas web abajo mencionados (**Supporting information/Supplementary Material**).

Es así que el lector puede consultar directamente estos archivos PDF de sus fuentes originales, disponibles en las plataformas web de cada editorial. A continuación se describen las ligas URL así como el *Digital Object Identifier* (DOI):

Proyecto 1

A NOVEL AND FACILE SYNTHESIS OF 1,4,5-TRISUBSTITUTED 1,2,3-TRIAZOLES FROM BENZYLIC ALCOHOLS THROUGH A ONE-POT, THREE-COMPONENT SYSTEM. *Tetrahedron Letters*, **2015**, *56*, 3, 514–516.

DOI: 10.1016/j.tetlet.2014.12.019
http://www.sciencedirect.com/science/article/pii/S0040403914020735

Proyecto 2

A STRAIGHTFORWARD AND VERSATILE APPROACH TO THE SYNTHESIS OF 1,4,5-TRISUBSTITUTED 1,2,3-TRIAZOLES FROM ALKYL HALIDES VIA A ONE-POT, THREE-COMPONENT REACTION. *Tetrahedron Letters*, **2015**, *56*, 13, 1713–1715.

DOI: 10.1016/j.tetlet.2015.02.049
http://www.sciencedirect.com/science/article/pii/S0040403915003202

Proyecto 3

AZIDE–ENOLATE 1,3-DIPOLAR CYCLOADDITION AS AN EFFICIENT APPROACH FOR THE SYNTHESIS OF 1,5-DISUBSTITUTED 1,2,3-TRIAZOLES FROM ALKYL/ARYL AZIDES AND Β-KETOPHOSPHONATES. *European Journal of Organic Chemistry*, **2016**, 668–672.
DOI: 10.1002/ejoc.201501465
http://onlinelibrary.wiley.com/doi/10.1002/ejoc.201501465/full

Proyecto 4

ANTIFUNGAL ACTIVITY OF 1′-HOMO-N-1,2,3-TRIAZOL-BICYCLIC CARBONUCLEOSIDES: A NOVEL TYPE OF COMPOUND AFFORDED BY AZIDE-ENOLATE (3+2) CYCLOADDITION. *Bioorganic Chemistry*, **2016**, 69, 1–6
DOI: 10.1016/j.bioorg.2016.09.003
http://www.sciencedirect.com/science/article/pii/S0045206816300694

Proyecto 5

AZIDE-ENOLATE 1,3-DIPOLAR CYCLOADDITION IN THE SYNTHESIS OF NOVEL TRIAZOLE-BASED MICONAZOLE ANALOGUES AS PROMISING ANTIFUNGAL AGENTS. *European Journal of Medicinal Chemistry*, **2016**, 112, 60-65
DOI: 10.1016/j.ejmech.2016.02.013
http://www.sciencedirect.com/science/article/pii/S0223523416300836

Proyecto 6

A STRAIGHTFORWARD AND VERSATILE PROTOCOL FOR THE DIRECT CONVERSION OF BENZYLIC AZIDES TO KETONES AND ALDEHYDES. *RSC Advances*, **2016**, 6, 83547-83550.
DOI: 10.1039/C6RA13088G
http://pubs.rsc.org/en/Content/ArticleLanding/2016/RA/C6RA13088G#!divAbstract

Los análisis microbiológicos descritos en los *papers* del **Proyecto 5** y **proyecto 6** fueron realizados por la M. en C. Q. Alejandra Ramírez Villalva y la Q.F.B. María G. Mejía Dionicio (miembros del grupo) como parte de las tareas, responsabilidades y objetivos multidisciplinarios de nuestro grupo de investigación. **Por lo que estos no pertenecen a los objetivos, metas y discusión de este trabajo** (no contemplados en el protocolo de investigación) sólo se presentan como resultados inherentes de la síntesis de los análogos nucleosídicos y del Miconazol.

Los trabajos descritos en el **Anexo 1** que definen la disertación del presente trabajo, se llevaron a cabo en el laboratorio del Departamento de Química Orgánica de la Facultad de Química de la UAEM, bajo la dirección del **Dr. Carlos González** y la **Dra. Aydeé Fuentes**. Los análisis microbiológicos se llevaron a cabo en el Departamento de Microbiología de la misma institución por la **M. en C. Q. Alejandra Ramírez** y la **Q.F.B. María G. Mejía Dionicio**, miembros de nuestro grupo de investigación.

De manera extracurricular se llevó a cabo una estancia de investigación en la Universidad de Cambridge (Reino Unido), bajo la dirección del **Prof. Steven V. Ley** con el proyecto titulado 'New flow reactor system for the catalytic reduction of nitriles to amines'. En el **Anexo 2** se adjunta un informe de dichas actividades.

Los resultados aquí escritos también han sido presentados en diferentes en congresos nacionales e internacionales.

CONGRESOS NACIONALES:

- "49º Congreso Mexicano de Química-33º Congreso Nacional de Educación Química", Mérida, Yucatán. **2014**.
- "50º Congreso Mexicano de Química-34º Congreso Nacional de Educación Química", Querétaro. **2015**.

CONGRESOS INTERNACIONALES:

"16th Tetrahedron Symposium: Challenges in Bioorganic and Organic Chemistry", Berlín, Alemania. **2015**.

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Al **Dr. J. Francisco Delgado Reyes**, a la **Dra. Susana Hernández López** y a la **Dra. M. Fernanda Ballesteros Rivas** por la valiosa revisión, comentarios y sugerencias a este escrito.

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Con solo dos manos no hubiese sido posible la culminación de todo este trabajo. Es por ello que quiero expresar un profundo agradecimiento a **Guadalupe Mejía**, **Itzel Santillán**, **Marco A. Morales** y **José Aguirre** de quienes tuve la oportunidad de fungir como co-asesor en sus tesis de licenciatura. La cooperación en equipo para el bien común es algo que aprendí de todos ellos.

A mi amiga y colega, la **M. en C. Q. Alejandra Ramírez** por su invaluable apoyo en el área microbiológica. Nuevamente comprendo que las verdaderas colaboraciones abren más puertas.

Al **Consejo Nacional de Ciencia y Tecnología** (CONACyT), al **Consejo Mexiquense de Ciencia y Tecnología** (COMECyT) y a la **Secretaría de Investigación y Estudios Avanzados** (SIEA) de la UAEM por las becas otorgadas durante mis estudios doctorales.

Al **Dr. Steven V. Ley** por la oportunidad de trabajar en el *Innovative Technology Centre, Department of Chemistry* de la *University of Cambridge*, Reino Unido, así como al **Dr. Ricardo Labes** por el *advisoring* durante dicha estancia.

El Grupo de Investigación agradece a la Secretaria de Investigaciones y Estudios Avanzados de la UAEM por el financiamiento otorgado (**No. Reg. 3804/2014/CID**)

CONTENIDO

1. Resumen

Se desarrollaron y estudiaron tres nuevas metodologías sintéticas para la obtención de 1,2,3-triazoles a través de cicloadiciones (3+2) azida-enolato (**Proyecto 1**, **Proyecto 2** y **Proyecto 3**). Los alcances así como la versatilidad de tales metodologías se demostraron mediante su aplicación en la síntesis de Análogos Nucleosídicos (**Proyecto 4**) y del Miconazol (**Proyecto 5**). Como parte de una colaboración multidisciplinaria, estos últimos fueron evaluados biológicamente (actividad antimicótica) en especies microbiológicas filamentosas y levaduriformes de importancia clínica.

Fortuitamente se descubrió, estudió y desarrollo un nuevo protocolo para la conversión directa de bencil azidas a grupos carbonilo (**Proyecto 6** –proyecto adicional–).

Para una comprensión versátil y general, se describen a continuación los *Graphical Abstract* y *Abstracts* para cada uno de estos, mismos que pueden ser vistos en las versiones electrónicas disponibles en las plataformas web de cada editorial.

Abstract:

Three new synthetic methodologies for the approach to 1,2,3-triazoles through an azide-enolate cycloaddition (Project 1, Project 2 and Project 3) were developed and studied. The scope and the versatility of such methodologies were demonstrated by their application in the synthesis of nucleoside (Project 4) and Miconazole (Project 5) analogs. As part of a multidisciplinary collaboration, the latter were biologically evaluated (antimycotic activity) in microbiological filamentous and yeast species of clinical importance.

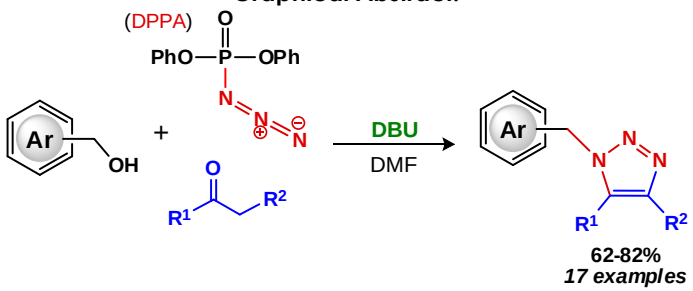
A new protocol for the direct conversion of benzyl azides to carbonyl groups has been discovered, studied and developed (Project 6 –additional project–)

For a versatile and general understanding, the Graphical Abstracts and Abstracts are described below for each of these ones, which can be seen in the electronic versions available on the web sites of each editorial.

Proyecto 1

A NOVEL AND FACILE SYNTHESIS OF 1,4,5-TRISUBSTITUTED 1,2,3-TRIAZOLES FROM BENZYLIC ALCOHOLS THROUGH A ONE-POT, THREE-COMPONENT SYSTEM. *Tetrahedron Letters*, **2015**, *56*, 3, 514–516.

Graphical Abstract:

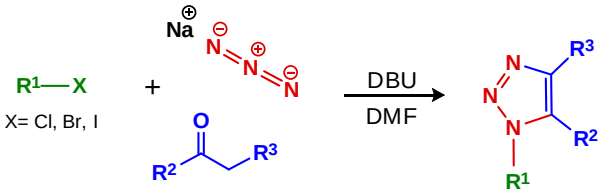


Abstract: A simple one-pot procedure has been developed to efficiently prepare 1,4,5-trisubstituted 1,2,3-triazoles from benzylic alcohols. The presence of diphenylphosphoryl azide (DPPA) and active ketones allows for an azide–enolate [3+2] cycloaddition by use of DBU.

Proyecto 2

A STRAIGHTFORWARD AND VERSATILE APPROACH TO THE SYNTHESIS OF 1,4,5-TRISUBSTITUTED 1,2,3-TRIAZOLES FROM ALKYL HALIDES VIA A ONE-POT, THREE-COMPONENT REACTION. *Tetrahedron Letters*, **2015**, *56*, 13, 1713–1715.

Graphical Abstract:

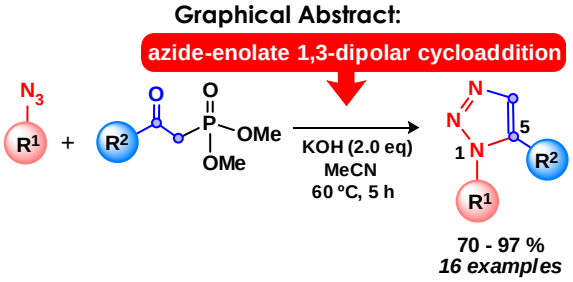


Abstract: The preparation of 1,4,5-trisubstituted 1,2,3-triazoles by the coupling of three components (alkyl halides, sodium azide, and active ketones) through an azide–enolate [3+2] cycloaddition (Dimroth cycloaddition) has been developed for the first time. A wide variety of halides (including chlorides, bromides, and iodides as well as primary and secondary derivatives) have demonstrated the versatility of this method, which is based on a one-pot system under mild reaction conditions.

Proyecto 3

AZIDE–ENOLATE 1,3-DIPOLAR CYCLOADDITION AS AN EFFICIENT APPROACH FOR THE SYNTHESIS OF 1,5-DISUBSTITUTED 1,2,3-TRIAZOLES FROM ALKYL/ARYL AZIDES AND Β-KETOPHOSPHONATES. *European Journal of Organic Chemistry*, **2016**, 668–672.

Graphical Abstract:

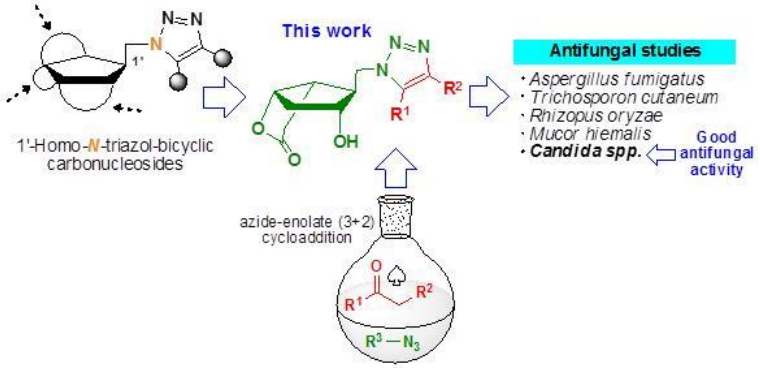


Abstract: A simple procedure to prepare 1,5-disubstituted 1,2,3-triazoles efficiently from alkyl/aryl azides and β-ketophosphonates in the presence of KOH by an azide–enolate 1,3-dipolar cycloaddition in good yields was developed.

Proyecto 4

ANTIFUNGAL ACTIVITY OF 1'-HOMO-N-1,2,3-TRIAZOL-BICYCLIC CARBONUCLEOSIDES: A NOVEL TYPE OF COMPOUND AFFORDED BY AZIDE-ENOLATE (3+2) CYCLOADDITION. *Bioorganic Chemistry*, **2016**, 69, 1–6

Graphical Abstract:

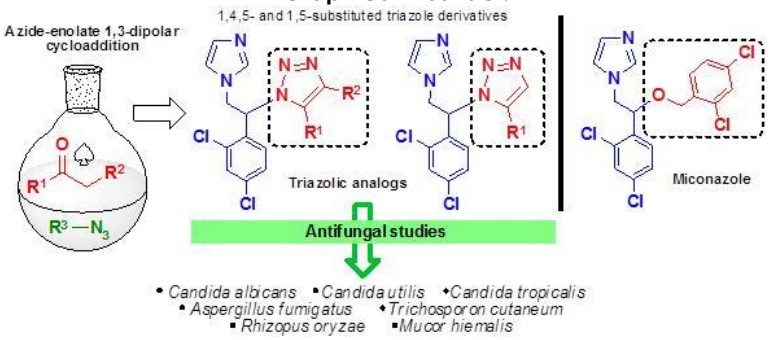


Abstract: The first report of 1'-homo-N-1,2,3-triazol-bicyclic carbonucleosides (7a and 7b) is described herein. Azide-enolate (3+2) cycloaddition afforded the synthesis of this novel type of compound. Antifungal activity was evaluated in vitro against four filamentous fungi (*Aspergillus fumigatus*, *Trichosporon cutaneum*, *Rhizopus oryzae* and *Mucor hiemalis*) as well as nine species of *Candida spp*. as yeast specimens. These pre-clinical studies suggest that compounds 7a and 7b are promising candidates for complementary biological studies due to their good activity against *Candida spp*.

Proyecto 5

AZIDE-ENOLATE 1,3-DIPOLAR CYCLOADDITION IN THE SYNTHESIS OF NOVEL TRIAZOLE-BASED MICONAZOLE ANALOGUES AS PROMISING ANTIFUNGAL AGENTS. *European Journal of Medicinal Chemistry*, **2016**, 112, 60-65

Graphical Abstract:

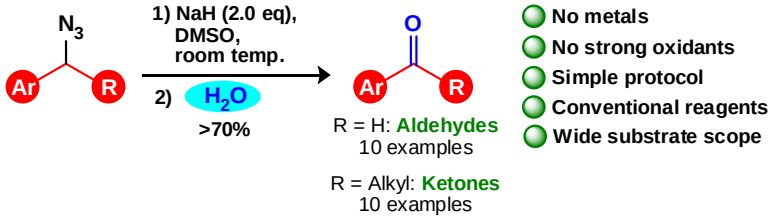


Abstract: Seven miconazole analogs involving 1,4,5-tri and 1,5-disubstituted triazole moieties were synthesized by azide-enolate 1,3-dipolar cycloaddition. The antifungal activity of these compounds was evaluated in vitro against four filamentous fungi, including *Aspergillus fumigatus*, *Trichosporon cutaneum*, *Rhizopus oryzae*, and *Mucor hiemalis* as well as three species of *Candida spp*. as yeast specimens. These pre-clinical studies suggest that compounds 4b, 4d and 7b can be considered as drug candidates for future complementary biological studies due to their good/excellent antifungal activities.

Proyecto 6

A STRAIGHTFORWARD AND VERSATILE PROTOCOL FOR THE DIRECT CONVERSION OF BENZYLIC AZIDES TO KETONES AND ALDEHYDES. *RSC Advances*, **2016**, 6, 83547-83550.

Graphical Abstract:



Abstract: The synthesis of carbonyl compounds from benzylic azides through benzylideneamides is described for the first time. NaH-mediated activation of benzyl azides allows a rapid water-promoted oxidation under a facile protocol with good yields.

2. Expectativas

2.1. Objetivo General

Desarrollar y estudiar tres nuevas metodologías sintéticas para la obtención de 1,2,3-triazoles a través de cicloadiciones 1,3-dipolar azida-enolato así como comprobar sus alcances y versatilidad en la síntesis de Análogos Nucleosídicos y del Miconazol.

2.2. Objetivos Específicos

2.2.1. Obtener 1,2,3-triazoles mediante cicloadiciones (3+2) azida-enolato a partir de alcoholes bencílicos (formación *in situ* de alquil azidas) y cetonas.

2.2.2. Desarrollar un protocolo para obtener 1,2,3-triazoles mediante cicloadiciones (3+2) azida-enolato a partir de halogenuros de alquilo (formación *in situ* de alquil azidas) y cetonas.

2.2.3. Sintetizar 1,2,3-triazoles mediante cicloadiciones (3+2) azida-enolato a partir de azidas y β-cetofosfonatos.

2.2.4. Generar análogos nucleosídicos mediante la aplicación de nuevas estrategias sintéticas.

2.2.5. Producir análogos del Miconazol mediante la aplicación de nuevas estrategias sintéticas.

2.3. Hipótesis:

2.3.1. Los heterociclos 1,2,3-triazoles pueden obtenerse vía cicloadiciones 1,3-dipolar mediante el acoplamiento entre una cetona activada del tipo R'$COCH_2$R'' y un alquil azida preparada *in situ* a partir de alcoholes bencílicos.

2.3.2. Los heterociclos 1,2,3-triazoles pueden obtenerse vía cicloadiciones 1,3-dipolar mediante el acoplamiento entre una cetona activada

del tipo R'$COCH_2$R'' y un alquil azida preparada *in situ* a partir de halogenuros de alquilo.

2.3.3. Los heterociclos 1,2,3-triazoles pueden obtenerse vía cicloadiciones 1,3-dipolar mediante el acoplamiento entre una cetona activada del tipo $RCOCH_2P(O)(OMe)_2$ y un alquil azida.

2.3.4. Es posible la obtención de análogos nucleosídicos mediante nuevas metodologías sintéticas del tipo cicloadiciones 1,3-dipolar.

2.3.5. Es posible la obtención de análogos del Miconazol mediante nuevas metodologías sintéticas del tipo cicloadiciones 1,3-dipolar.

2.4. Justificación:

El núcleo 1,2,3-triazole es un importante farmacóforo por lo que su síntesis de manera versátil, fácil y sencilla siempre será motivo de intensa investigación debido a los factores de **COSTO/BENEFICIO**. Por lo tanto, este trabajo permitirá ampliar la biblioteca de los métodos de síntesis de estos apreciables heterociclos.

El *Centers for Disease Control and Prevention* de EUA describe a las enfermedades micóticas como un problema de salud pública a nivel mundial y de incidencia para todas las clases sociales.[1] Dicho problema se ve aún más afectado por la **RESISTENCIA FARMACOLÓGICA** de los microorganismos fúngicos.[2] Este hecho ha obligado a la química orgánica medicinal a una continua y obligada búsqueda de nuevos agentes anti-fúngicos.[3] Este trabajo pretende incursionar en la solución de los problemas antes mencionados mediante la modificación estructural de fármacos líderes (síntesis de sus correspondientes análogos), una estrategia muy recurrente en la química medicinal. [4]

[1] http://www.cdc.gov/fungal/global/index.html (fuente consultada en Abril de **2017**).
[2] (a) Z. A. Kanafani, J. R. Perfect, *Clin. Infect. Dis.***2008**, 46, 120–128. (b) M. A. Pfaller, *Am. J. Med*. **2012**, 125, S3–S13. (c) G. Morace, F. Perdoni, E. Borghi, *Am. J. Med*. **2014**, 2, 254–259. (d) G. Morace, F. Perdoni, E. Borghi, *J. Global Antim. Resis*. **2014**, 2, 254–259. (e) J. B. Anderson, *Nature Reviews Microbiology* **2005**, 3, 547–556.
[3] Para un completo entendimiento de este tema ver los siguientes *Reviews*: (a) M. K. Kathiravan, A. B. Salake, A. S. Chothe, P. B. Dudhe, R. P. Watode, M. S. Mukta, S. Gadhwe, *Bioorg. Med. Chem*. **2012**, 20, 5678–5698. (b) A. B. Petersen, M. H. Rønnest, T. O. Larsen, M. H. Clausen, *Chem. Rev*.**2014**, 12088–12107. (c) J. Heeres, L. Meerpoel P. Lewi, *Molecules* **2010**, 15, 4129–4188.
[4] W. R. J. D. Galloway, A. Bender, M. Welch, D. R. Spring, *Chem. Commun*. **2009,** 2446–2462.

3. Antecedentes

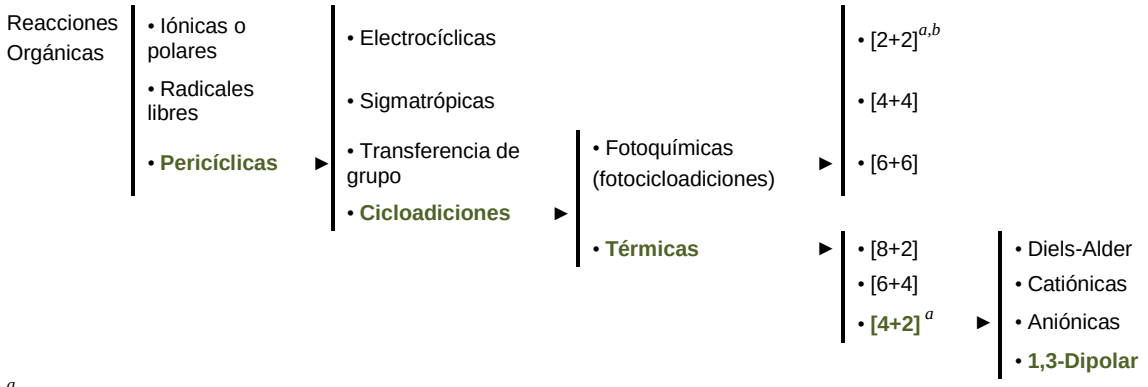
IMPORTANTE: Las publicaciones (**Anexo 1**) de los trabajos que aquí se reportan han involucrado de manera inherente, una descripción sustancial, apropiada y concisa de antecedentes para cada uno de los trabajos; antecedentes que necesariamente fueron evaluados, discutidos y sugeridos por réferis internacionales así como por los mismos editores de cada una de las revistas. Con la intención de **evitar la redundancia** y **demasía**, en esta sección solo se abordaran conceptos que no fueron descritos en dichos *papers*.

3.1. La cicloadición 1,3-dipolar: Una breve contextualización

Las reacciones orgánicas *podrían* ser clasificadas en tres categorías exclusivas, conveniente a los propósitos del presente trabajo: (a) reacciones iónicas o polares, (b) por radicales y (c) **pericíclicas** (Esquema 1). La característica principal que diferencia a las últimas de las primeras es que las reacciones pericíclicas tienen estructuras de transición cíclicas, los electrones se mueven en un círculo donde no hay cargas positivas o negativas en ningún intermediario, de hecho, no hay intermediarios en lo absoluto, ya que la formación y ruptura de enlaces toma lugar de manera concertada en un estado de transición.[5]

[5] Calsificación de las reacciones pericíclicas: (a) I. Fleming, *Pericyclic Reactions*, Oxford Chemistry Primers, USA, **1998**, pp. 1–7. (b) S. Kumar, V. Kumar, S.P. Singh, *Pericyclic Reactions: A Mechanistic and Problem Solving Approach.*

Las **cicloadiciones 1,3-dipolar** pertenecen a un grupo especial de los más versátiles en las reacciones pericíclicas refiriéndose a la reacción entre un **1,3-dipolo** y un **dipolarófilo** para formar ciclos de cinco miembros involucrando un sistema **[4+2]**.



[a] Sistemas también involucrados en otro tipo de reacciones pericíclicas: Quelatrópicas .
[b] Sistemas también involucrados en procesos térmicos, principalmente cuando el dipolo involucra a una cetena o un isocianato.

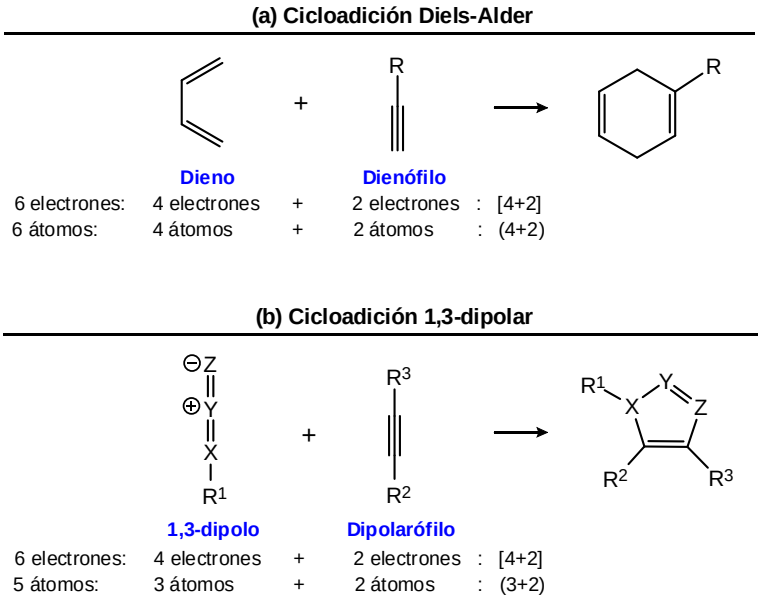
Esq. 1: Clasificación de las reacciones orgánicas. La cicloadición 1,3-dipolar pertenece a las reacciones pericíclicas del tipo [4+2].

3.2. La naturaleza de los 1,3-dipolos y dipolarófilos

Si consideramos la naturaleza de una reacción Diels-Alder entre un dieno y un dienófilo –cicloadición [4+2]: 6 electrones; (4+2): 6 átomos involucrados– para formar así un anillo de seis miembros [Esquema 2, Eq. (a)], entonces concluimos que para la formación de un anillo de cinco es necesario involucrar: (i) un componente solamente de tres átomos, pero capaz de comportarse como un equivalente a cuatro electrones de un dieno, y (ii) un componente de 2 átomos capaz de involucrar solo 2 electrones (mismas condiciones que para un dienófilo) que nos llevaría a una cicloadición **[4+2]** pero del tipo **(3+2)**. Para el caso (i), el componente de tres átomos ('X', 'Y' y 'Z') es de naturaleza isoeléctrica, esto es, fragmento que forma un dipolo electrónico a nivel molecular por deslocalización electrónica a lo largo de los tres átomos, teniendo un sistema conjugado de tres orbitales *p* a lo largo de los mismos, y cuatro electrones en el sistema conjugado. Ya que los átomos extremos (X,Z o 1,3) tienen naturaleza nucleofílica-electrofílica (un ataque nucleofílico en Y^+ no es posible), dicho componente molecular es en

Chapter 1– Pericyclic Reactions and Molecular Orbital Symmetry, Academic Press- Elsevier, **2016**, pp. 1-3 DOI: 10.1016/B978-0-12-803640-2.00001-4

efecto un **1,3-dipolo**, mientras que a su contraparte (dienófilo equivalente) se le conoce como **dipolarófilo**, llevando a una clasificación de cicloadiciones muy particular: las **cicloadiciones 1,3-dipolar** [Esquema 2, Eq. (b)]. Dado que la reacción forma un producto cíclico, a través de un estado de transición cíclico mediante la adición de un sistema 4π-electrones (1,3-dipolo) a un sistema 2π-electrones (dipolarófilo), también puede describirse como reacción de cicloadición [$\pi^4s + \pi^2s$]. La letra 's' indica que la reacción tiene lugar **suprafacialmente** en ambos componentes.[6]



Esq. 2: Comparación entre la cicloadición Diels-Alder y 1,3-dipolar. Un 1,3-dipolo es la contraparte de un dieno y un dipolarófilo la de un dienófilo.

3.3. Alquil azidas como especies 1,3-dipolares

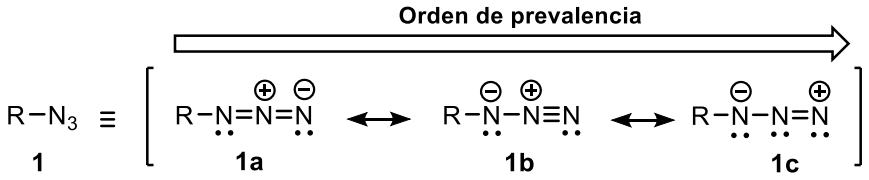
Las azidas son intermediarios sintéticos altamente versátiles y su química es muy conocida. Libros[7] y *Reviews*[8] han compilado el papel de estos valiosos compuestos nitrogenados como mediadores entre la química, la medicina, la

[6] S. Kumar, V. Kumar, S.P. Singh, *Pericyclic Reactions: A Mechanistic and Problem Solving Approach. Chapter 4– Cycloaddition Reactions*, Academic Press- Elsevier, **2016**, pp. 164-165. DOI: 10.1016/B978-0-12-803640-2.00004-X

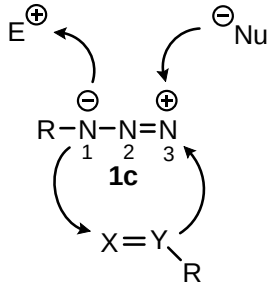
[7] (a) *Organic Azides: Syntheses and Applications*, ed. S. Brase, K. Banert, John Wiley & Sons, Ltd, Chichester, England, UK, **2010**, DOI: 10.1002/9780470682517; (b) *Supplement F2: The Chemistry of Amino, Nitroso, Nitro and Related Groups*, ed. S. Pata, John Wiley & Sons, Ltd, Chichester, England, **1996**, ISBN: 0-471-95171-4.

[8] (a) S. Brase, C. Gil, K. Knepper, V. Zimmermann, *Angew. Chem., Int. Ed*., **2005**, *44*, 5188–5240. (b) W. P. Fehlhammer, W. Beck, *Z. Anorg. Allg. Chem*., **2015**, *641*, 1599–1678. (c) W. P. Fehlhammer, W. Beck, *Z. Anorg. Allg. Chem*., **2013**, *639*, 1053–1082. (d) S. Chiba, *Synlett*, **2012**, *23*, 21–44. (e) T. M. Klapotke, *Chem. Ber*., **1997**, *130*, 443–452. (f) E. F. V. Scriven, K. Turnbull, *Chem. Rev*., **1988**, *88*, 297–368.

biología y la ciencia de los materiales. Una base para la diversidad química de las azidas proviene de las propiedades fisicoquímicas de estas. Algunas de estas propiedades pueden explicarse considerando sus estructuras mesoméricas polares (Esquema 3).



Esq. 3: Estructuras resonantes dipolares de las azidas.



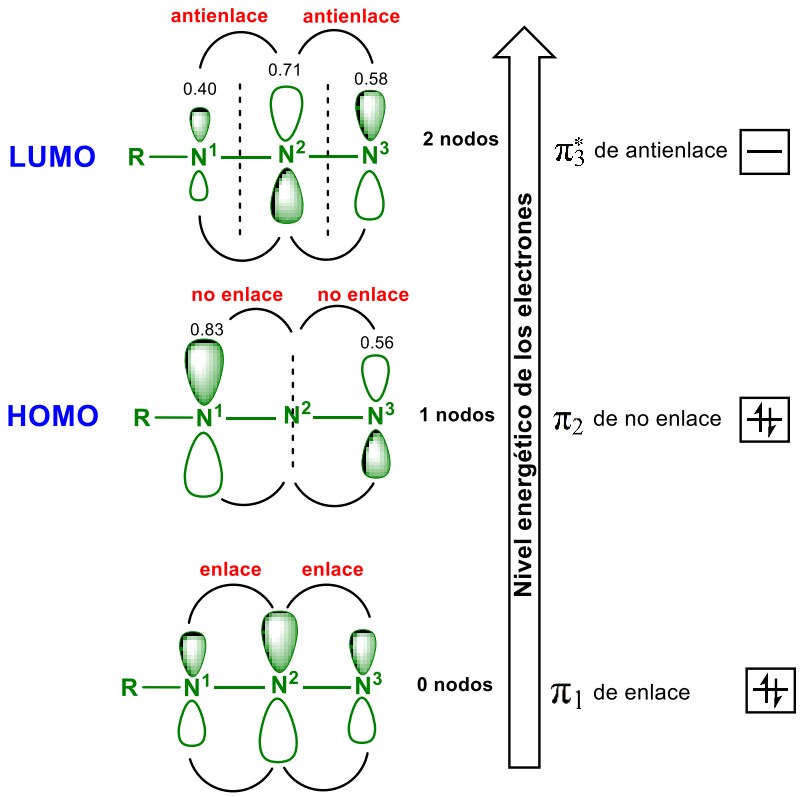
Esq. 4: Principales reacciones de las azidas.

Las estructuras **1b** y **1c** pueden explicar mucho de sus propiedades químicas. La forma resonante **1c** (predominante, aunque también depende de la naturaleza de R) representa en efecto a una especie 1,3-dipolar que además de actuar en procesos de cicloadición (Esquema 4), esta naturaleza le confiere la capacidad de reaccionar regioselectivamente con electrófilos y nucleófilos (ataque en N^3 por nucleófilos –e.g. reacción de Staudinger–, mientras que los electrófilos son atacados por N^1 –e.g. reacción de Mitzunobu–).[9]

3.4. Alquil azidas y la teoría de los orbitales moleculares frontera

Antes de describir la influencia de los **orbitales moleculares frontera (HOMO-LUMO)** de las azidas en las cicloadiciones 1,3-dipolar, primero es necesario considerar algunas generalidades de los **orbitales moleculares (OM)** para el grupo R–N_3 (Esquema 5).

[9] S. Brase, C. Gil, K. Knepper, V. Zimmermann, *Angew. Chem., Int. Ed*., **2005**, *44*, 5188–5240.



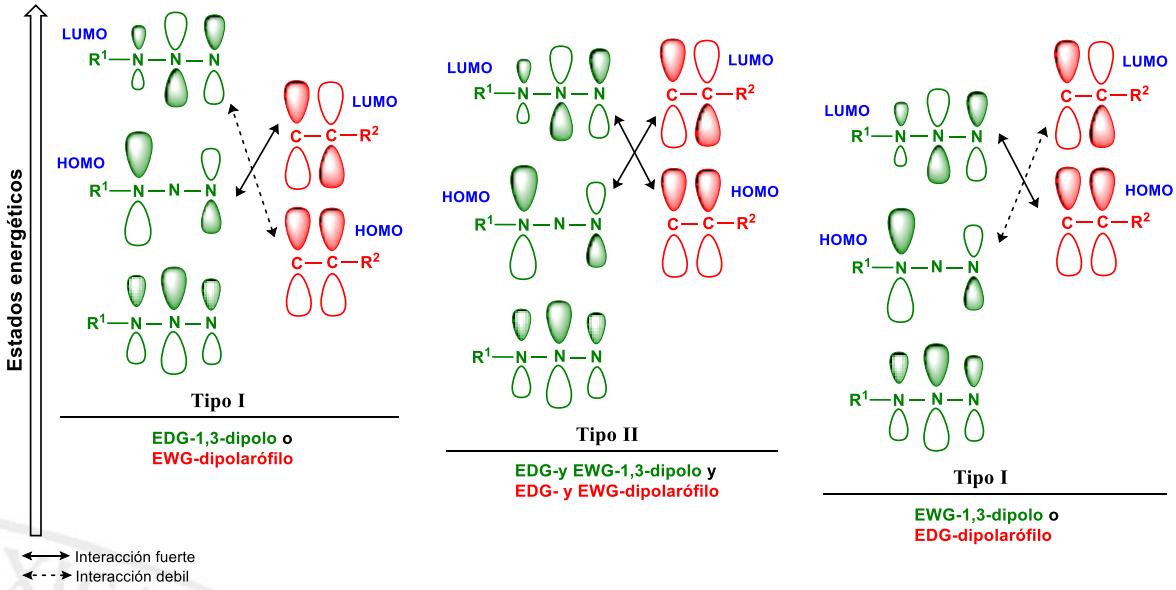
Esq. 5: Tres OM para las alquil azidas, uno de enlace (π_1), uno de no enlace (π_2), y otro de antienlace (π_3^*).

Ya que el número de orbitales moleculares (OM) siempre es igual al número de los orbitales atómicos p utilizados para formar los OM, podemos construir los 3 OM de un alquil azida a partir de sus 3 orbitales atómicos p (sobre N^1, N^2 y N^3). Estos tres OM tienen características muy particulares. El primer OM (π_1) es completamente **de enlace** (traslape constructivo de los núcleos en fase), y corresponde al estado basal con mayor densidad electrónica. El segundo (π_2) tiene un nodo simétrico que coincide con el átomo N^2 central; este orbital como el primero habrán de ser orbitales llenos. Y el tercero (π_3^*) con 2 nodos y debido a que es el OM de energía más alta, es completamente de **antienlace**. Al igual que cualquier otro sistema, esperamos que la mitad de los OM sean de enlace y la mitad de antienlace; sin embargo, con un número impar de OM no puede dividirse de manera simétrica. Uno de los OM debe aparecer a la mitad de los niveles de energía, ni de enlace ni de antienlace. Este es un orbital molecular de **no enlace** (π_2). Los electrones en un orbital de no enlace tienen la misma energía que en un orbital p aislado. La estructura del orbital π_2 puede aparecer extraña debido a que hay densidad electrónica cero en el orbital p central (N^2). Este es el caso debido al cual π_2 debe tener un nodo y sólo la posición simétrica para un

nodo está en el centro de la molécula atravesando N^2. A través de esta estructura podemos decir que π_2 debe ser de no enlace, debido a que N^1 y N^3 tienen traslape cero con N^2. En tal esquema se colorean de verde las funciones de onda positiva del orbital molecular p y sin color para la fase (o función) negativa con el fin de enfatizar la diferencia de las fases. Se describen los correspondientes coeficientes (***orbital coefficients***) para el grupo alquil azida[10] tratando de asemejar en la mayor manera posible el tamaño de cada uno de los lóbulos con respecto a tales coeficientes los cuales describen las densidades electrónicas.

Las azidas al igual que otros 1,3-dipolos son reactivos capaces de usar tanto su HOMO como su LUMO que puede depender en gran manera del tipo de dipolarófilo empleado (rico o deficiente de electrones). Aunque la regioselectividad (muchas veces predecible) de las cicloadiciones 1,3-dipolares depende de efectos electrónicos y estéricos, la teoría de los OM proporciona una elegante interpretación de las interacciones 1,3-dipolo-dipolarófilo.

Antes de describir qué o quién determina la regioselectividad en las cicloadiciones (3+2) azida-enolato, primero será conveniente explicar los factores que determinan la regioselectividad en otros sistemas.



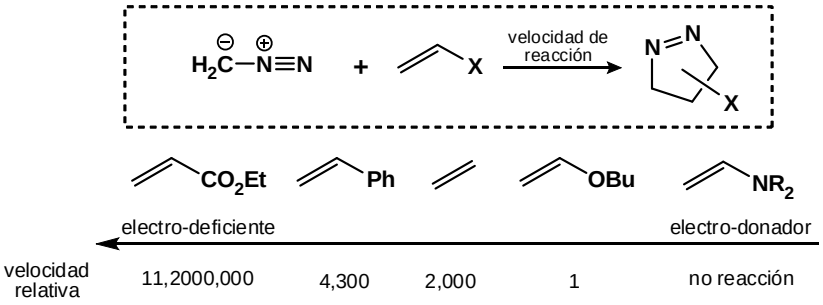
Esq. 6: Tres interacciones HOMO-LUMO (Tipo I, Tipo II, Tipo III) describen a las cicloadiciones 1,3-dipolares.

[10] (a) K. N. Houk, et. al. *J. Am. Chem. Soc*., **1973**, *95*, 7287-7301. (b) ver Fig. 10.15 en: F. A. Carey, R. J. Sundberg, *Advanced Organic Chemistry: Part A: Structure and Mechanisms*, 5th ed., Springer, New York, **2007**, p. 881. e-ISBN-13: 978-0-387-44899-3

Cualquier cicloadición 1,3-dipolar es caracterizada por tres tipos de interacciones HOMO-LUMO descritos en el Esquema 6. Consideremos el sistema azida-olefina:[11]

Tipo I. *Sustituyentes electro-donadores (EDG) en el 1,3-dipolo o sustituyentes electro-atractores (EWG) en el dipolarófilo*: El dipolo tiene un HOMO alto que se superpone con LUMO del dipolarófilo. Un dipolo de esta clase se denomina a veces como un 'dipolo HOMO-controlado' o 'dipolo nucleofílico' capaces de añadirse fácilmente a los alquenos electrofílicos. Los grupos electronegativos (EWG) en el dipolarófilo acelerarían la reacción bajando el LUMO, mientras que los grupos donadores de electrones (EDG) desacelerarían la reacción al elevar el HOMO.

Adicionalmente considere las velocidades de reacción encontradas para el diazometano con diferentes dipolarófilos:[12]

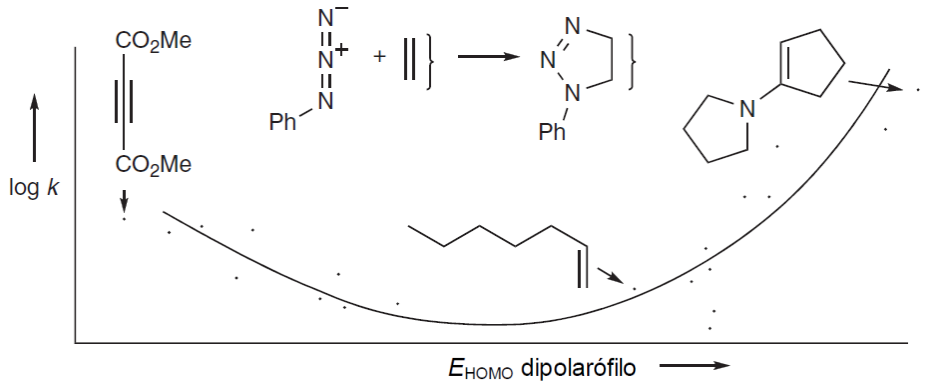


Tipo II. *Sustituyentes electro-donadores (EDG) y electroatractores (EWG) tanto en el 1,3-dipolo y dipolarófilo*: El HOMO del dipolo puede emparejarse con el LUMO del dipolarófilo. Alternativamente, el HOMO del dipolarófilo puede emparejarse con LUMO del dipolo. Esta interacción de dos vías surge porque la brecha de energía en cualquier dirección es similar. Un dipolo de esta clase se denomina un dipolo 'HOMO-LUMO-controlado' o 'dipolo ambifílico'. Cualquier sustituyente en el dipolarófilo aceleraría la reacción reduciendo el espacio de energía entre los dos orbitales que interactúan, es decir, un EWG reduciría el LUMO mientras que un EDG elevaría el HOMO.

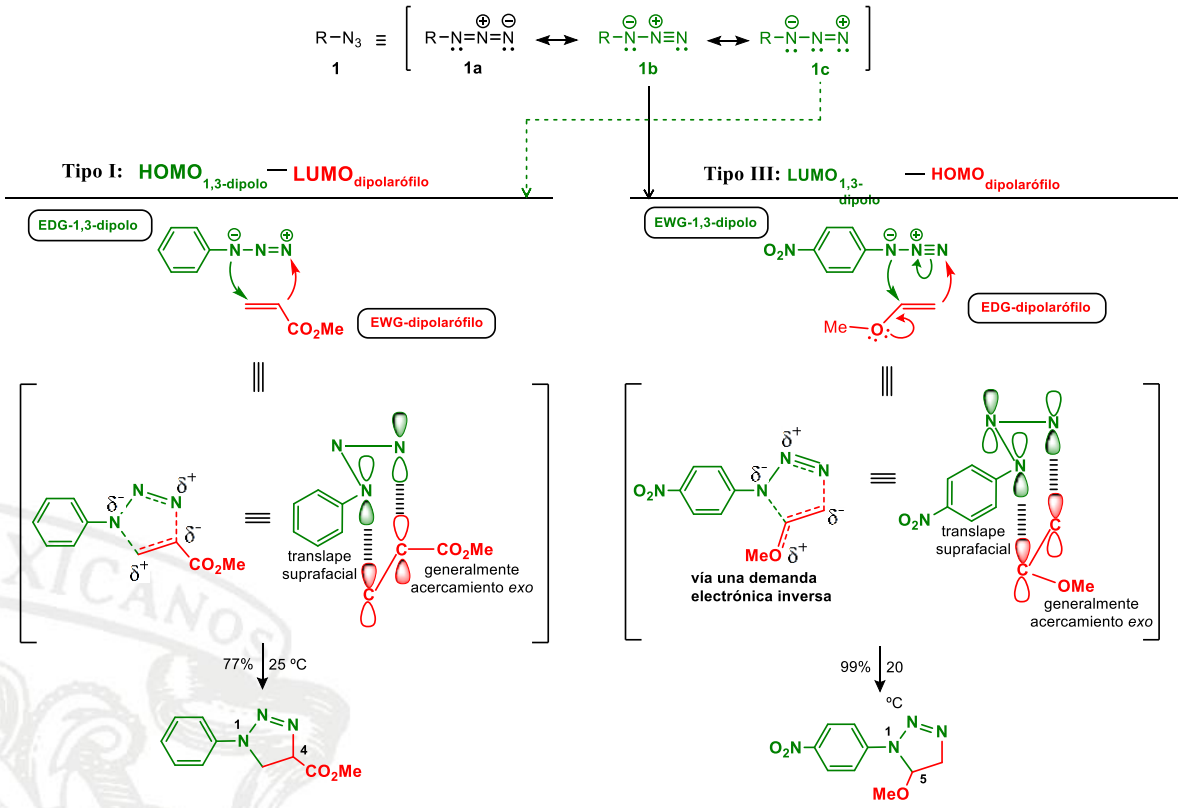
Tipo III. *Sustituyentes electro-atractores (EWG) en el 1,3-dipolo o sustituyentes electro-donadores (EDG) en el dipolarófilo*: El dipolo

[11] R. Huisgen, *J. Org. Chem*. **1976**, *41*, 403-419.
[12] J. Geittner, R. Huisgen, *Tetrahedron Lett*. **1977**, *18*, 881–884.

tiene un LUMO bajo que se superpone con el HOMO del dipolarófilo. Un dipolo de esta clase se denomina un 'dipolo LUMO-controlado' o 'dipolo electrofílico'. Los EWG sobre el dipolarófilo desaceleran la reacción, mientras que los EDG aceleran la reacción.



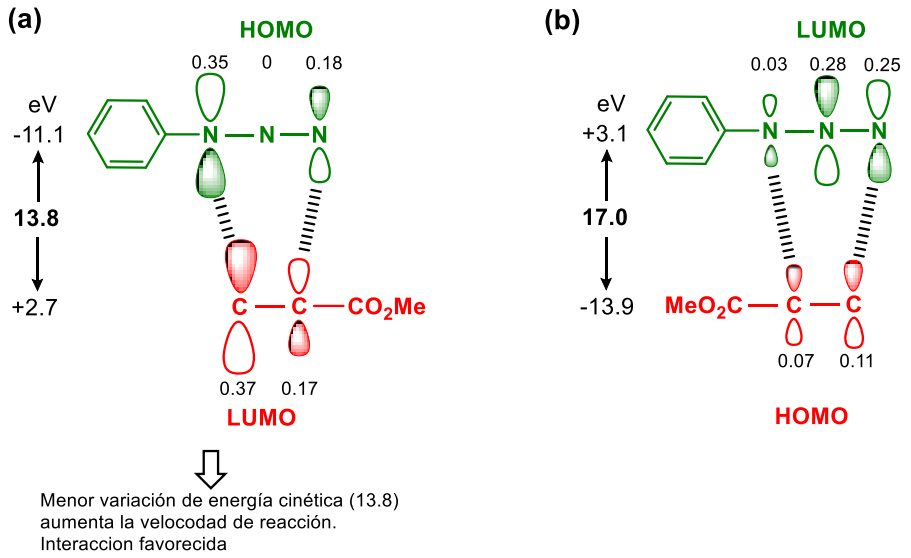
Esq. 7: Correlación entre la energía del HOMO de algunos dipolarófilos y sus velocidades de reacción con la PhN_3



Esq. 8: Características principales en las cicloadiciones (3+2) azida-olefina del tipo I y III.

Según la naturaleza del dipolarófilo, en el Esquema 7[13] se pueden apreciar gráficamente los tres tipos de interacciones HOMO-LUMO antes mencionados para la bencil azida (ni particularmente nucleofílico ni particularmente electrofílico).

Sin embargo, en necesario mencionar algunas otras características importantes sobre estas interacciones HOMO-LUMO Tipo I, Tipo II y Tipo III de la cicloadición 1,3-dipolar. Consideremos algunos ejemplos particulares. En el Esquema 8 se describe detalladamente la cicloadición entre el 4-nitrofenilazida y metil vinil éter así como entre la bencil azida y el éster acrílico (**Tipo I** y **Tipo III**).



Esq. 9: Velocidades de reacción dependiente de las interacciones orbitales donador-receptor dominantes

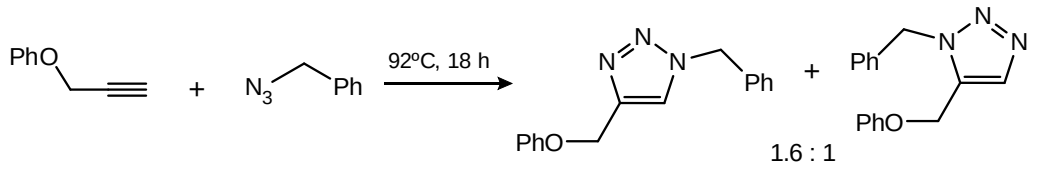
Aunque la regioselectividad se puede entender definitivamente por los acercamientos electrostáticos (control de carga electrónica), si consideramos el control por sus OM, aún se observarán dos posibilidades de orientación a considerar (Esquema 9),[14] explicadas por la variación de energía cinética que experimenta el electrón en los OM, representada por sus valores en **eV** (electronvoltio), que determinará entonces la velocidad de reacción dependiente de las interacciones orbitales donador-receptor dominantes. A menor valor de eV, mayor es la velocidad de reacción (producto favorecido) [Esquema 9, Eq. (a)]. Por otro lado, se ha observado que acercamientos del tipo

[13] I. Fleming, *Molecular Orbitals and Organic Chemical Reactions*, Student ed., John Wiley & Sons Ltd, UK, **2009**, p. 243. ISBN 978-0-470-74660-8

[14] (a) R. Huisgen, *J. Org. Chem.* **1976**, *41*, 403-419. (b) ver también Fig. 6.36 en: I. Fleming, *Molecular Orbitals and Organic Chemical Reactions*, *op. cit.* p.249.

exo determinan la estereoquímica. No olvidar otros factores importantes de regio y estereoselectividad como el impedimento estérico. El traslape de los orbitales moleculares para *todas* las cicloadiciones 1,3-dipolar siempre es **suprafacial**.

Las interacciones HOMO-LUMO del **Tipo II** resultan ser las menos versátiles en términos prácticos debido a la mezcla de regioisómeros si estas no están gobernadas por otros factores, e.g efectos estéricos, o en casos más sofisticados, por catalizadores metálicos inductores de regio y estereoselectividad. Un ejemplo emblemático es la cicloadición alquino-azida de Huisgen[15] que hasta antes del *improvement* por Meldal-Sharpless,[16] esta parecía no tener utilidad práctica debido a la inevitable mezcla de regioisómeros entendible por la magnitud similar de energías del HOMO-LUMO tanto para la azida como del alquino (Esquema 10).[17]



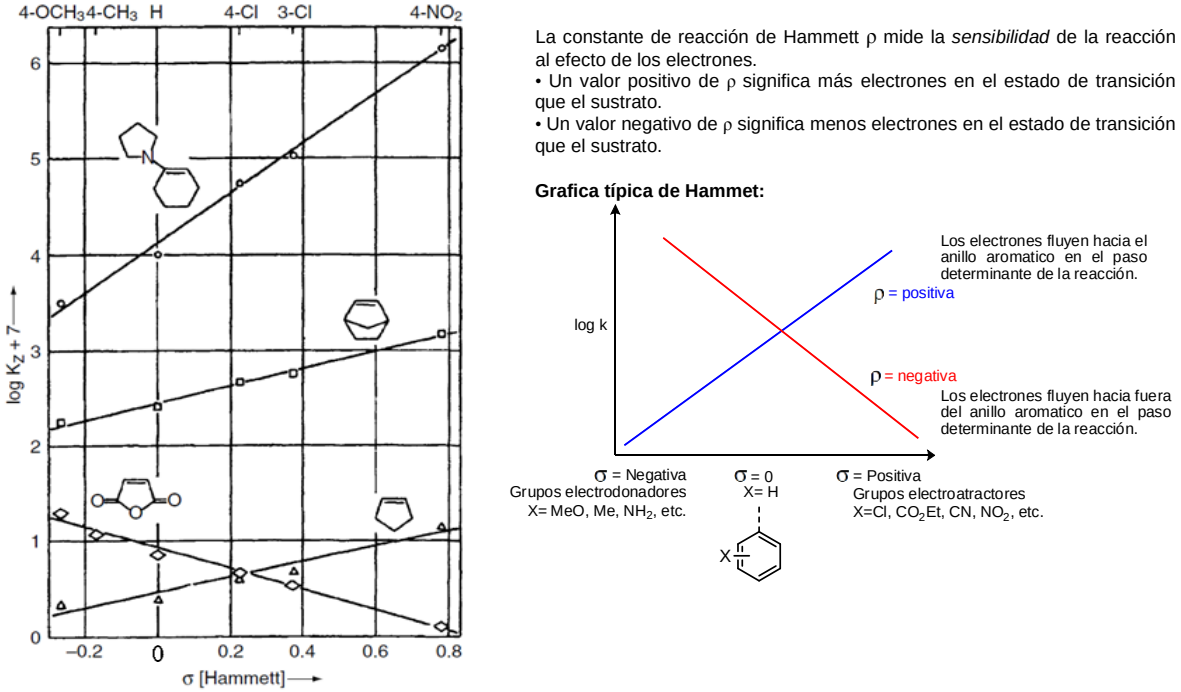
Esq. 10: Cicloadición alquino-azida como ejemplo emblemático del acoplamiento Tipo II.

3.5. Constantes de reacción de Hammett (σ, ρ): Cuantificando los efectos electrónicos de los sustituyentes en el 1,3-dipolo

Lo que idealmente nos gustaría hacer es encontrar una manera de *cuantificar* los efectos que los grupos electro-donadores o atractores tienen sobre el estado de transición durante el transcurso de una reacción. Esto nos dará una idea de cómo es realmente el estado de transición. La primera pregunta es: ¿podemos definir exactamente cuán eficiente es un grupo dado en donar o retirar electrones? Se han desarrollado muchas correlaciones importantes entre los grupos sustituyentes de un anillo aromático y sus propiedades químicas. En muchos casos, las relaciones estructura-reactividad pueden expresarse *cuantitativamente* de manera que sean útiles tanto para la interpretación de mecanismos de reacción como para la predicción de velocidades de reacción y

[15] (a) R. Huisgen, *Angew. Chem. Int. Ed. Engl*. **1963**, *2*, 565–598. (b) *Angew. Chem*. **1963**, *75*, 604–637.
[16] M. Meldal, C. W. Tornøe, *Chem. Rev*. **2008**, *108*, 2952–3015.
[17] V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem. Int. Ed.*, **2002**, *41*, 2596-2599.

equilibrios. La más ampliamente aplicada de estas relaciones es la **ecuación de Hammett**, que correlaciona velocidades y equilibrios para muchas reacciones de compuestos que contienen grupos fenilo-sustituidos.[18]



Esq. 11: Los '*Hammett plots*' representan las velocidades de cicloadición de arilazidas sustituidas con alquenos nucleófilos, electrofílicos y no sustituidos que muestran el carácter ambifílico de las arilazidas. La reacción con anhídrido maléico (electrofílico) es favorecida por los sustituyentes donantes en el Ar-N_3. La reacción con pirrolidinociclohexeno (nucleófilo) es favorecida por los sustituyentes aceptores. Las reacciones con ciclopenteno y norborneno son favorecidas moderadamente por los sustituyentes aceptores.

Hasta ahora hemos considerado *cualitativamente* los efectos de los sustituyentes en los 1,3-dipolos. Por último, las constantes de reacción de Hammett nos pueden dar las últimas pesquisas a cerca de las cicloadiciones 1,3-dipolar de manera **cuantitativa**. La ecuación de Hammett describe una relación lineal de energía libre que relaciona a las velocidades de reacción y las constantes de equilibrio para muchas reacciones, entre ellos a los sistemas R–Ar–N_3 con dos parámetros: una **constante de sustituyente (σ)** y **una constante de reacción o *sensibilidad* (ρ).** El Esquema 11 ilustra esta relación para las arilazidas. El ρ de Hammett es positivo para la reacción con enaminas nucleofílicas pero negativo para el dipolarófilo electrofílico anhídrido maleico, mostrando que la dirección del efecto sustituyente depende de la importancia relativa de las dos interacciones

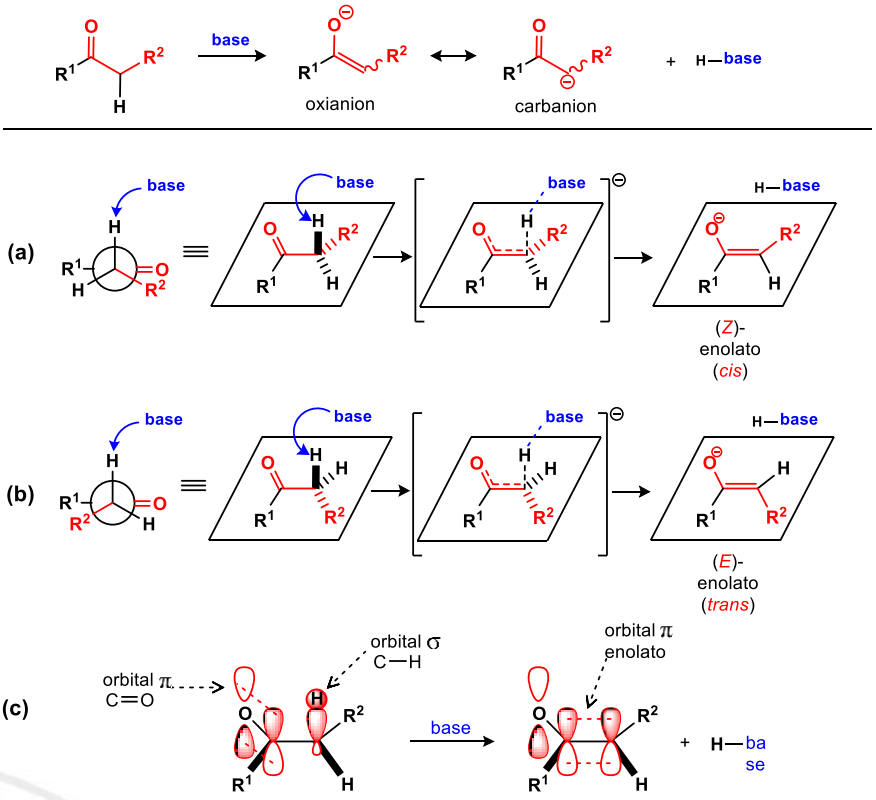
[18] F. A. Carey, R. J. Sundberg, *Advanced Organic Chemistry: Part A: Structure and Mechanisms*, 5th ed., Springer, New York, **2007**, pp. 335–336. e-ISBN-13: 978-0-387-44899-3

HOMO-LUMO. Los alquenos no funcionalizados, ciclopenteno y norborneno tienen un carácter nucleofílico, pero menos que la enamina.[19]

3.6. Enolatos como dipolarófilos

Hasta ahora hemos estudiado la naturaleza del 1,3-dipolo en las reacciones pericíclicas considerando su comportamiento frente a ciertos dipolarófilos. Ahora considerando el comportamiento de estas de manera muy particular frente a los **iones enolato** como dipolarófilos.

La química y conceptos de los enoles/enolatos ha constituido de alguna u otra manera un tema central en los fundamentos de la química orgánica. Libros completos[20] o capítulos de libro de síntesis básica/avanzada han copilado la inmensa y formidable información acerca de estos sustratos. Evidentemente sólo algunos conceptos convenientes a este trabajo serán brevemente discutidos.



Esq. 12: Perspectiva general de la desprotonación α-C de las cetonas.

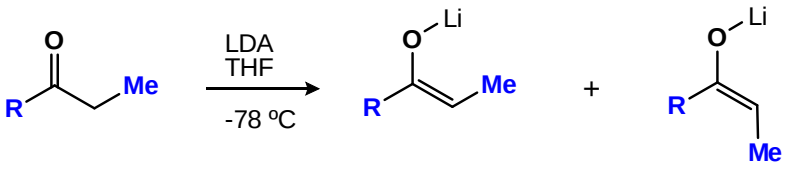
[19] (a) Ibídem, pp. 877–878. (b) J. Clayden, N. Greeves, S. Warren, *Organic Chemistry*, 2nd ed, Oxford University Press, New York, **2012**, p. 1044. ISBN 978-0-19-927029-3

[20] M. Braun, *Modern Enolate Chemistry: From Preparation to Applications in Asymmetric Synthesis*, Wiley-VCH Verlag, **2016**, Online ISBN: 9783527671069. DOI: 10.1002/9783527671069

El estudio de la **formación de los enolatos** a partir de sus correspondientes carbonilos, involucra inherentemente conceptos de **selectividad** [(E) vs (Z): estéricos, electrónicos] y de **regioselectividad** (termodinámicos vs cinéticos, estéricos), conceptos que deberán ser considerados si se advierte que tales tendrán consecuencias directas, en una segunda etapa, en los productos de reacción de dichos enolatos. Para el primer caso, el control de la estereselectividad dependerá de la presencia de los centros estereogénicos α–CO, estéricos, estereoelectrónicos y/o geométricos sin considerar el uso de agentes quirales usados durante la formación de los mismos. En el Esquema 12 se describe muy someramente y a manera de introducción un primer esbozo de la formación de los enolatos, con la intención de visualizar, a conveniencia y propósitos de este trabajo, la transformación y naturaleza de los OM de las materias de partida ($R^2CH_2COR^1$) a los productos ($R^2CH{=}C{=}OR^1$). Los enolatos normalmente son formados por desprotonacion. Esto es favorecido cuando el enlace C–H es perpendicular al enlace C=O permitiendo el traslape del orbital σ a un orbital π.[21]

Dos posibles conformaciones son permitidas según el esquema. La primera [Esquema 12, Eq. (a)] es dada como resultado en la formación del *cis*-enolato; la conformación inicial (proyección de Newman) es similar al estado de transición observándose una menor interacción estérica entre R^1 y R^2. La segunda conformación [Esquema 12, Eq. (b)] toma lugar cuando el enlace C–H esta perpendicular al C=O llevando al producto *trans*-enolato. La Tabla 1 esquematiza estos conceptos de manera muy versátil. En otros casos, la interacción estérica de otras bases o el uso de aditivos (e.g. HMPA) también deberán ser consideradas al tratar de predecir la estereoselectividad de la reacción.

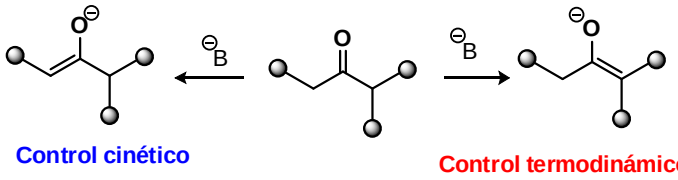
Tabla 1: Estereoselectividad en la formación de los enolatos influenciada por efectos estéricos.



R	*cis*	:	*trans*
Et	30	:	70
i-Pr	60	:	40
t-Bu	>98	:	<2
OMe	5	:	95
NEt_2	>97	:	<3

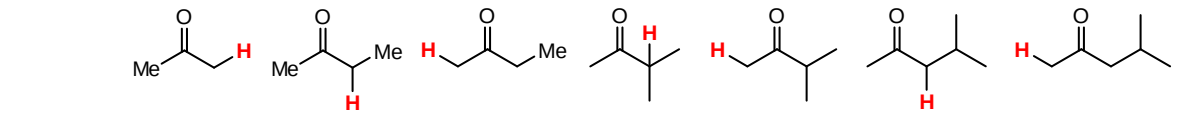
[21] P. Wyatt, S. Warren, *Organic Synthesis: Strategy and Control*, John Wiley & Sons Ltd, Chichester, **2007**, pp. 43-53. ISBN: 978-0-470-48940-5

El segundo concepto importante de describir, continuando con la formación de los enolatos, es la **regioselectividad** la cual es gobernada principalmente por aspectos **cinéticos** y **termodinámicos**.



Hay numerosos estudios acerca de las velocidades de desprotonación de los compuestos de carbonilo. Estos datos son de interés no sólo porque definen la relación entre la acidez termodinámica y cinética de estos compuestos, sino también porque son necesarios para comprender mecanismos de reacciones en las que los enolatos están implicados como intermedios.

El Esquema 13[22] muestra algunos datos sobre las velocidades de deuteración de algunas alquilcetonas. A partir de estos datos, el orden de reactividad hacia la desprotonación es CH_3> RCH_2> R_2CH. El impedimento estérico al acercamiento de la base es el factor principal en el establecimiento de este orden. Es decir, este proceso depende de la manera **más rápida** de formar al enolato (**proceso cinético**)



Velocidades relativas	100	41.5	45	<0.1	45	0.45	5.1

Esq. 13: Velocidades relativas para la deuteración de algunas cetonas catalizadas por base (Na_2CO_3 aq.).

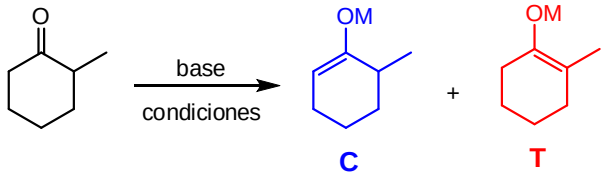
Por otro lado, dado que los enoles/enolatos *son alquenos, los enlaces dobles más sustituidos son los más estables*. Los grupos alquilo son donadores de electrones y contribuyen a la densidad electrónica del enlace π. Así, en principio, debido a que los hidrógenos impedidos necesitarán de una mayor energía de activación deberán sufrir un **proceso termodinámico** para dar productos más estables (en contraste, la vía cinética proporcionaría productos menos estables). La formación del enolato más estable requiere un mecanismo de equilibrio entre los dos enolatos por la transferencia de protones. Una base como el hidruro de potasio es fuerte, pero pequeña, y por lo tanto no tiene dificultad de quitar el

[22] F. A. Carey, R. J. Sundberg, *Advanced Organic Chemistry. Part A: Structure and Mechanisms*, 5th ed., Springer, New York, **2007**, pp. 594. e-ISBN-13: 978-0-387-44899-3

protón más impedido y se puede usar en condiciones que permitan el equilibrio enolato.[23]

La Tabla 2[24] y el Esquema 14 ejemplifican y simplifican sustancialmente los conceptos arriba mencionados.

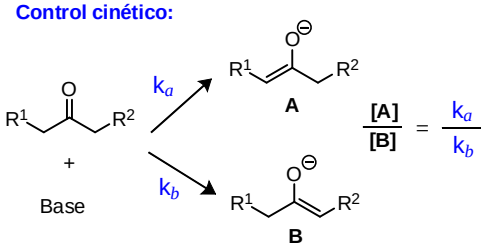
Tabla 2: Control cinético vs termodinámico para la formación de los enolatos.



Base	Temp	C/T	Control
LiN(*i*-C_3H_7)$_2$	0 °C	99:1	Cinético
KN($SiMe_3$)$_2$	-78 °C	95:5	Cinético
Ph_3CLi	-78 °C	90:10	Cinético
Ph_3CK	25 °C	67:33	Cinético
NaH	25 °C	26:74	Termodinámico
Ph_3CLi	25 °C	10:90	Termodinámico

Regioselectividad en la formación de enolatos

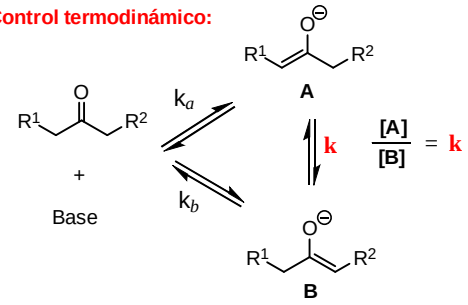
Control cinético:



La reacción es:
-Irreversible.
-El producto mayoritario es el que se forma más rápido.
-Favorecida por bases fuerte, impedidas (e.g. LDA), bajas temperaturas, tiempos de reacción cortos.

Los enolatos cinéticos son:
-Menos sustituidos.
-Menos estables.

Control termodinámico:



La reacción es:
-Uno o ambas reacciones son reversibles.
-El producto mayoritario es el más estable.
-Favorecida por el exceso de la cetona, altas temperaturas, tiempos de reacciónprologados.

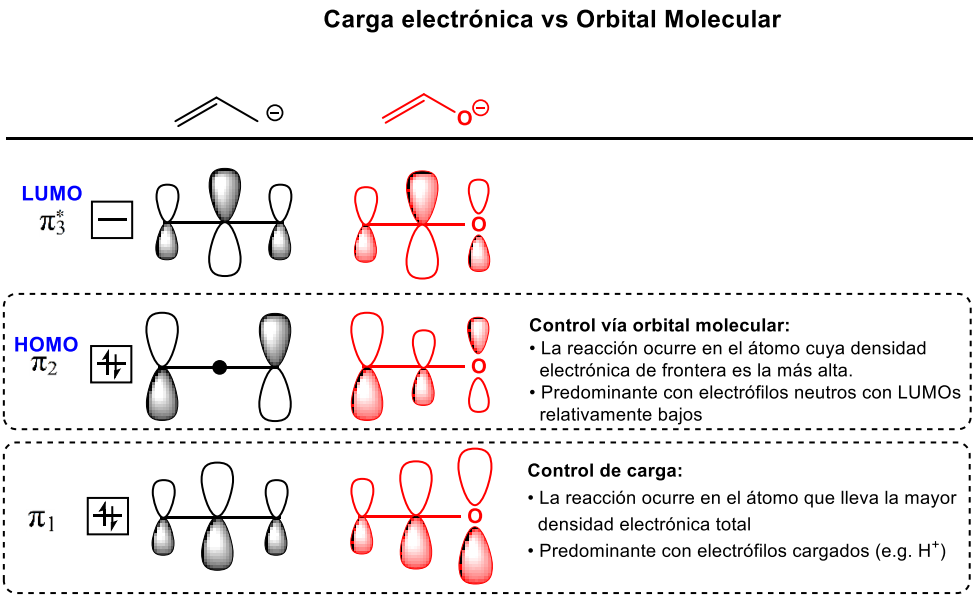
Los enolatos termodinámicos son:
-Más sustituidos.
-Más estables.

Esq.14: Resumen y esquematización de las principales características del control cinético y termodinámico para la formación de los enolatos.

[23] (a) F. A. Carey, R. J. Sundberg, Advanced Organic Chemistry. Part B: Reactions and Synthesis. 5th ed., Springer, New York, **2007**, pp. 5-11. e-ISBN: 0-306-47380-1 (b) J. Clayden, N. Greeves, S. Warren, *Organic Chemistry*, 2nd ed, Oxford University Press, New York, **2012**, p. 599. ISBN 978-0-19-927029-3

[24] H.O. House, et. al. *J. Org. Chem*, **1969**, *34*, 2324. (b) C. A. Brown, *J.Org. Chem*. **1974**, *39*, 3913. (c) G. Stork, P. F. Hudrlik, *J. Am. Chem. Soc*. **1968**, *90*, 4464.

3.7. Control de carga y de OM de los enolatos



Esq. 15: Reacciones OM-controladas vs carga-controladas.

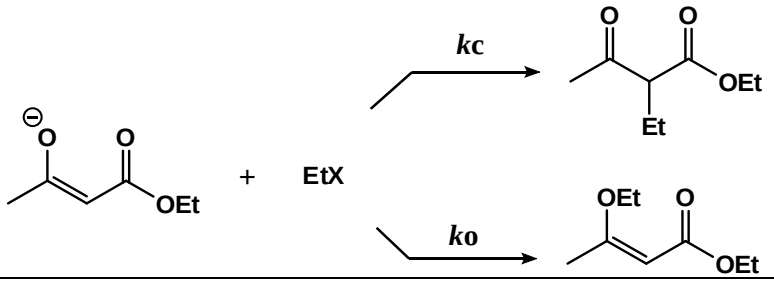
Mientras que el anión alilo (Esquema 15), con un plano de simetría a través del átomo central, tiene un nodo en el átomo central en π_2 (semejante a lo que describimos para las azidas), las amidas, ésteres, enaminas, o iones enolato no tienen un nodo precisamente en el átomo central. Si bien el traslape entre los orbitales atómicos en el O y el C adyacente representa un fuerte enlace en π_1, estos mismos son de antienlace en π_2 (un nodo no simétrico). Sin embargo, tanto π_1 como π_2 contribuyen al enlace pi de entre los dos átomos de carbono. Esta es una de las razones por la que suele ser aconsejable dibujar iones enolato con la carga sobre el oxígeno en lugar de carbaniones estabilizados con carbonilo, no sólo porque hay una carga electrónica mayor sobre el oxígeno, sino que el grado de enlace pi se ilustra mejor de esta manera. La utilidad del esquema nos ayudará a definir un parámetro muy importante respecto a identificar que átomo debe ser considerado en ciertas reacciones características de estas especies, las cuales se definen por dos vías: **reacciones OM-controladas** y las **reacciones carga-controladas**.[25] Las reacciones que involucran a las primeras se referirán a las *C*-alquilaciones (reacción sobre el carbanión del enolato) y las segundas a las *O*-alquilaciones (reacción sobre el oxígeno del enolato).

[25] I. Fleming, *Molecular Orbitals and Organic Chemical Reactions*, Student ed., John Wiley & Sons Ltd, UK, **2009**, pp. 124-125. ISBN 978-0-470-74660-8

El factor dominante, para tales reacciones dependerá del nucleófilo y electrofilo involucrados. Los nucleófilos que contienen átomos electronegativos pequeños (como O o Cl), que llamamos «duros», tienden a reaccionar bajo un control predominantemente electrostático, mientras que los nuclófilos «blandos» que contienen átomos más grandes (incluido el azufre de los tioles, pero también P, I, o Se) están predominantemente sujetos a reacciones OM-controladas.

Con electrófilos cargados, entonces, el sitio de ataque será oxígeno, como es de hecho el caso, cinéticamente, con protones y carbocationes. Con los electrófilos que tienen poca carga y LUMOs relativamente bajos, la reacción tendrá lugar en el carbono. En otras palabras, los electrófilos duros reaccionan en el oxígeno y los electrófilos blandos en el carbono. El disolvente, por supuesto, también impide la reacción en los sitios de mayor solvatación, que generalmente serán los átomos que llevan la carga total más alta.

Tabla 3: Proporción entre la *C*- y *O*-alquilación como una función del grupo saliente X en EtX



X^-	I^-	Br^-	TsO^-	$EtSO_4^-$	$CF_3SO_3^-$
kc/ko	>100	60	6.6	4.8	3.7

También se puede explicar por qué la naturaleza del grupo saliente en un haluro de alquilo (o tosilato, por ejemplo) afecta a la proporción de *C*- u *O*-alquilación en ciertos enolatos tales como el derivado del acetoacetato de etilo (Tabla 3): cuanto más duro es el grupo saliente (es decir, cuanto más ácido sea el ácido conjugado del grupo saliente), menor es la proporción de la *C*-alquilación. Cuanto más suave sea el grupo saliente, menor será la energía del LUMO. Además, cuanto más duro es el grupo saliente, más polarizado es su enlace con el carbono, y por lo tanto más carga habrá sobre el carbono en la estructura de transición.

Resumiendo estos conceptos:

Reactividad dura/blanda:

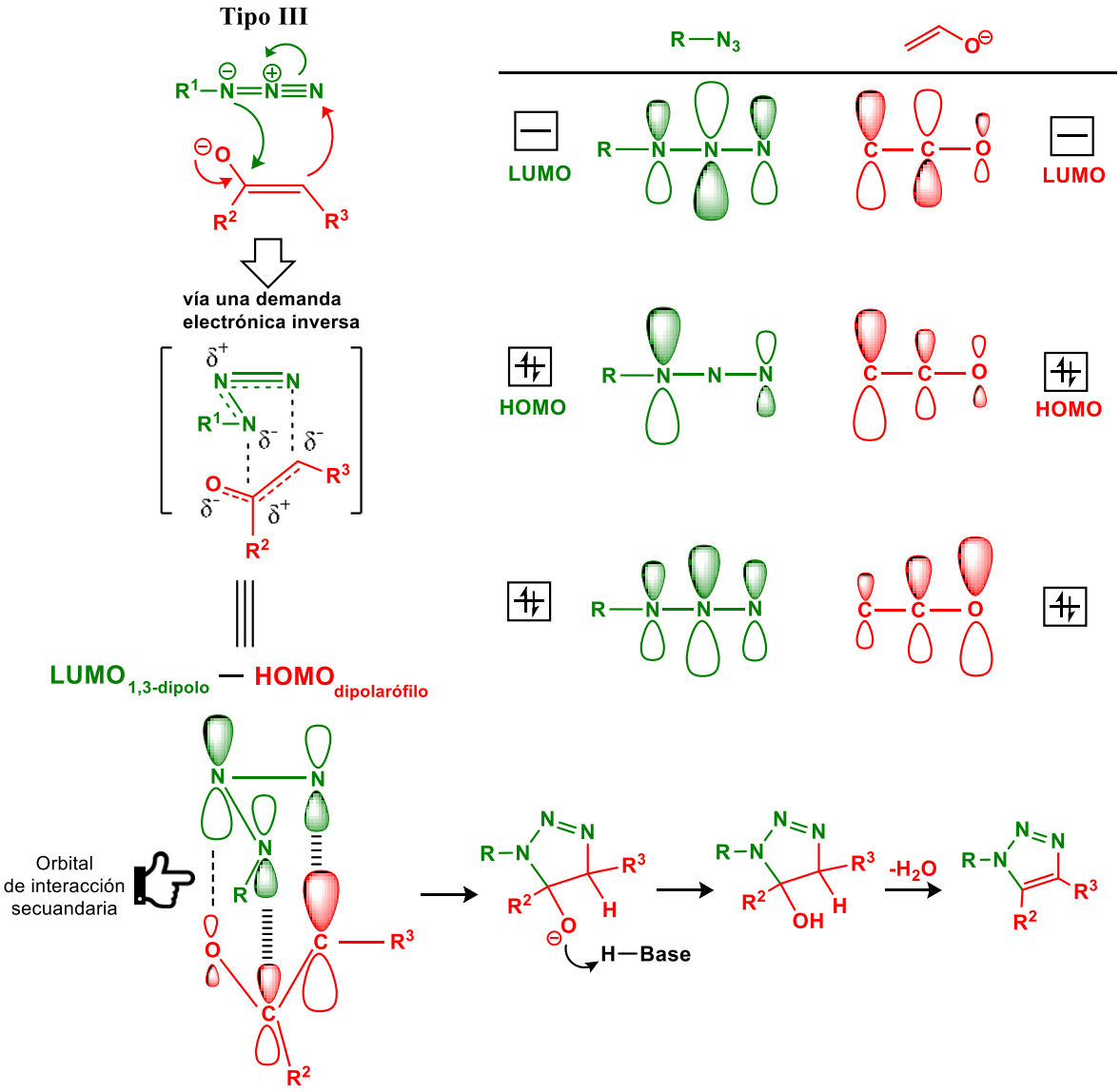
- Las reacciones de las especies duras están dominadas por cargas y efectos electrostáticos.
- Las reacciones de las especies blandas están dominadas por los efectos orbitales.
- Los nucleófilos duros tienden a reaccionar bien con los electrófilos duros.
- Los nucleófilos suaves tienden a reaccionar bien con electrófilos blandos.

3.8. La cicloadición (3+2) azida-enolato: Su naturaleza

En este momento podemos describir definitivamente las características que gobiernan la cicloadición 1,3-dipolar azida-enolato las cuales se encuentran resumidas en el Esquema 16. Tales aspectos son mencionados de manera concluyente, ya que los fundamentos han sido discutidos en los párrafos anteriores.

I. La cicloadición 1,3-dipolar azida-enolato deberá ocurrir bajo una interacción HOMO-LUMO del Tipo III para la azida, denominada 'dipolo LUMO-controlado' ($LUMO_{1,3\text{-dipolo}}$–$HOMO_{dipolarófilo}$).
II. La cicloadición ocurre vía demanda electrónica inversa.
III. El estudio de la reacción deberá tener una constante ρ positiva para la ecuación de Hammett.
IV. La reacción deberá ser OM-controlada para el enolato.
V. La interacción HOMO-LUMO es suprafacial como cualquier otro tipo de cicloadiciones 1,3-dipolar.
VI. La regioselectividad depende únicamente del enolato (dipolarófilo).
VII. A diferencia de otras cicloadiciones 1,3-dipolares con interacción *exo*, es mucho muy probable que esta reacción ocurra por una interacción del tipo *endo*, debido a un posible orbital de interacción secundaria entre el orbital p del O (dipolarófilo) y el orbital p del N central (1,3-dipolo), interacciones ampliamente conocidas en la literatura.[26] Esta interacción no conduce a un enlace, pero puede contribuir a disminuir la energía de la estructura de transición.

[26] (a) *Ibídem*, p. 235. (b) I. Fleming, *Pericyclic Reactions*, Oxford Chemistry Primers, USA, **1998**, pp. 49.



Esq. 16: La ciloadición 1,3-dipolar azida-enolato. Generalidades.

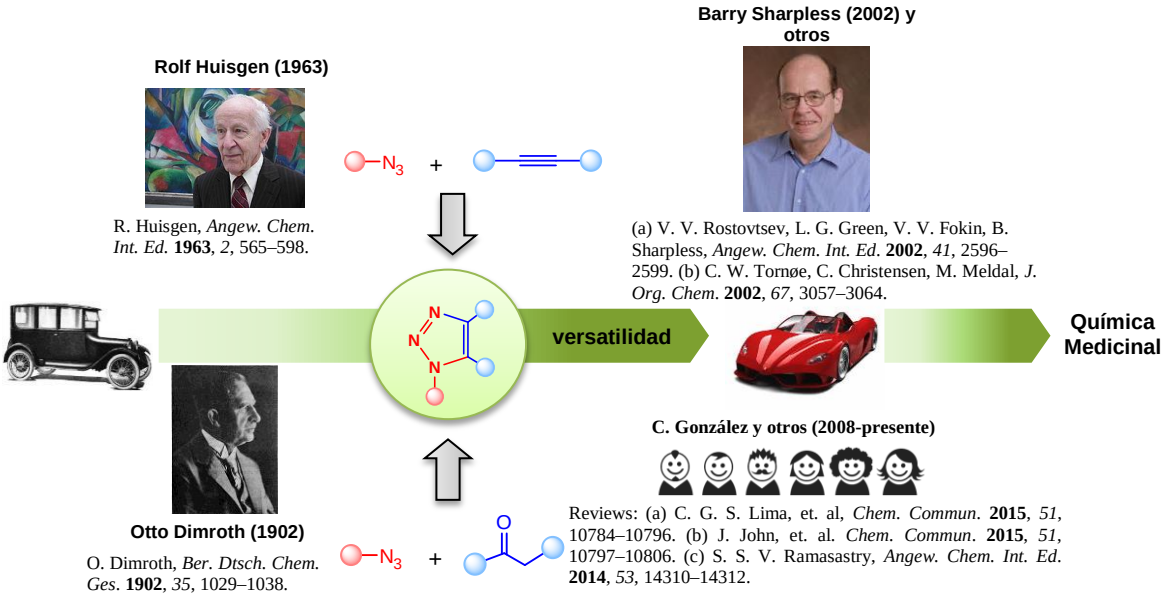
4. Discusión de Resultados

IMPORTANTE: Las publicaciones (**Anexo 1**) de los trabajos que aquí se reportan han involucrado de manera inherente, una descripción sustancial, apropiada y concisa de la discusión de los resultados para cada uno de los trabajos; mismos que necesariamente fueron evaluados, discutidos y sugeridos por réferis internacionales así como por los mismos editores de cada una de las revistas. Con la intención de **evitar la redundancia** y **demasía**, en esta sección solo se abordaran conceptos generales que no fueron descritos en dichos *papers*.

La Cicloadición Alquino-Azida Catalizada por Cobre (CuAAC) ha sido el método tradicional para obtener 1,2,3-triazoles gracias a las mejoras realizadas a esta reacción durante los últimos años, y su versatilidad se ve reflejada por sus aplicaciones en otros campos tales como la química medicinal[27] (Esquema 17).

Inspirados por los grandes impactos de la CuAAC en la síntesis orgánica y química medicinal, decidimos incursionar en el estudio y desarrollo de los 1,2,3-triazoles pero por otro tipo de cicloadiciones 1,3-dipolar, la cicloadición de Dimroth azida-enolato, descrita por primera vez en 1902, pero poco explorada hasta ahora. A partir de 2008, grupos de investigación como el de Ramachary, Wang, Bressy, Rademann y C. González (nuestro grupo) –solamente– han retomado dicha metodología pionera con el fin de mejorarla y lograr lo que la CuAAC ha demostrado: aplicación versátil en la química medicinal.

[27] *Reviews* completos acerca de este tema: (a) Thirumurugan, P.; Matosiuk, D.; Jozwiak, K. *Chem. Rev.* **2013**, *113*, 4905–4979; (b) S.G. Agalave, S.R. Maujan, V.S. *Chem. Asian J.* **2011**, *6*, 2696–2718; (c) Lauria, A.; Delisi, R.; Mingoia, F.; Terenzi, A.; Martorana, A.; Barone, G.; Almerico, A. M. *Eur. J. Org. Chem.* **2014**, 3289–3306. (d) C. D. Hein, X. M. Liu, D. Wang, *Pharm Res.* **2008**, *25*, 10, 2216–2230.



Esq. 17: La aplicación de las cicloadiciones 1,3-dipolar (CuAAC y azida-enolato) han dependido principalmente del mejoramiento de las metodologías pioneras.

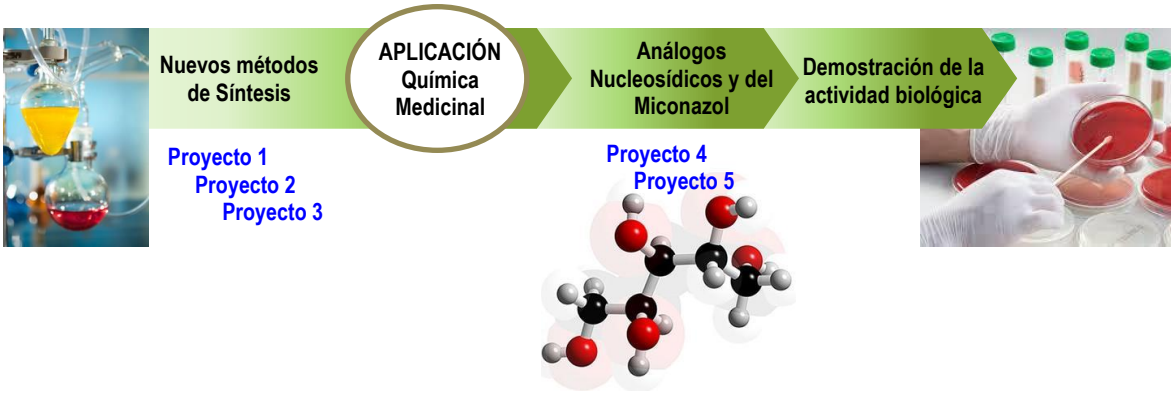
Por todo lo anterior, en este trabajo (Esquema 18) se desarrollaron y estudiaron tres nuevas metodologías sintéticas para la obtención de 1,2,3-triazoles a través de cicloadiciones (3+2) azida-enolato a partir de:

(a) Alcoholes bencílicos (formación *in situ* de alquil azidas) y cetonas (**Proyecto 1**).
(b) Halogenuros de alquilo (formación *in situ* de alquil azidas) y cetonas (**Proyecto 2**)
(c) Azidas y β-cetofosfonatos (**Proyecto 3**).

Los alcances así como la versatilidad de tales metodologías se demostraron mediante su aplicación en la síntesis de Análogos Nucleosídicos (**Proyecto 4**) y del Miconazol (**Proyecto 5**).

Como parte de una colaboración multidisciplinaria, estos últimos fueron evaluados biológicamente (actividad antimicótica) en especies microbiológicas filamentosas y levaduriformes de importancia clínica.

Fortuitamente se descubrió, estudió y desarrollo un nuevo protocolo para la conversión directa de bencil azidas a grupos carbonilo (**Proyecto 6** –proyecto adicional–).



Esq. 18: Esquematización de los proyectos realizados en este trabajo.

5. Desarrollo Experimental

El desarrollo experimental (**Generalidades, Metodología General y Metodologías particulares**), la **caracterización** de cada uno de los compuestos (^{1}H- ^{13}C-RMN, espectrometría de masas de baja –MS– y alta resolución –HRMS–, puntos de fusión, R_F y aspectos físicos –solido/liquido/color–) y rendimientos de reacción así como las **copias de los espectros analíticos** han sido **COMPLETAMENTE** descritos para cada uno de los compuestos en cada uno trabajos publicados (**Anexo 1**) y pueden ser consultados en el artículo principal y/o en su material de suplementario, **por lo que se prescinde de todo ello en este apartado**.

6. Conclusiones

Se logró el desarrollo y estudio de tres nuevas metodologías sintéticas para la obtención de 1,2,3-triazoles a través de cicloadiciones (3+2) azida-enolato a partir del: (a) acoplamiento de alcoholes bencílicos (formación *in situ* de alquil azidas) y cetonas, (b) acoplamiento de halogenuros de alquilo (formación *in situ* de alquil azidas) y cetonas; y (c) a partir del acoplamiento de alquil/aril azidas y β-cetofosfonatos.

Los alcances, así como la versatilidad de tales metodologías se demostraron mediante su aplicación en la síntesis de Análogos Nucleosídicos y del Miconazol.

Como parte de una colaboración multidisciplinaria, estos últimos fueron evaluados biológicamente (actividad antimicótica) en especies microbiológicas filamentosas y levaduriformes de importancia clínica.

Fortuitamente se descubrió, estudió y desarrollo un nuevo protocolo para la conversión directa de bencil azidas a grupos carbonilo (–proyecto adicional–).

Anexo 1

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A novel and facile synthesis of 1,4,5-trisubstituted 1,2,3-triazoles from benzylic alcohols through a one-pot, three-component system

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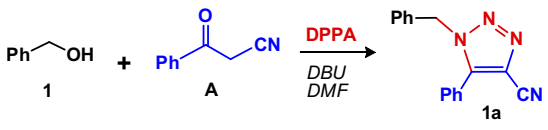
ABSTRACT

A simple one-pot procedure has been developed to efficiently prepare 1,4,5-trisubstituted 1,2,3-triazoles from benzylic alcohols. The presence of diphenylphosphoryl azide (DPPA) and active ketones allows for an azide–enolate [3+2] cycloaddition by use of DBU.

The triazole ring system is a key pharmacophore[1] for an increasingly important series of nitrogen heterocycles that display a wide range of therapeutic and biological activity.[2] Several methods for the synthesis of 1,4-disubstituted 1,2,3-triazoles[3] and 1,5-disubstituted 1,2,3-triazoles[4] have been described in literature. In the last decade, the 1,4,5-trisubstituted 1,2,3-triazole framework has received much attention in medicinal chemistry due to its biological activity against cancer,[5] HIV-RT,[6] Cantagalo Virus,[7] and *Lachesis muta* snake venom,[8] as well as its use as an antiplatelet agent,[9] among other applications.[10] Hence, reports on synthetic methods to obtain 1,4,5-trisubstituted 1,2,3-triazole moieties are increasingly common in literature.[11] An outstanding synthetic method is azide–enolate [3+2] cycloaddition, best known as 'Dimroth Cycloaddition',[12] which has been improved[13] by several research groups. Recently, Cao et al. have given versatility to this method through an attractive three-component synthesis of 1,4,5-trisubstituted 1,2,3-triazoles, starting from primary alcohols and using a NaN_3/TsIm/TEA/TBAI/KOH system.[14] Thus, the development of an efficient synthesis of these valuable heterocycles—particularly from readily accessible and common substrates—is of ever increasing importance.

During one of our ongoing research projects, focused on the development of novel methodologies for the construction of triazole carbocyclic nucleosides,[15] we observed that an excess of 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) in Thompson's azidation procedure[16] of benzyl alcohol **1** leads to the highly regioselective synthesis of 1,4,5-trisubstituted 1,2,3-triazole **1a** in the presence of active ketone benzoylacetonitrile **A** (78% yield) by a one-pot system.



Consequently, we decided to investigate the coupling of **1**, **A**, and diphenylphosphoryl azide (DPPA) in greater detail, finding that triazolyzation was very inefficient using stoichiometric amounts of DBU. Moreover, the evident use of only benzylic alcohols when some alkylic alcohols (e.g., menthol, octyl alcohol, and phenethyl alcohol) failed under our procedure is in accordance with Thompson's discussion. Conventional heating (60–70 °C upon adding ketone) and a 6 h reaction period were adopted as the standard. The coupling reactions of various benzylic alcohols in the presence of benzoylacetonitrile **A**, ethyl acetoacetate **B**, dibenzoylmethane **C**, and/or acetylacetone **D** as active ketones were then examined under these optimized conditions (Table 1).[17]

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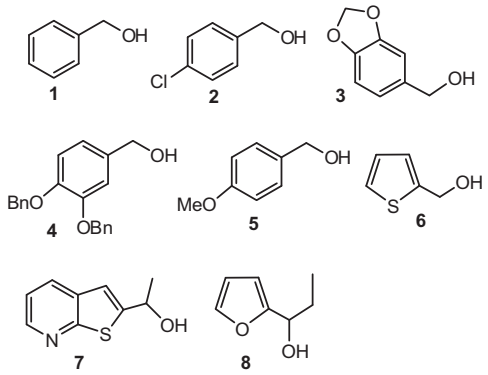
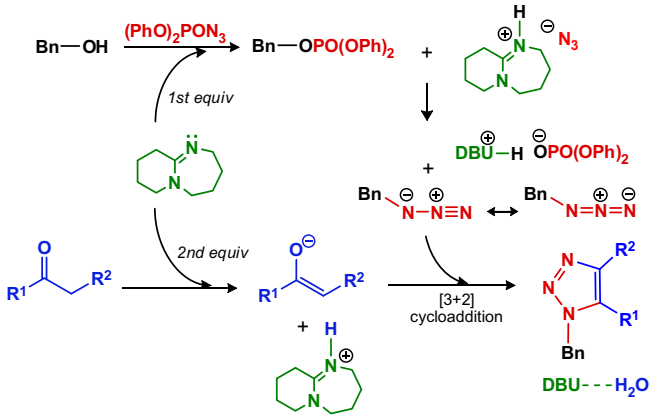
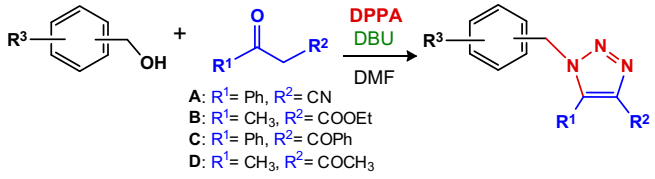




Scheme 1. Proposed plausible mechanism for azide–enolate [3+2] cycloaddition.

Table 1
Synthesis of 1,4,5-trisubstituted 1,2,3-triazoles from benzylic alcohols by coupling with active ketones



Entry	Benzyl alcohol	Ketone	Triazole[a]	Yield[b] (%)
1	**1**	**A**	**1a**	78
2	**1**	**C**	**1c**	80
3	**2**	**D**	**2d**	82
4	**2**	**B**	**2b**	65[c]
5	**2**	**C**	**2c**	76
6	**3**	**D**	**3d**	75
7	**3**	**C**	**3c**	74
8	**4**	**D**	**4d**	77
9	**4**	**B**	**4b**	63[c]
10	**4**	**A**	**4a**	72
11	**5**	**D**	**5d**	76
12	**5**	**B**	**5b**	62[c]
13	**6**	**D**	**6d**	73
14	**6**	**B**	**6b**	66[c]
15	**7**	**D**	**7d**	82
16	**7**	**C**	**7c**	80
17	**8**	**A**	**8a**	75

[a] Confirmed by ^{1}H NMR, ^{13}C NMR, and HRMS.
[b] Yields refer to chromatographically pure isolated compounds.
[c] In these cases, the reactions require longer times (36 h) upon adding ketone.

The presence of moderate EWG in the aromatic ring (*p*-Cl, entry 3) led to slightly higher yields than those observed for electron-rich benzylic alcohols (*p*-OCH_3, entry 11, considering acetylacetone **D** for these examples). However, the formation of a less stable enolate in the reaction (when ethyl acetoacetate **B** is used) leads to the synthesis of triazoles in low yields (entries 4, 9, 12, and 14). Furthermore, we have used the method with heterocycles (**6**, **7** and **8**) as aryl moieties. These results are consistent for both primary (**1**–**6**) and secondary (**7** and **8**) benzylic alcohols.

Mechanistically, we believe the reaction takes place in four discrete steps (Scheme 1). One DBU equivalent is necessary for an effective Thompson azidation. The enolate generated in situ by the action of a second DBU equivalent leads to azide–enolate [3+2] cycloaddition.

In summary, we developed a simple one-pot, three-component procedure for the direct conversion of alcohols to 1,4,5-trisubstituted 1,2,3-triazoles through highly regioselective synthesis under mild conditions.

Acknowledgments

Financial support from UAEMéx (Project No. 3512/2013CHT) and CONACYT – Mexico (postgraduate scholarship) is gratefully acknowledged. The authors would like to thank the referee for valuable comments and suggestions, Signa S.A. de C.V. for some graciously donated solvents and reagents, M.N. Zavala-Segovia and L. Triana-Cruz (CCIQS UAEMéx–UNAM) for technical support.

Supplementary data

Supplementary data (characterization data of all compounds and copies of ^{1}H NMR, ^{13}C NMR and High Resolution Mass spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.12.019.

References and notes

1. Agalave, S. G.; Maujan, S. R.; Pore, V. S. *Chem. Asian J.* **2011**, *6*, 2696–2718.
2. For extensive reviews see: (a) Lauria, A.; Delisi, R.; Mingoia, F.; Terenzi, A.; Martorana, A.; Barone, G.; Almerico, A. M. *Eur. J. Org. Chem.* **2014**, 3289–3306; (b) Thirumurugan, P.; Matosiuk, D.; Jozwiak, K. *Chem. Rev.* **2013**, *113*, 4905–4979; (c) Lutz, J. F.; Zarafshani, Z. *Adv. Drug Deliv. Rev.* **2008**, *60*, 958–970; (d) Zhou, C. H.; Wang, Y. *Curr. Med. Chem.* **2012**, *19*, 239–280.
3. The Cu-catalyzed azide-alkyne cycloaddition (CuAAC) has become perhaps the best-know tool to obtain these triazole derivatives. For extensive reviews see: (a) Meldal, M.; Tornøe, C. W. *Chem. Rev.* **2008**, *108*, 2952–3015; (b) Amblard, F.; Cho, J. H.; Schinazi, R. F. *Chem. Rev.* **2009**, *109*, 4207–4220; (c) Schulze, B.; Schubert, U. S. *Chem. Soc. Rev.* **2014**, *43*, 2522–2571; (d) Bock, V. D.; Hiemstra, H.; Van Maarseveen, J. H. *Eur. J. Org. Chem.* **2006**, 51–68.
4. (a) Wang, Y. C.; Xie, Y. Y.; Qu, H. E.; Wang, H. S.; Pan, Y. M.; Huang, F. P. *J. Org. Chem.* **2014**, *79*, 4463–4469; (b) Wu, L.; Chen, Y.; Luo, J.; Sun, Q.; Peng, M.; Lin, Q. *Tetrahedron Lett.* **2014**, *55*, 3847–3850; (c) Shafi, S.; Banday, A. H.; Ismail, T.; Kumar, H. M. S. *Synlett* **2007**, 1109–1111; (d) Kayet, A.; Pathak, T. *J. Org. Chem.* **2013**, *78*, 9865–9875; (e) Meza-Aviña, M. E.; Patel, M. K.; Lee, C. B.; Dietz, T. J.; Croatt, M. P. *Org. Lett.* **2011**, *13*, 2984–2987; (f) Smith, C. D.; Greaney, M. F. *Org. Lett.* **2013**, *15*, 4826–4829; (g) Rasmussen, L. K.; Boren, B. C.; Fokin, V. V. *Org. Lett.* **2007**, *9*, 5337–5339.
5. (a) Demchuk, D. V.; Samet, A. V.; Chernysheva, N. B.; Ushkarov, V. I.; Stashina, G. A.; Konyushkin, L. D.; Raihstat, M. M.; Firgang, S. I.; Philchenkov, A. A.; Zavelevich, M. P.; Kuiava, L. M.; Chekhun, V. F.; Blokhin, D. Y.; Kiselyov, A. S.; Semenova, M. N.; Semenov, V. V. *Bioorg. Med. Chem.* **2014**, *22*, 738–755; (b) Kamal, A.; Shankaraiah, N.; Devaiah, V.; Reddy, K. L.; Juvekar, A.; Sen, S.; Kurian, N.; Zingde, S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1468–1473.
6. Da Silva, F. C.; De Souza, M. C. B. V.; Frugulhetti, I. I. P.; Castro, H. C.; De, O.; Souza, S. L.; De Souza, T. M. L.; Rodrigues, D. Q.; Souza, A. M. T.; Abreu, P. A.; Passamani, F.; Rodrigues, C. R.; Ferreira, V. F. *Eur. J. Med. Chem.* **2009**, *44*, 373–383.
7. Jordão, A. K.; Afonso, P. P.; Ferreira, V. F.; De Souza, M. C. B. V.; Almeida, M. C. B.; Beltrame, C. O.; Paiva, D. P.; Wardell, S. M. S. V.; Wardell, J. L.; Tiekink, E. R. T.; Damaso, C. R.; Cunha, A. C. *Eur. J. Med. Chem.* **2009**, *44*, 3777–3783.
8. Campos, V. R.; Abreu, P. A.; Castro, H. C.; Rodrigues, C. R.; Jordão, A. K.; Ferreira, V. F.; De Souza, M. C. B. V.; Santos, F. C.; Moura, L. A.; Domingos, T. S.; Carvalho, C.; Sanchez, E. F.; Fuly, A. L.; Cunha, A. C. *Bioorg. Med. Chem.* **2009**, *17*, 7429–7434.

9. Jordão, A. K.; Ferreira, V. F.; Lima, E. S.; De Souza, M. C. B. V.; Carlos, E. C. L.; Castro, H. C.; Geraldo, R. B.; Rodrigues, C. R.; Almeida, M. C. B.; Cunha, A. C. *Bioorg. Med. Chem.* **2009**, *17*, 3713–3719.
10. (a) Alam, M. S.; Kajiki, R.; Hanatani, H.; Kong, X.; Ozoe, F.; Matsui, Y.; Matsumura, F.; Ozoe, Y. *J. Agric. Food Chem.* **2006**, *54*, 1361–1372; (b) Taddei, M.; Ferrini, S.; Giannotti, L.; Corsi, M.; Manetti, F.; Giannini, G.; Vesci, L.; Milazzo, F. M.; Alloatti, D.; Guglielmi, M. B.; Castorina, M.; Cervoni, M. L.; Barbarino, M.; Foderà, R.; Carollo, V.; Pisano, C.; Armaroli, S.; Cabri, W. *J. Med. Chem.* **2014**, *57*, 2258–2274; (c) He, J. B.; Feng, L. L.; Li, J.; Tao, R. J.; Ren, Y. L.; Wan, J.; He, H. W. *Bioorg. Med. Chem.* **2014**, *22*, 89–94.
11. (a) Wang, B.; Liu, N.; Chen, W.; Huang, D.; Wang, X.; Hu, Y. *Adv. Synth. Cat.* **2014**. http://dx.doi.org/10.1002/adsc.201400471. Early View; (b) Chen, Z.; Yan, Q.; Yi, H.; Liu, Z.; Lei, A.; Zhang, Y. *Chem. Eur. J.* **2014**, *20*, 13692–13697; (c) Thomas, J.; John, J.; Parekh, N.; Dehaen, W. *Angew. Chem., Int. Ed.* **2014**, *53*, 10155–10159; (d) Hein, J. E.; Tripp, J. C.; Krasnova, L. B.; Sharpless, B.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2009**, *48*, 8018–8021; (e) Li, L.; Hao, G.; Zhu, A.; Fan, X.; Zhang, G.; Zhang, L. *Chem. Eur. J.* **2013**, *19*, 14403–14406; (f) Bhaumik, A.; Samanta, S.; Pathak, T. *J. Org. Chem.* **2014**, *79*, 6895–6904; (g) Huang, J.; Macdonald, S. J. F.; Cooper, A. W. J.; Fisher, G.; Harrity, J. P. A. *Tetahedron Lett.* **2009**, *50*, 5539–5541; (h) Xie, Y. Y.; Wang, Y. C.; Qu, H. E.; Tan, X. C.; Wang, H. S.; Pan, Y. M. *Adv Synth. Cat.* **2014**; (i) Boren, B. C.; Narayan, S.; Rasmussen, L. K.; Zhang, L.; Zhao, H.; Lin, Z.; Jia, G.; Fokin, V. V. *J. Am. Chem. Soc.* **2008**, *130*, 8923–8930; (j) Al-Azmi, A.; Kalarikkal, A. K. *Tetrahedron* **2013**, *69*, 11122–11129.
12. (a) Dimroth, O. *Ber. Dtsch. Chem. Ges.* **1902**, *35*, 1029–1038; For a concise discussion about this issue see: (b) Hill, M. D. In *Name Reactions in Heterocyclic Chemistry II*; Li, J. J., Ed.; John Wiley & Sons: New Jersey, 2011.
13. (a) Seus, N.; Goldani, B.; Lenardão, E. J.; Savegnago, L.; Paixão, M. W.; Alves, D. *Eur. J. Org. Chem.* **2014**, 1059–1065; (b) Kamalraj, V. R.; Senthil, S.; Kannan, P. *J. Mol. Struct.* **2008**, *892*, 210–215; (c) Pokhodylo, N.; Matiychuk, V. S.; Obushak, M. D. *Synthesis* **2009**, 2321–2323; (d) Danence, L. J. T.; Gao, Y.; Li, M.; Huang, Y.; Wang, J. *Chem. Eur. J.* **2011**, *17*, 3584–3587; (e) Rozin, Y. A.; Leban, J.; Dehaen, W.; Nenajdenko, V. G.; Muzalevskiy, V. M.; Eltsov, O. S.; Bakulev, V. A. *Tetrahedron* **2012**, *68*, 614–618; (f) Singh, H.; Sindhu, J.; Khurana, J. M. *RSC Adv.* **2013**, *3*, 22360–22366; (g) Zhang, J.; Jin, G.; Xiao, S.; Wu, J.; Cao, S. *Tetrahedron* **2013**, *69*, 2352–2356.
14. Jin, G.; Zhang, J.; Fu, D.; Wu, J.; Cao, S. *Eur. J. Org. Chem.* **2012**, 5446–5449.
15. González-González, C. A.; Fuentes-Benítez, A.; Cuevas-Yáñez, E.; Corona-Becerril, D.; González-Romero, C.; González-Calderón, D. *Tetrahedron Lett.* **2013**, *54*, 2726–2728.
16. Thompson, A. S.; Humphrey, G. R.; DeMarco, A. M.; Mathre, D. J.; Grabowsky, E. J. J. *J. Org. Chem.* **1993**, *58*, 5886–5888.
17. *Experimental procedure*: To a cold solution (0 °C) of benzyl alcohol **1** (0.108 g, 1.0 mmol) and diphenylphosphoryl azide (0.236 mL, 1.1 mmol) in anhydrous DMF (2.5 mL) was added DBU (0.3 mL, 2.0 mmol). The solution was stirred for 15 min at 0 °C under nitrogen atmosphere, and then brought to room temperature with continuous stirring for 3 h. Afterwards, TLC indicated the disappearance of the starting material. Benzoylacetonitrile **A** (0.145 g, 1.0 mmol) was then added to the reaction mixture, which was stirred for 3 h at 60–70 °C. Brine (~40 mL) was added to the reaction mixture and washed with EtOAc (3 × 10 mL). The organic layer was dried (Na_2SO_4) and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography to give the brown highly viscous oil **1a** (0.2 g, 78%).

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A straightforward and versatile approach to the synthesis of 1,4,5-trisubstituted 1,2,3-triazoles from alkyl halides via a one-pot, three-component reaction

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ABSTRACT

The preparation of 1,4,5-trisubstituted 1,2,3-triazoles by the coupling of three components (alkyl halides, sodium azide, and active ketones) through an azide–enolate [3+2] cycloaddition (Dimroth cycloaddition) has been developed for the first time. A wide variety of halides (including chlorides, bromides, and iodides as well as primary and secondary derivatives) have demonstrated the versatility of this method, which is based on a one-pot system under mild reaction conditions.

In 1902[1] Otto Dimroth first described the azide–enolate [3+2] cycloaddition to obtain 1,4,5-trisubstituted 1,2,3-triazoles under strong basic conditions (NaOEt as base). For nearly 100 years this reaction remained *almost* forgotten.

During the last decade several research groups[2] took renewed interest in this synthetic method and strove to improve it, because the 1,4,5-trisubstituted 1,2,3-triazole core had shown potent pharmacological activities.[3] Although these improved protocols have brought back this synthetic method in a new setting, there are still certain limitations. For instance, the use of azide substrate as the starting material requires that this uncommon reagent be obtained from other common functional groups. Recently, Cao and co-workers, reported a one-pot, three-component synthesis of 1,4,5-trisubstituted 1,2,3-triazoles starting from primary alcohols and using a NaN_3/TsIm/TEA/TBAI/KOH system.[4] Unfortunately, the exclusive use of primary substrates and strongly basic conditions limits it use. Previously we published the use of a BnOH/DPPA/DBU system[5] as a facile approach to the synthesis of these compounds, but its scope is limited by the exclusive use of benzylic alcohols. Thus, there is a need to develop new alternatives for an effective approach to this important class of heterocycle compounds, preferably starting from conventional functional groups and using mild reaction conditions.

Alkyl halides in the presence of sodium azide (NaN_3) have been highly efficient in Cu-catalyzed azide–alkyne cycloaddition (CuAAC) for the synthesis of 1,4-disubstituted 1,2,3-triazoles through a one-pot, three-component system.[6] This has proven to be a very rapid and *elegant* way to access triazole building blocks. The reasons are evident, the azide substrate generated in situ requires only a simple and rapid displacement (S_N2) of a halide by an azide ion, providing this potential functional group in a one-pot reaction.

Rationalizing these facts, we decided to investigate the use of alkyl halides in the synthesis of 1,4,5-trisubstituted 1,2,3-triazoles via a one-pot, three-component reaction. The aim was to improve the synthetic strategies for the total synthesis of triazole carbocyclic nucleosides.[7]

Optimization studies for this coupling synthesis were carried out on benzyl chloride **1** and benzoylacetonitrile **B**. Mixing halide with a 1.1 equivalent of sodium azide in anhydrous DMF solution produced the desired alkyl azide in quantitative yield with short reaction times at 50 °C. The reaction with the enolate substrate, which was generated in situ by the action of a 1.1 equiv of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) on a 1.1 equi of active ketone **A** led the building of the desired 1,4,5-trisubstituted 1,2,3-triazole block in 80% yield. In contrast with Khurana's procedure,[2f] the catalytic use of DBU failed under our protocol.

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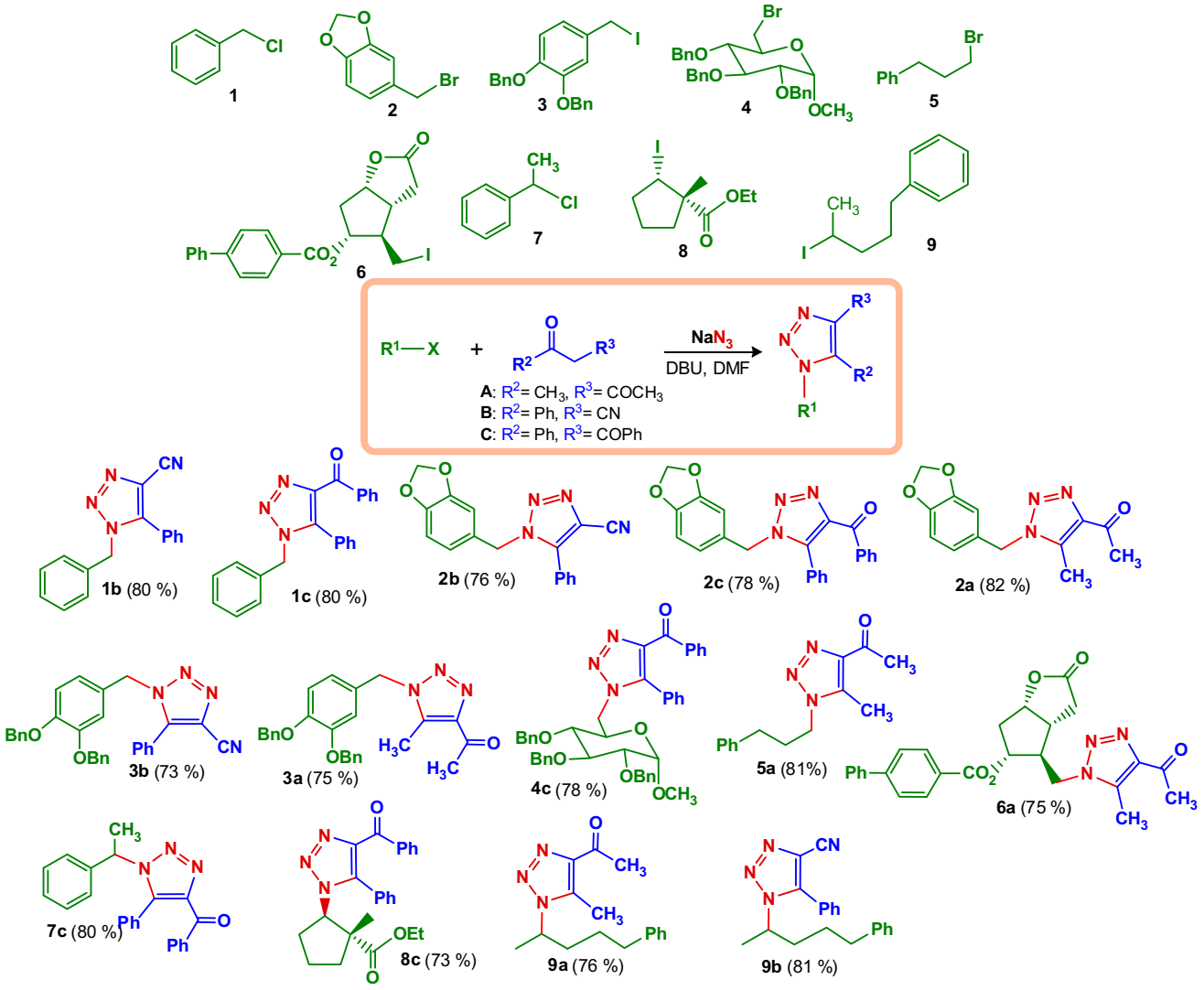
Optimized conditions were then used to study the coupling of a series of halide compounds in the presence of acetylacetone **A**, benzoylacetonitrile **B**, and/or dibenzoylmethane **C** as active ketones (Scheme 1).[8]

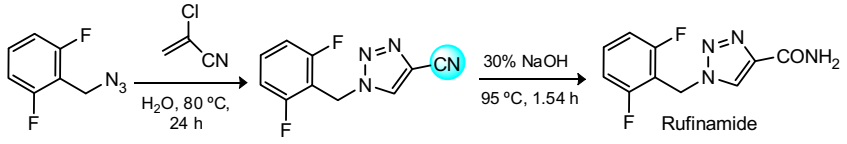
As the data in Scheme 1 indicate, acceptable yields of 1,4,5-trisubstituted 1,2,3-triazoles were obtained by using chlorides (**1** and **7**), bromides (**2**, **4** and **5**), and iodides (**3**, **6**, **8** and **9**) as well as primary (**1**–**6**) and secondary (**7**–**9**) derivatives. The inversion of configuration in an asymmetric center (e.g., **8**→**8c**) must be expected in order to a S_N2 mechanism.[9]

Rufinamide is an anticonvulsant medication approved by the FDA in 2008 which was discovered by Novartis Pharmaceuticals and is currently manufactured by Eisai Co., Japan, and marketed under the brand name Banzel. Classical approach to rufinamide is described in Scheme 2.[10] Synthetically, the use of benzoylacetonitrile **B** under our method may represent the obtaining of potential intermediates (**1b**, **2b**, **3b**, and **9b**) for the synthesis of rufinamide analogues.

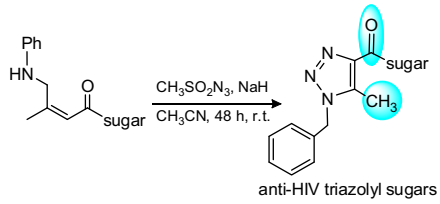
On the other hand, the formation of 1,2,3-triazole core in carbohydrates has become one of the most important issues in medicinal chemistry to obtain 1,2,3-triazole nucleosides, nucleotides, and oligonucleotides.[11] Triazolyl saccharide derivative **4c** obtained from halosugar **4** represents an interesting reaction for the synthesis of aforementioned compounds. Furthermore, this protocol is a facile alternative to obtain 4-carbonyl-5-methyl-triazole derivatives (e.g., **2a**, **3a**, **5a**, **6a**, and **9a**) which are very functionalizable intermediates to obtain anti-HIV triazolyl sugars, previously reported by Ferreira et al. (Scheme 3).[3c]



Scheme 1. Synthesis of 1,4,5-trisubstituted 1,2,3-triazoles from alkyl halides by coupling with sodium azide and active ketones. The products were confirmed by ^{1}H NMR, ^{13}C NMR, MS, and HRMS.



Scheme 2. Reported synthetic approach to rufinamide.



Scheme 3. Ferreira's synthesis for anti-HIV triazolyl sugars

In summary, we report the first one-pot procedure for the direct conversion of alkyl halides to 1,4,5-trisubstituted 1,2,3-triazoles via an azide–enolate [3+2] cycloaddition. These reactions were efficiently performed under mild conditions. The method circumvents the problems encountered with the isolation of organic azides, and complements the library of synthetic methods for obtaining these valuable heterocycles.

Acknowledgments

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Supplementary data

Supplementary data (characterization data of all compounds and copies of ^{1}H NMR, ^{13}C NMR and HRMS) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.02.049.

References and notes

1. (a) Dimroth, O. *Ber. Dtsch. Chem. Ges.* **1902**, *35*, 1029–1038; For a concise discussion about this issue see: (b) Dimroth, M. D. Triazole Synthesis. In *Name Reactions in Heterocyclic Chemistry II*; Li, J. J., Ed.; John Wiley & Sons: New Jersey, 2011. Chapter 5.
2. (a) Seus, N.; Goldani, B.; Lenardão, E. J.; Savegnago, L.; Paixão, M. W.; Alves, D. *Eur. J. Org. Chem.* **2014**, 1059–1065; (b) Kamalraj, V. R.; Senthil, S.; Kannan, P. *J. Mol. Struct.* **2008**, *892*, 210–215; (c) Pokhodylo, N.; Matiychuk, V. S.; Obushak, M. D. *Synthesis* **2009**, 2321–2323; (d) Danence, L. J. T.; Gao, Y.; Li, M.; Huang, Y.; Wang, J. *Chem. Eur. J.* **2011**, *17*, 3584–3587; (e) Rozin, Y. A.; Leban, J.; Dehaen, W.; Nenajdenko, V. G.; Muzalevskiy, V. M.; Eltsov, O. S.; Bakulev, V. A. *Tetrahedron* **2012**, *68*, 614–618; (f) Singh, H.; Sindhu, J.; Khurana, J. M. *RSC Adv.* **2013**, *3*, 22360–22366; (g) Zhang, J.; Jin, G.; Xiao, S.; Wu, J.; Cao, S. *Tetrahedron* **2013**, *69*, 2352–2356.
3. (a) Demchuk, D. V.; Samet, A. V.; Chernysheva, N. B.; Ushkarov, V. I.; Stashina, G. A.; Konyushkin, L. D.; Raihstat, M. M.; Firgang, S. I.; Philchenkov, A. A.; Zavelevich, M. P.; Kuiava, L. M.; Chekhun, V. F.; Blokhin, D. Y.; Kiselyov, A. S.; Semenova, M. N.; Semenov, V. V. *Bioorg. Med. Chem.* **2014**, *22*, 738–755; (b) Kamal, A.; Shankaraiah, N.; Devaiah, V.; Reddy, K. L.; Juvekar, A.; Sen, S.; Kurian, N.; Zingde, S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1468–1473; (c) Da Silva, F. C.; De Souza, M. C. B. V.; Frugulhetti, I. I. P.; Castro, H. C.; Souza, S. L.; DeSouza, T. M. L.; Rodrigues, D. Q.; Souza, A. M. T.; Abreu, P. A.; Passamani, F.; Rodrigues, C. R.; Ferreira, V. F. *Eur. J. Med. Chem.* **2009**, *44*, 373–383; (d) Jordão, A. K.; Afonso, P. P.; Ferreira, V. F.; De Souza, M. C. B. V.; Almeida, M. C. B.; Beltrame, C. O.; Paiva, D. P.; Wardell, S. M. S. V.; Wardell, J. L.; Tiekink, E. R. T.; Damaso, C. R.; Cunha, A. C. *Eur. J. Med. Chem.* **2009**, *44*, 3777–3783; (e) Campos, V. R.; Abreu, P. A.; Castro, H. C.; Rodrigues, C. R.; Jordão, A. K.; Ferreira, V. F.; De Souza, M. C. B. V.; Santos, F. C.; Moura, L. A.; Domingos, T. S.; Carvalho, C.; Sanchez, E. F.; Fuly, A. L.; Cunha, A. C. *Bioorg. Med. Chem.* **2009**, *17*, 7429–7434; (f) Jordão, A. K.; Ferreira, V. F.; Lima, E. S.; De Souza, M. C. B. V.; Carlos, E. C. L.; Castro, H. C.; Geraldo, R. B.; Rodrigues, C. R.; Almeida, M. C. B.; Cunha, A. C. *Bioorg. Med. Chem.* **2009**, *17*, 3713–3719.
4. Jin, G.; Zhang, J.; Fu, D.; Wu, J.; Cao, S. *Eur. J. Org. Chem.* **2012**, 5446–5449.
5. González-Calderón, D.; Santillán-Iniesta, I.; González-González, C. A.; Fuentes-Benítes, A.; González-Romero, C. *Tetrahedron Lett.* **2015**, *56*, 514–516.
6. (a) Odlo, K.; Høydahl, E. A.; Hansen, T. V. *Tetrahedron Lett.* **2007**, *48*, 2097–2099; (b) Kacprzak, K. *Synlett* **2005**, 943–946; (c) Huang, L.; Liu, W.; Wu, J.; Fu, Y.; Wang, K.; Huo, C.; Du, Z. *Tetrahedron Lett.* **2014**, *55*, 2312–2316; (d) Kumar, B. S. P. A.; Reddy, K. H. V.; Madhav, B.; Ramesh, K.; Nageswar, Y. V. D. *Tetrahedron Lett.* **2012**, *53*, 4595–4599; (e) Mukherjee, N.; Ahammed, S.; Bhadra, S.; Ranu, B. C. *Green Chem.* **2013**, *15*, 389–397; (f) Ladouceur, S.; Soliman, A. M.; Zysman-Colman, E. *Synthesis* **2011**, 3604–3611; (g) Sharghi, H.; Khalifeh, R.; Doroodmand, M. M. *Adv. Synth. Catal.* **2009**, *351*, 207–218.
7. González-González, C. A.; Fuentes-Benítez, A.; Cuevas-Yáñez, E.; Corona-Becerril, D.; González-Romero, C.; González-Calderón, D. *Tetrahedron Lett.* **2013**, *54*, 2726–2728.
8. *Experimental procedure*: A 10-mL round-bottom flask was equipped with a magnetic stir bar and a reflux condenser. Then 0.4 mmol of alkyl halide and 0.44 mmol of sodium azide were added to 1.5 mL of anhydrous dimethylformamide. The reaction mixture was stirred at 60 °C for 2 h under nitrogen atmosphere. After cooling to room temperature, TLC indicated the disappearance of the starting material. 0.44 mmol of active ketone and 0.44 mmol of DBU were then added to the reaction mixture, which was stirred for 3 h at 60 °C. Brine (~40 mL) was added to the reaction mixture and washed with EtOAc (3 × 10 mL). The organic layer was dried (Na_2SO_4) and the solvent evaporated under reduced pressure. Flash column chromatography afforded the pure triazole.
9. Rablen, P. R.; McLarney, B. D.; Karlow, B. J.; Schneider, J. E. *J. Org. Chem.* **2014**, *79*, 867–879.
10. Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; Del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432–2506. and references therein.
11. For representative reviews see: (a) Aragão-Leoneti, V.; Campo, V. L.; Gomes, A. S.; Field, R. A.; Carvalho, I. *Tetrahedron* **2010**, *66*, 9475–9492; (b) Amblard, F.; Cho, J. H.; Schinazi, R. F. *Chem. Rev.* **2009**, *109*, 4207–4220.

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Communication

1,3-Dipolar Cycloaddition

Azide–Enolate 1,3-Dipolar Cycloaddition as an Efficient Approach for the Synthesis of 1,5-Disubstituted 1,2,3-Triazoles from Alkyl/Aryl Azides and β-Ketophosphonates

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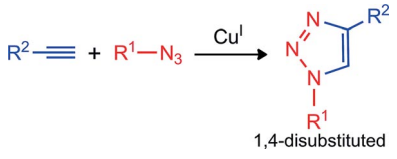
Abstract: A simple procedure to prepare 1,5-disubstituted 1,2,3-triazoles efficiently from alkyl/aryl azides and β-ketophosphonates in the presence of KOH by an azide–enolate 1,3-dipolar cycloaddition in good yields was developed.

Introduction

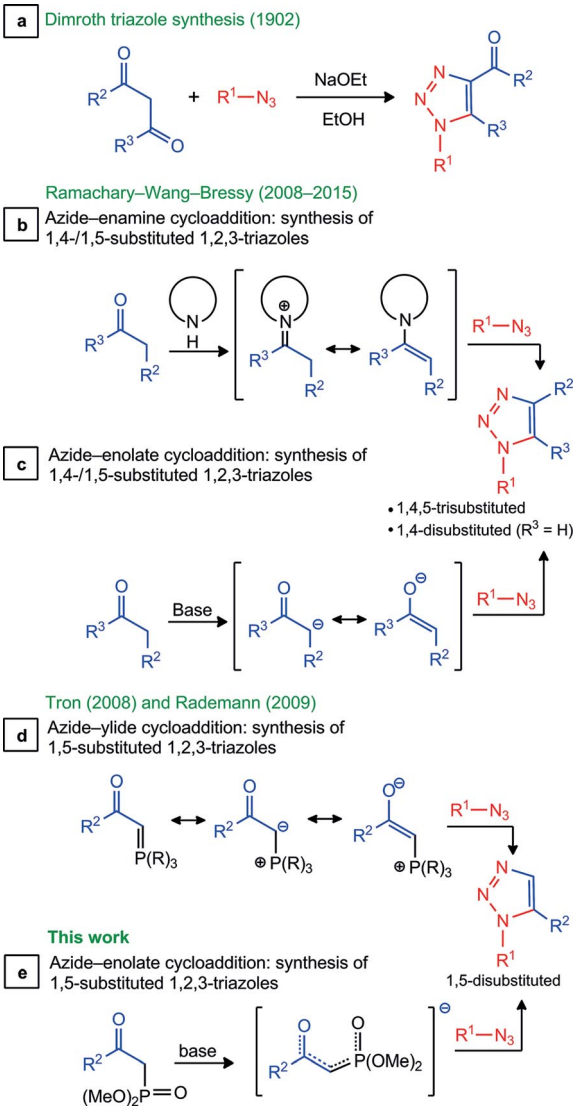
In 2002, Meldal[1] and Sharpless[2] reported Cu-catalyzed alkyne–azide cycloaddition (CuAAC) as an enhanced protocol of the Huisgen cycloaddition (1963);[3] this reaction enables the highly regioselective synthesis of 1,4-disubstituted 1,2,3-triazoles (Scheme 1). This improvement has become, for the time being, the most powerful tool to furnish 1,2,3-triazole scaffolds.[4]



Scheme 1. CuAAC by Meldal and Sharpless: Highly regioselective synthesis of 1,4-disubstituted 1,2,3-triazoles.

In very recent years, Ramachary, Wang, Bressy, Tron, and Rademann independently reported azide–carbonyl [3+2] cycloaddition as a novel strategy to afford 1,2,3-triazole moieties (Scheme 2).[5–7] The use of a wide variety of carbonyl derivatives (e.g., aldehydes, ketones, esters, and nitriles that are easily prepared and inexpensive) has demonstrated significant advantages over the CuAAC.

Similar to the Huisgen-type CuAAC reaction, azide–carbonyl cycloaddition has emerged from the "archives". In 1902, Dimroth reported[8] the first azide–enolate cycloaddition [Scheme 2, Equation (a)]. The synthesis of Dimroth triazoles is a stepwise



Scheme 2. Azide–carbonyl 1,3-dipolar cycloaddition as an emerging field to provide a versatile approach to substituted 1,2,3-triazoles.

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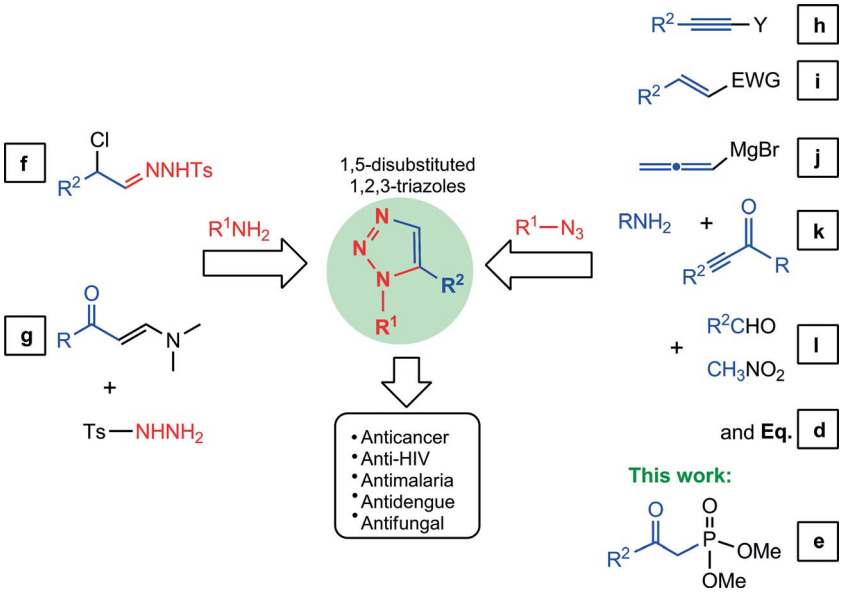


Scheme 3. Background and proposed approach to the synthesis of 1,5-disubstituted 1,2,3-triazoles involving the coupling of azide derivatives with certain substrates (ref.[7,22–26]) as well as synthesis by azide-free reactions (ref.[20,21]). These synthetic protocols have allowed biological studies of such compounds (ref.[14–19]).

addition/condensation process that occurs with complete regioselectivity and is most commonly achieved by using alkoxide bases in alcohol solvents (polar protic).[9] Consequently, several authors have proposed[10] other alternatives for such reactions. Nowadays, Ramachary, Wang, Bressy, Tron, and Rademann have returned to Dimroth cycloaddition but in a new setting. The main outstanding aspects of these novel methodologies are highlighted in recent reviews by Westermann and Paixão,[11] Dehaen,[12] and Ramasastry.[13] In contrast with azide–enamine [Scheme 2, Equation (b)][5] and azide–enolate [Scheme 2, Equation (c)][6] cycloaddition (synthetic approaches to 1,4,5-trisubstituted and 1,4-disubstituted 1,2,3-triazoles only), the coupling with phosphorus compounds [Scheme 2, Equation (d)][7,10b,10c] leads exclusively to 1,5-disubstituted 1,2,3-triazoles.

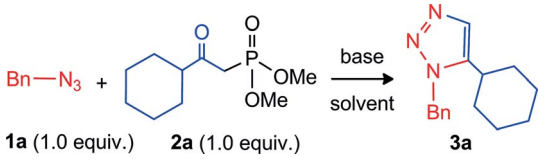
The 1,5-disubstituted 1,2,3-triazole core is now known to be a very important pharmacophore[14] owing to its considerable biological applications (e.g., against cancer,[15] HIV,[16] malaria,[17] dengue,[18] and fungus[19]). From increasingly common reports on synthetic methods to obtain 1,5-disubstituted 1,2,3-triazole moieties, general methods can be sorted as (1) the cycloaddition of primary amines with α-chlorotosylhydrazones [Scheme 3, Equation (f)][20] or with enaminones/tosylhydrazine [Scheme 3, Equation (g)][21] and (2) the coupling of azide substrates with alkynes [Scheme 3, Equation (h)],[22] vinyl electron-withdrawing group substrates [Scheme 3, Equation (i)],[23] allenylmagnesium bromides [Scheme 3, Equation (j)],[24] amines/propynones [Scheme 3, Equation (k)],[25] and aldehydes/nitromethane [Scheme 3, Equation (l)].[26] Thus, the development of an efficient synthesis of these nitrogen heterocycles is of increasing importance.

Results and Discussion

Recently, we reported[27] the synthesis of 1,4,5-trisubstituted 1,2,3-triazoles from benzylic alcohols by azidation with the use of diphenylphosphoryl azide (DPPA) in the presence of active ketones (then benzoylacetonitrile, ethyl acetoacetate, dibenzoylmethane, and acetylacetone were used). At this stage, β-ketophosphonates **2** were subjected to such conditions. Afterwards, we noticed that instead of the 1,4,5-trisubstituted 1,2,3-triazoles, the 1,5-disubstituted 1,2,3-triazoles derivatives were obtained in low yields (30 %). This observation was not very surprising given that, as aforementioned, phosphorus compounds lead exclusively to 1,5-disubstituted 1,2,3-triazoles.

Hence, we decided to investigate the coupling of azides with β-ketophosphonates in greater detail. Optimization studies for this cycloaddition process were performed with compounds **1a** and **2a**. In accordance with the outcome described in Table 1, low yields were observed upon using basic tertiary amines, such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; Table 1, entries 1, 7, and 8), Et_3N (Table 1, entries 2 and 9), and 4-(dimethylamino)pyridine (DMAP; Table 1, entry 3), as well as strong bases, such as sodium hydride (Table 1, entry 5), *n*BuLi (Table 1, entries 16 and 17), and lithium diisopropylamide (LDA; Table 1, entries 18 and 19). Triazolation with the use of KOH was accomplished and provided the products in moderate to excellent yields. KOH-promoted cycloaddition is dependent on the solvent. With dry solvents (Table 1, entries 4, 10, and 12), the reaction afforded the products in moderate yields. However, with reagent-grade solvents (particularly Table 1, entries 14 and 15), the highest yields were observed. Therefore, we adopted the standard of using a solution of KOH (2.0 equiv.) in reagent-

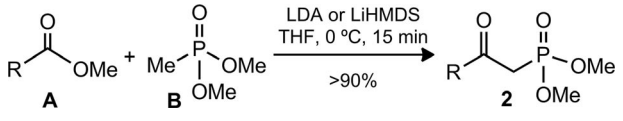
Table 1. Optimization of the reaction conditions: Effect of solvent and base.



Entry	Solvent	Base[b]	Time [h]	Yield[c] [%]
1	DMF (anhyd.)	DBU	12	31
2	DMF (anhyd.)	Et_3N	12	34
3	DMF (anhyd.)	DMAP	12	23
4	DMF (anhyd.)	KOH	12	53
5	DMF (anhyd.)	NaH	12	42
6	DMF	KOH	12	64
7	MeCN (anhyd.)	DBU	12	37
8	MeCN	DBU	12	46
9	MeCN	Et_3N	12	40
10	MeCN (anhyd.)	KOH	5	63
11	MeCN	KOH	5	74
12	THF (anhyd.)	KOH	5	56
13	THF	KOH	5	75
14	MeCN	KOH (2.0 equiv.)	5	95
15	THF	KOH (2.0 equiv.)	5	90
16[d]	THF (anhyd.)	BuLi	3	55
17[d]	THF (anhyd.)	BuLi (2.0 equiv.)	3	60
18[d]	THF (anhyd.)	LDA	3	64
19[d]	THF (anhyd.)	LDA (2.0 equiv.)	3	68

[a] Unless otherwise stated, reactions were run at 60 °C. [b] Unless otherwise stated, reactions were performed by using 1.1 equiv. of base [c] Yields refer to chromatographically pure isolated compounds. [d] These experiments were performed at 0 °C.

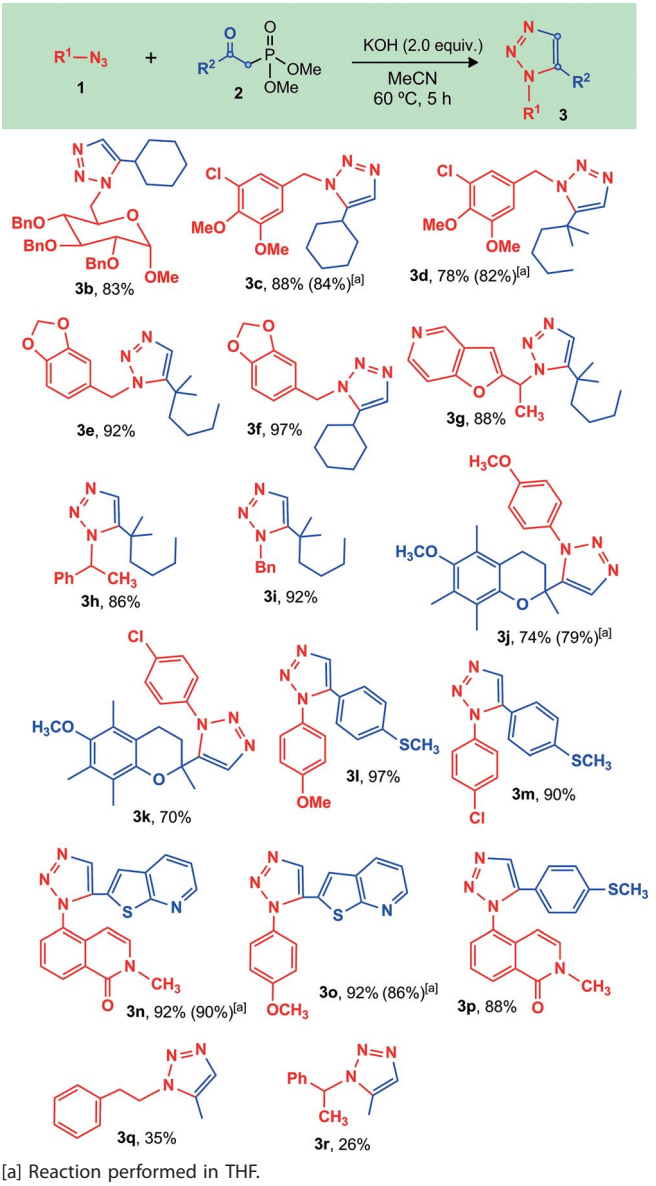
grade acetonitrile or tetrahydrofuran with conventional heating at 60 °C for 5 h. To demonstrate the reproducibility and scope of such results, a library of β-ketophosphonates **2** was readily prepared according to the mild and high-yielding procedures described by Maloney[28] and Milburn[29] (Scheme 4).



Scheme 4. Facile condensation of esters **A** with dimethyl methylphosphonate (**B**) afforded high yields of β-ketophosphonates **2** under noncryogenic conditions.[28,29]

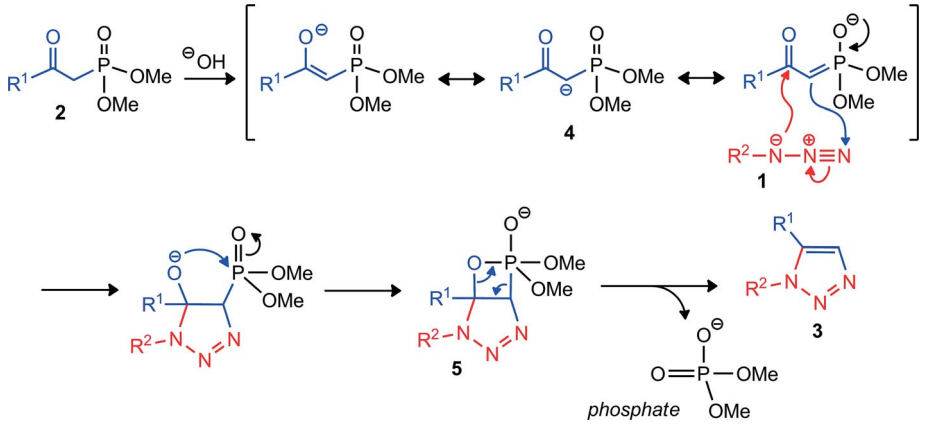
The cycloaddition of various alkyl and aryl azides **1** in the presence of diverse β-ketophosphonates **2** under the optimized conditions is summarized in Table 2. The scope and versatility of this protocol is displayed by the efficient synthesis of 1-alkyl-substituted (**3a**–**i**, from alkyl azides) and 1-aryl-substituted (**3j**–**p**, from aryl azides) 1,2,3-triazoles as well as 5-alkyl-substituted (**3b**–**k**, from R^2 = alkyl derivatives) and 5-aryl-substituted (**3l**–**p**, from R^2 = aryl derivatives) 1,2,3-triazoles in good yields, both with the use of acetonitrile and tetrahydrofuran. Unfortunately, upon subjecting commercial dimethyl 2-oxopropylphosphonate [$CH_3COCH_2P(O)(OCH_3)_2$] to our protocol, desired triazoles **3q** and **3r** were obtained in very low yields (35 and 26 %, respectively). A reasonable competitive deprotonation between the α carbon atoms of such a 2-oxophosphonate may explain these outcomes.

Table 2. Cycloaddition of azides **1** with β-ketophosphonates **2** under optimized conditions. Reaction conditions: A mixture of compound **1** (0.1 mmol), compound **2** (0.1 mmol), and KOH (0.2 mmol) in CH_3CN (1.5 mL) was stirred at 60 °C for 5 h.



[a] Reaction performed in THF.

A plausible reaction pathway is shown in Scheme 5. Phosphoryl-stabilized carbanion **4**, promoted by the hydroxy group, enables highly regioselective coupling with azide moiety **1** to form corresponding oxaphosphetane **5**. Aromatization of the ring produces the free phosphate byproduct, which is readily separated from desired product **3** by simply washing with water.



Scheme 5. Proposed plausible mechanism for azide–enolate 1,3-dipolar cycloaddition.

Conclusions

In summary, we developed a simple and efficient approach to obtain 1,5-disubstituted 1,2,3-triazoles through a highly regioselective synthesis. The coupling of aryl/alkyl azides with β-ketophosphonates was promoted by KOH in reagent-grade solvents (acetonitrile or tetrahydrofuran) with good to excellent yields.

Experimental Section

Dimethyl 2-[4-(Methylthio)phenyl]-2-oxoethylphosphonate; Representative Procedure[28,29] for the Synthesis of Compounds 3l and 3m: A solution of 2.0 M LDA in THF (1.56 mL, 11.52 mmol) was added dropwise to a cold solution (–5 °C) of methyl 4-(methylthio)benzoate (1.0 g, 5.49 mmol) and dimethyl methylphosphonate (0.654 mL, 6.028 mmol) in anhydrous THF (30 mL) keeping the internal temperature below 0 °C. After complete addition, stirring was continued at 0 °C for 45 min. A satd. aq. solution of NH_4Cl (ca. 40 mL) was added to the mixture, which was washed with EtOAc (3 × 20 mL). The organic layer was dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. The crude extract was purified by flash column chromatography to afford the title compound as a white solid (1.4 g, 93 %).

Triazole 3a; Representative Procedure: Potassium hydroxide (0.11 g, 2.0 mmol) was added to a solution of benzyl azide (**1a**; 0.133 g, 1.0 mmol) and β-ketophosphonate **2a** (0.23 g, 1.0 mmol) in reagent-grade acetonitrile (2.0 mL). The solution was stirred at 60 °C for 5 h. Brine (ca. 20 mL) was added to the mixture, which was washed with EtOAc (3 × 8 mL). The organic layer was dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. The crude extract was purified by flash column chromatography to afford **3a** (0.23 g, 95 %) as a colorless oil.

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Keywords: Azides · Enolates · Cycloaddition · Nitrogen heterocycles · β-Ketophosphonates

[1] C. W. Tornøe, C. Christensen, M. Meldal, *J. Org. Chem.* **2002**, *67*, 3057–3064.
[2] V. V. Rostovtsev, L. G. Green, V. V. Fokin, B. Sharpless, *Angew. Chem. Int. Ed.* **2002**, *41*, 2596–2599; *Angew. Chem.* **2002**, *114*, 2708–2711 .
[3] R. Huisgen, *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 565–598; *Angew. Chem.* **1963**, *75*, 604–637.
[4] a) S. Hassan, T. J. J. Müller, *Adv. Synth. Catal.* **2015**, *357*, 617–666; b) B. Dervaux, F. E. Du Prez, *Chem. Sci.* **2012**, *3*, 959–966; c) M. Meldal, C. W. Tornøe, *Chem. Rev.* **2008**, *108*, 2952–3015; d) V. D. Bock, H. Hiemstra, J. H. van Maarseveen, *Eur. J. Org. Chem.* **2006**, 51–68; e) J. Totobenazara, A. J. Burke, *Tetrahedron Lett.* **2015**, *56*, 2853–2859.
[5] a) W. Li, Q. Jia, Z. Du, J. Wang, *Chem. Commun.* **2013**, *49*, 10187–10189; b) Q. Jia, G. Yang, L. Chen, Z. Du, J. Wei, Y. Zhong, J. Wang, *Eur. J. Org. Chem.* **2015**, 3435–3440; c) W. Li, Z. Du, J. Huang, Q. Jia, K. Zhang, J. Wang, *Green Chem.* **2014**, *16*, 3003–3006; d) D. B. Ramachary, A. B. Shashank, *Chem. Eur. J.* **2013**, *19*, 13175–13181; e) D. K. J. Yeung, T. Gao, J. Huang, S. Sun, H. Guo, J. Wang, *Green Chem.* **2013**, *15*, 2384–2388; f) L. J. T. Danence, Y. Gao, M. Li, Y. Huang, J. Wang, *Chem. Eur. J.* **2011**, *17*, 3584–3587; g) M. Belkheira, D. El Abed, J. M. Pons, C. Bressy, *Chem. Eur. J.* **2011**, *17*, 12917–12921; h) D. B. Ramachary, K. Ramakumar, V. V. Narayana, *Chem. Eur. J.* **2008**, *14*, 9143–9147.
[6] a) D. B. Ramachary, A. B. Shashank, S. Karthik, *Angew. Chem. Int. Ed.* **2014**, *53*, 10420–10424; *Angew. Chem.* **2014**, *126*, 10588–10592; b) W. Li, J. Wang, *Angew. Chem. Int. Ed.* **2014**, *53*, 14186–14190; *Angew. Chem.* **2014**, *126*, 14410–14414; c) A. B. Shashank, S. Karthik, R. Madhavachary, D. B. Ramachary, *Chem. Eur. J.* **2014**, *20*, 16877–16881; d) D. González-Calderón, J. G. Aguirre-De Paz, C. A. González-González, A. Fuentes-Benítes, C. González-Romero, *Tetrahedron Lett.* **2015**, *56*, 1713–1715. Additional important work on this issue by other authors: e) D. González-Calderón, J. G. Aguirre-De Paz, C. A. González-González, A. Fuentes-Benítes, C. González-Romero, *Tetrahedron Lett.* **2015**, *56*, 1713–1715; f) N. Seus, B. Goldani, E. J. Lenardão, L. Savegnago, M. W. Paixão, D. Alves, *Eur. J. Org. Chem.* **2014**, 1059–1065; g) J. Zhang, G. Jin, S. Xiao, J. Wu, S. Cao, *Tetrahedron* **2013**, *69*, 2352–2359; h) H. Singh, J. Sindhu, J. M. Khurana, *RSC Adv.* **2013**, *3*, 22360–22366; i) G. Jin, J. Zhang, D. Fu, J. Wu, S. Coa, *Eur. J. Org. Chem.* **2012**, 5446–5449; j) Y. A. Rozin, J. Leban, W. Dehaen, V. G. Nenajdenko, V. M. Muzalevskiy, O. S. Eltsov, V. A. Bakulev, *Tetrahedron* **2012**, *68*, 614–618; k) N. T. Pokhodylo, V. S. Matiychuk, M. D. Obushak, *Synthesis* **2009**, 2321–2323.
[7] a) L. Cafici, T. Pirali, F. Condorelli, E. Del Grosso, A. Massarotti, G. Sorba, P. L. Canonico, G. C. Tron, A. A. Genazzani, *J. Comb. Chem.* **2008**, *10*, 732–

740; b) Ahsanullah, P. Schmieder, R. Kühne, J. Rademann, *Angew. Chem. Int. Ed.* **2009**, *48*, 5042–5045; *Angew. Chem.* **2009**, *121*, 5143–5147; c) Ahsanullah, J. Rademann, *Angew. Chem. Int. Ed.* **2010**, *49*, 5378–5382; *Angew. Chem.* **2010**, *122*, 5506–5510.

[8] O. Dimroth, *Ber. Dtsch. Chem. Ges.* **1902**, *35*, 1029–1038.

[9] M. D. Hill, "Dimroth Triazole Synthesis" in *Name Reactions in Heterocyclic Chemistry II* (Ed.: J. J. Li), John Wiley & Sons, Hoboken, NJ, **2011**, ch. 5.

[10] a) M. E. Munk, Y. K. Kim, *J. Am. Chem. Soc.* **1964**, *86*, 2213–2217; b) G. R. Harvey, *J. Org. Chem.* **1966**, *31*, 1587–1590; c) U. Hepp, *Justus Liebigs Ann. Chem. Ann. Chem.* **1973**, 578–583.

[11] C. G. S. Lima, A. Ali, S. S. van Berkel, B. Westermann, M. W. Paixão, *Chem. Commun.* **2015**, *51*, 10784–10796.

[12] J. John, J. Thomas, W. Dehaen, *Chem. Commun.* **2015**, *51*, 10797–10806.

[13] S. S. V. Ramasastry, *Angew. Chem. Int. Ed.* **2014**, *53*, 14310–14312; *Angew. Chem.* **2014**, *126*, 14536–14538.

[14] A. Massarotti, S. Aprile, V. Mercalli, E. Del Grosso, G. Grosa, G. Sorba, G. C. Tron, *ChemMedChem* **2014**, *9*, 2497–2508.

[15] T. M. Beale, P. J. Bond, J. D. Brenton, D. S. Charnock-Jones, S. V. Ley, R. M. Myers, *Bioorg. Med. Chem.* **2012**, *20*, 1749–1759.

[16] V. R. Sirivolu, S. K. V. Verneka, T. Ilina, N. S. Myshakina, M. A. Parniak, Z. Wang, *J. Med. Chem.* **2013**, *56*, 8765–8780.

[17] Y. Chen, M. López-Sánchez, D. N. Savoy, D. D. Billadeau, G. S. Dow, A. P. Kozikowski, *J. Med. Chem.* **2008**, *51*, 3437–3448.

[18] S. K. V. Vernekar, L. Qiu, J. Zhang, J. Kankanala, H. Li, R. J. Geraghty, Z. Wang, *J. Med. Chem.* **2015**, *58*, 4016–4028.

[19] V. S. Pore, M. A. Jagtap, S. G. Agalave, A. K. Pandey, M. I. Siddiqi, V. Kumar, P. K. Shukla, *MedChemComm* **2012**, *3*, 484–488.

[20] H. W. Bai, Z. J. Cai, S. Y. Wang, S. J. Ji, *Org. Lett.* **2015**, *17*, 2898–2901.

[21] J.-P. Wan, S. Cao, Y. Liu, *J. Org. Chem.* **2015**, *80*, 9028–9033.

[22] For Ru-catalyzed coupling, see: a) L. Zhang, X. Chen, P. Xue, H. H. Y. Sun, I. D. Williams, K. B. Sharpless, V. V. Fokin, G. Jia, *J. Am. Chem. Soc.* **2005**, *127*, 15998–15999; b) L. K. Rasmussen, B. C. Boren, V. V. Fokin, *Org. Lett.* **2007**, *9*, 5337–5339; c) B. C. Boren, S. Narayan, L. K. Rasmussen, L. Zhang, H. Zhao, Z. Lin, G. Jia, V. V. Fokin, *J. Am. Chem. Soc.* **2008**, *130*, 8923–8930; coupling by other metals: d) A. Krasiński, V. V. Fokin, K. B. Sharpless, *Org. Lett.* **2004**, *6*, 1237–1240; e) L. Li, T. Shang, X. Ma, H. Guo, A. Zhu, G. Zhang, *Synlett* **2015**, *26*, 695–699; f) C. D. Smith, M. F. Greaney, *Org. Lett.* **2013**, *15*, 4826–4829; g) L. Hong, W. Lin, F. Zhang, R. Liu, X. Zhou, *Chem. Commun.* **2013**, *49*, 5589–5591; for metal-free coupling, see: h) S. W. Kwok, J. R. Fotsing, R. J. Fraser, V. O. Rodionov, V. V. Fokin, *Org. Lett.* **2010**, *12*, 4217–4219; i) M. E. Meza-Aviña, M. K. Patel, C. B. Lee, T. J. Dietz, M. P. Croatt, *Org. Lett.* **2011**, *13*, 2984–2987; j) L. Wu, Y. Chen, M. Tang, X. Song, G. Chen, X. Song, Q. Lin, *Synlett* **2012**, *23*, 1529–1533.

[23] a) Y. Chen, G. Nie, Q. Zhang, S. Ma, H. Li, Q. Hu, *Org. Lett.* **2015**, *17*, 1118–1121; b) A. Kayet, T. Pathak, *J. Org. Chem.* **2013**, *78*, 9865–9875; c) D. Sahu, S. Dey, T. Pathak, B. Ganguly, *Org. Lett.* **2014**, *16*, 2100–2103; d) L. Wu, Y. Chen, J. Luo, Q. Sun, M. Peng, Q. Lin, *Tetrahedron Lett.* **2014**, *55*, 3847–3850; e) Y. C. Wang, Y. Y. Xie, H. E. Qu, H. S. Wang, Y. M. Pan, F. P. Huang, *J. Org. Chem.* **2014**, *79*, 4463–4469.

[24] S. Shafi, A. H. Banday, T. Ismail, H. M. S. Kumar, *Synlett* **2007**, 1109–1111.

[25] G. Cheng, X. Zeng, J. Shen, X. Wang, X. Cui, *Angew. Chem. Int. Ed.* **2013**, *52*, 13265–13268; *Angew. Chem.* **2013**, *125*, 13507–13510.

[26] J. Thomas, J. John, N. Parekh, W. Dehaen, *Angew. Chem. Int. Ed.* **2014**, *53*, 10155–10159; *Angew. Chem.* **2014**, *126*, 10319–10323.

[27] D. González-Calderón, I. Santillán-Iniesta, C. A. González-González, A. Fuentes-Benítes, C. González-Romero, *Tetrahedron Lett.* **2015**, *56*, 514–516.

[28] K. M. Maloney, J. Y. L. Chung, *J. Org. Chem.* **2009**, *74*, 7574–7576.

[29] R. R. Milburn, K. McRae, J. Chan, J. Tedrow, R. Larsen, M. Faul, *Tetrahedron Lett.* **2009**, *50*, 870–872.

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Short communication

Antifungal activity of 1′-homo-*N*-1,2,3-triazol-bicyclic carbonucleosides: A novel type of compound afforded by azide-enolate (3+2) cycloaddition

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ABSTRACT

The first report of 1′-homo-*N*-1,2,3-triazol-bicyclic carbonucleosides (**7a** and **7b**) is described herein. Azide-enolate (3+2) cycloaddition afforded the synthesis of this novel type of compound. Antifungal activity was evaluated *in vitro* against four filamentous fungi (*Aspergillus fumigatus*, *Trichosporon cutaneum*, *Rhizopus oryzae* and *Mucor hiemalis*) as well as nine species of *Candida* spp. as yeast specimens. These pre-clinical studies suggest that compounds **7a** and **7b** are promising candidates for complementary biological studies due to their good activity against *Candida* spp.

1. Introduction

The chemistry and biology of nucleoside analogs has consolidated a very particular and proper field of study in organic and medicinal chemistry [1]. A certain classification of such compounds, convenient for the purpose of the present study, is described in Fig. 1. One of the most important modifications of nucleosides **Aa** [2] has been the replacement of the oxygen atom of the furanose ring with a methylene group, resulting in carbocyclic nucleosides **Ab** [3] (also called 'carbonucleosides' in short form). The recognition of 1,2,3-triazole scaffolds as potent pharmacophores [4] has revolutionized nucleoside analogs allowing for their conversion to the corresponding triazole derivatives **Ba** [5] and **Bb** [6].

1′-Homonucleosides (**Ca** [7] and **Cb** [8]) are a special class of modified nucleosides, in which the nucleobase (Het) and the sugar moiety (at its 1′-position) are separated by a carbon bridge. In addition to greater conformational flexibility and rotational freedom, this gives them more resistance to hydrolytic or enzymatic cleavage compared to the relatively reactive aminal linkage of common nucleosides [9]. Modified triazolic nucleosides **D** [10] can be found in literature, and the discovery of certain natural bicyclic nucleosides **Ea** [11] (*e.g.* Ezomycin [12] and Octosyl [13]) along with their potent antifungal activity [14] has sparked new research into the design and synthesis of novel carbonucleoside derivatives **Eb** [15] as well as their 1′-homo mimetics **F** [16].

Sesquiterpene lactones (carbobicyclic lactones) are amongst the most abundant natural products. More than 8000 structures have been reported [17], and they have broad structural and functional diversity including their antifungal activity [*e.g.* Sclareolide [18] (Fig. 2)]. The introduction of these scaffolds to nucleosides analogs (**H** and **I**) has been performed by Castillón [19]. The chemical structure of certain antifungal nucleoside analogs (**J** [20] and **K** [21] among others [22]) has inspired the design and synthesis of 1′-homo-*N*-1,2,3-triazol-bicyclic carbonucleosides **7a** and **7b**. To the best of our knowledge, this type of compound (**G**) has not yet been reported.

2. Results and discussion

2.1. Chemistry

The Cu-catalyzed azide-alkyne cycloaddition (CuAAC) has largely been the conventional approach for synthesizing triazole nucleosides [5]. In recent years, azide-enolate (3+2) cycloaddition (AEC) has emerged as a novel and potent tool for the synthesis of

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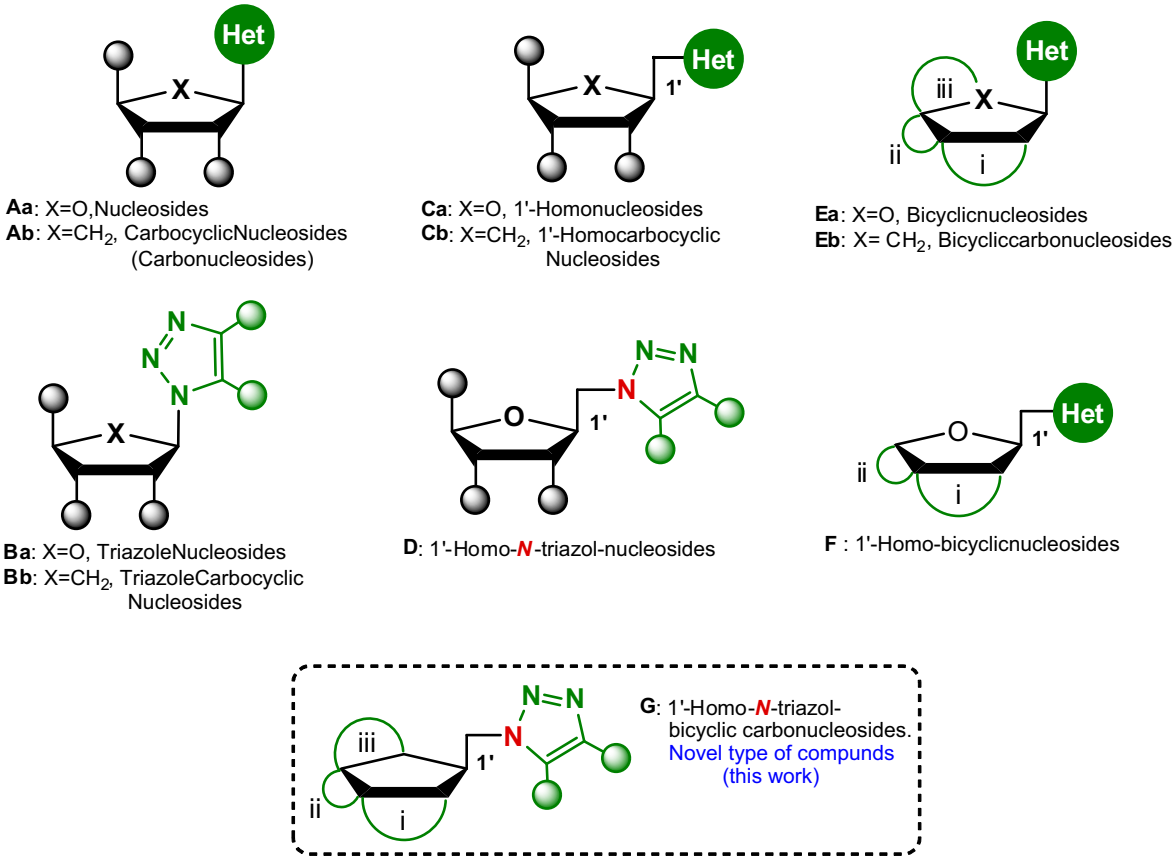


Fig. 1. General classification of nucleoside analogs reported in literature. Possible positions (i, ii, and iii) for bicyclic derivatives **E** and **F** are known. A novel type of compound **G** is herein proposed.

1,2,3-triazole moieties [23]. As a pioneering strategy we describe the synthesis of **7a** and **7b** afforded by a versatile AEC (Scheme 1).

Our initial study began by obtaining silylated 'Corey lactone' **2**, according to our previous report [24], as the key precursor for the present synthesis. This compound is an excellent supplier of the pseudosugar ring (cyclopentane) required for the highly stereospecific configuration of all suitable functional groups. A convenient protection–deprotection strategy for alcohols was planned for the present study involving the esterification of **2** with *p*-phenylbenzoyl chloride (PBCl) in dichloromethane and pyridine to form the ester lactone **3**.

Previously [25], we investigated the $AlCl_3{\cdot}6H_2O$ cleavage of silyl ethers in methanol. Thus, desilylation of **3** was accomplished by such a protocol to afford alcohol **4**, which was functionalized to the corresponding iodide derivative **5** according to the Garegg-Samuelsson procedure (PPh_3/I_2/Im/ROH system) [26], On the other hand, we recently [27] published a straightforward approach to the synthesis of 1,4,5-trisubstituted 1,2,3-triazoles by the coupling of three-components (alkyl halides, sodium azide, and ketones) through an AEC. This method proved to be a very rapid and *elegant* way to access triazole building blocks **6a** and **6b** by the coupling of acetylacetone and 2-benzoylacetophenone, respectively. Finally, transesterification of **6a** and **6b** by treatment with DBN in MeOH gave the corresponding carbonucleosides **7a** and **7b**.

Compounds **7a** and **7b** were evaluated for their *in vitro* antifungal activity against four filamentous fungi (*Aspergillus fumigatus* ATCC-16907, *Trichosporon cutaneum* ATCC-28592, *Rhizopus oryzae* ATCC-10329 and *Mucor hiemalis* ATCC-8690), as well as *Candida utilis* ATCC-9226, *Candida albicans* ATCC-10231 and *Candida tropicalis* ATCC-13803 as yeast specimens. In addition, other strains for *Candida* spp. (*C. lipolytica*, *C. pseudotropicalis*, *C. krusei*, *C. parapsilosis*, *C. glabrata*, and *Candida famata*) were collected from inpatients and evaluated under the aforementioned protocol. CLSI standardized methods were employed to carry out the microbiological tests. We used the M38-A2 [28] microdilution method to determine the sensitivity of filamentous fungi, and the M27-A3 [29] method for *Candida* yeasts. The antifungal activity of compounds **7a** and **7b** was compared with itraconazole, a standard antifungal drug. The minimum inhibitory concentration (MIC) values of compounds and standard drugs, expressed in micrograms per milliliter, were determined in 96-well plates by using RPMI 1640 medium buffered with MOPS (3-[*N*-morpholino]propane sulfonic acid; Sigma-Aldrich).

2.2. Antifungal activity

The antifungal activity of the evaluated compounds is summarized in Table 1. Compounds **7a** and **7b** showed good activity in some of the yeast strains, including *C. utilis, C. lipolytica, C. glabrata* and *C. famata,* demonstrating 'sensitivity'[a] according to the parameters of document M27-A3 (Table 2). Only slight

[a] 'S', 'SDD' and 'R' are represented by standardized values (breakpoints) used to appreciate the clinical value of the *in vitro* antifungal testing result and predicting the response of patients infected. Sensitivity is dependent on achieving the maximum dosages in plasma (breakpoints) to obtain optimal response. For itraconazole, an MIC within the susceptible-dose dependent (SDD) range indicates the need for plasma concentrations 0.25–0.5 μg/mL for an optimal response. Actual breakpoints are described in Table 4 (see Ref. [29b]).

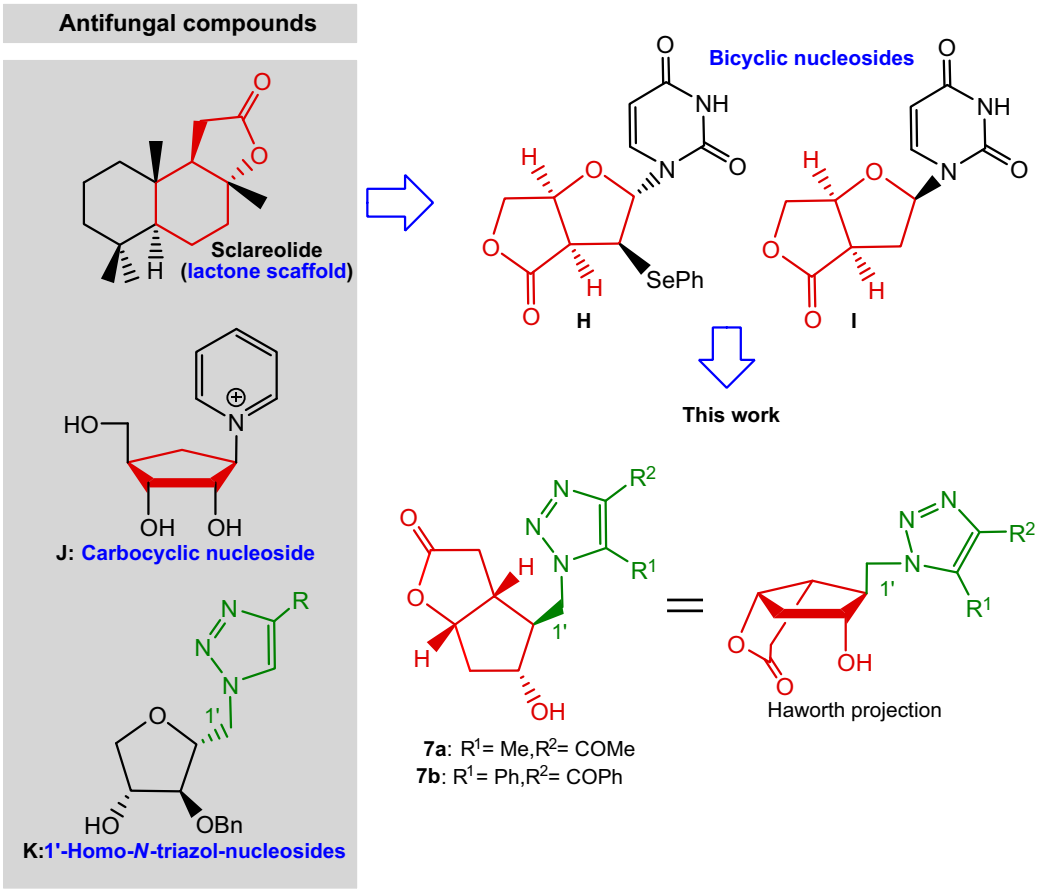
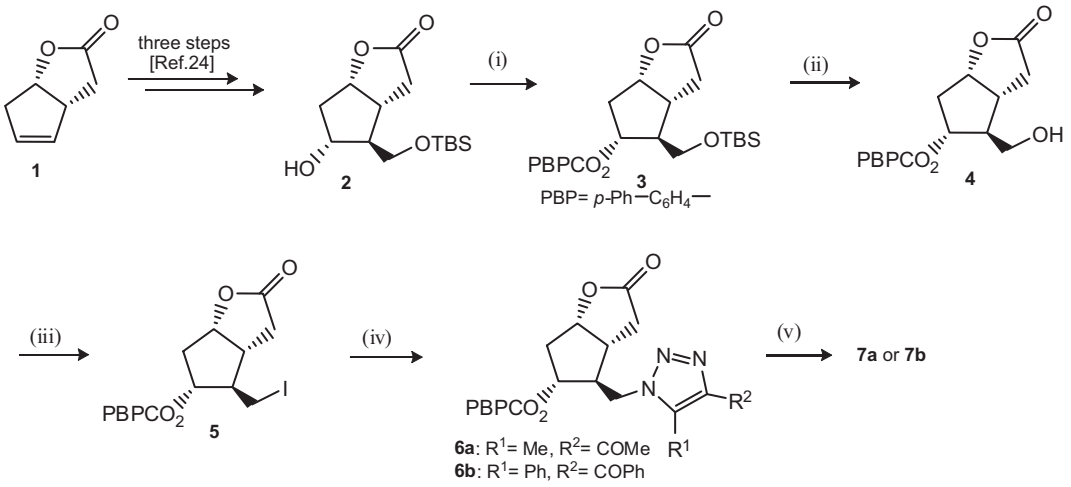


Fig. 2. The current antifungal compounds Sclareolide, **J** and **K** as well as **H** and **I** inspired the design of novel nucleoside analogs **7a** and **7b**.



Scheme 1. *Reagents and conditions*: (i) PBCl (1.1 eq), Py anh., DCM, r.t., N_2, 1 h, 90%. (ii) $AlCl_3{\cdot}6H_2O$ cat, MeOH, 60 °C, 12 h, 93%. (iii) PPh_3 (2.5 eq), I_2 (2.0 eq.), Im (2.5 eq.), MeCN anh., 80 °C, N_2, 3 h, 85%. (iv) For **6a**: NaN_3 (1.1 eq), DMF anh., 60 °C, N_2, 6 h, then acetylacetone (1.1 eq), DBU (1.1 eq), 12 h, 60 °C, 72%. For **6b**: NaN_3 (1.1 eq), DMF anh, 60 °C, N_2, 6 h, then 2-benzoylacetophenone (1.1 eq), DBU (1.1 eq), 12 h, 60 °C, 67%. (v) Both **7a** and **7b**: DBN cat, MeOH, r.t. 12 h, 87% and 81% respectively.

antifungal activity against *C. albicans, C. tropicalis, C. pseudotropicalis, C. krusei,* and *C. parapsilosis* was observed. Whereas there was evident resistance by *M. hiemalis*, slight activity was found against the rest of the filamentous fungi tested (*A. fumigatus, T. cutaneum, and R. oryzae*).

3. Conclusion

In conclusion, we report the first synthesis of a novel type of compound, represented by 1′-homo-*N*-1,2,3-triazol-bicyclic carbonucleosides **7a** and **7b**, which showed good activity against

Table 1
In vitro antifungal activities of synthetized compounds (MIC, μg/mL).

Comp.	Yeast fungi									Filamentous fungi			
	C. alb.	*C. trop.*	*C. uti.*	*C. lipo.*	*C. pseu.*	*C. kru.*	*C. para.*	*C. gla.*	*C. fam.*	*M. hie.*	*A. fum.*	*T. cut.*	*R. ory.*
1	0.25	0.5	0.12	0.12	0.5	4	2	0.5	0.06	>16	4	8	4
2	2	2	0.12	0.12	1	4	4	0.5	0.5	>16	8	>16	8
Standard[a]	0.03	0.25	0.25	0.03	0.12	0.25	0.12	0.06	0.06	4	0.5	2	1

Abbreviations: C. alb., Candida albicans; *C. trop., Candida tropicalis*; *C. uti., Candida utilis*; *C. lipo., Candida lipolytica*; *C. pseu., Candida pseudotropicalis*; *C. kru., Candida krusei*; *C. para., Candida parapsilosis*; *C. gla., Candida glabrata*; *C. fam., Candida famata*; *M. hie., Mucor hiemalis*; *A. fum., Aspergillus fumigatus*; *T. cut., Trichosporon cutaneum*; *R. ory., Rhizopus oryzae*.
[a] Itraconazole.

Table 2
Sensitivity of yeast strains according to the document M27-A3: Susceptible (S), dose dependent sensitive (SDD) and resistant (R).

Compound	*C. alb.*	*C. trop.*	*C. uti.*	*C. lipo.*	*C. pseu.*	*C. kru.*	*C. para.*	*C. gla.*	*C. fam.*
1	SDD	SDD	S	S	SDD	R	R	SDD	S
2	R	R	S	S	R	R	R	SDD	SDD
Standard[a]	S	SDD	SDD	S	S	SDD	S	S	S

[a] Itraconazole. Interpretive criteria: Breakpoints (MIC, μg/mL) = 0.12 [S], 0.25–0.5 [SDD], 1 [R].

some of the yeast strains tested. Moreover, AEC was employed as a synthetic strategy. These advances make the present study a breakthrough in the field of nucleoside chemistry. The preclinical study of these compounds show a good antifungal scope for *Candida* spp., representing new leads for further development of pharmacomodulator in this series.

4. Experimental

4.1. General

The reagents were purchased from Aldrich Chemical Co. and were used without further purification. Dichloromethane, pyridine, acetonitrile, and dimethylformamide were dried according to literature [30]. **Flash column chromatography**: SiO_2 *60* (230–400 mesh). **TLC**: Silica-gel plates (SiO_2; 0.20-mm thickness); visualization with UV light at 254 nm or by staining with base soln. of $CoCl_2/H_2SO_4$ ac. (2 g/100 mL H_2SO_4 10%) followed by heating ~140 °C. **m.p.**: *Fischer-Johns Scientific* melting point apparatus; uncorrected. **^{1}H and ^{13}C NMR spectra**: *Bruker Avance 300 MHz* and a *Varian 500 MHz*; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. **MS**: *Shimadzu GCMS-QP2010 Plus*; in *m*/*z* (rel.%).

4.1.1. (3aR,4S,5R,6aS)-4-((tert-butyldimethylsilyloxy)methyl)-2-oxo hexahydro-2H-cyclopenta[b]furan-5-yl biphenyl-4-carboxylate (3)

To a solution of Corey lactone-alcohol **2** (2.0 g, 6.98 mmol) in anhydrous dichloromethane (DCM, 15.0 mL) and anhydrous pyridine (Py, 5.0 mL) at room temperature under inert atmosphere was added *p*-phenylbenzoyl chloride (1.66 g, 7.68 mmol). The reaction mixture was stirred for 1 h, and then water (~70 mL) was added to the reaction mixture and washed with DCM (3 × 10 mL). In order to remove the excess Py, the organic layer was washed with $CuSO_4$ 5% sol. (5–8 × 20 mL until strong blue color of watery layer gradually turned to slightly blue color). The organic layer was dried with anhydrous Na_2SO_4 and the solvent was concentrated in *vacuo*. The crude product was purified by flash column chromatography to give the white solid **3** (2.94 g, 90%). m.p. 91–95 °C. R_f: 0.35 (Hex/EtOAc 8:2). ^{1}H NMR: (300 MHz, $CDCl_3$) δ = 8.06 (d, *J* = 8.4 Hz, 2 Ar—H), 7.64 (dd, *J* = 15.7, 7.7 Hz, 4 Ar—H), 7.49–7.33 (m, 3 Ar—H), 5.37 (dt, *J* = 5.8, 2.9 Hz, 1 H), 5.09 (t, *J* = 5.9 Hz, 1 H), 3.72 (qd, *J* = 10.2, 4.7 Hz, 2 H), 3.00–2.86 (m, 2 H), 2.65–2.42 (m, 2 H), 2.34 (d, *J* = 17.2 Hz, 2 H), 0.90 (s, 9 H), 0.07 (s, 6 H) ppm. ^{13}C NMR: (75 MHz, $CDCl_3$) δ = 176.86 (C═O), 165.86 (C═O), 145.84 (C), 139.92 (C), 130.14 (2 CH), 128.89 (2 CH), 128.52 (C), 128.12 (CH), 127.24 (2 CH), 127.12 (2 CH), 85.42 (CH), 78.78 (CH), 63.43 (CH_2), 55.16 (CH), 40.53 (CH), 39.07 (CH_2), 36.24 (CH_2), 25.84 (3 CH_3), 18.17 (C), −5.53 (2 CH_3) ppm. MS-EI$^+$ *m*/*z* (%): 409 [$C_{23}H_{25}O_5Si^•$] (20), 256 (100), 211 (69), 182 (76), 152 (90), 127 (23), 91 (20), 75 (43), 57 [C_4H_9] (20).

4.1.2. (3aR,4S,5R,6aS)-4-(hydroxymethyl)-2-oxohexahydro-2H-cyclopenta [b]furan-5-yl biphenyl-4-carboxylate (4)

To a solution of silyl ether **3** (2.0 g, 4.29 mmol) in methanol (18.0 mL) was added a catalytic amount of $AlCl_3{\cdot}6H_2O$ (0.05 g, 0.2 mmol). The reaction mixture was stirred at 60 °C for 12 h. The solvent was removed under reduced pressure. The crude product was purified by flash column chromatography affording a white solid **4** (1.4 g, 93%). m.p. 147–150 °C. R_f: 0.3 (Hex/EtOAc 2:8). ^{1}H NMR: (300 MHz, $CDCl_3$+$(CD_3)_2SO$) δ = 8.04 (d, *J* = 8.4 Hz, 2 Ar—H), 7.63 (dd, *J* = 14.3, 7.6 Hz, 4 Ar—H), 7.50–7.33 (m, 3 Ar—H), 5.43 (dt, *J* = 5.5, 2.7 Hz, 1 H), 5.10 (t, *J* = 5.7 Hz, 1 H), 4.55 (t, *J* = 5.1 Hz, 1 H), 3.60 (td, *J* = 5.4, 3.2 Hz, 2 H), 3.01–2.86 (m, 2 H), 2.65–2.38 (m, 2 H), 2.38–2.26 (m, 2 H) ppm. ^{13}C NMR: (75 MHz, $CDCl_3$+$(CD_3)_2SO$) δ = 177.00 (C═O), 165.53 (C═O), 145.43 (C), 139.52 (C), 129.99 (2 CH), 128.86 (2 CH), 128.56 (C), 128.11 (CH), 127.02 (2 CH), 126.85 (2 CH), 85.10 (CH), 78.47 (CH), 61.99 (CH_2), 55.26 (CH), 40.14 (CH), 38.44 (CH_2), 36.21 (CH_2), ppm. MS-EI$^+$ *m*/*z* (%): 353 [M^++1] (73), 200 (100), 183 (82), 180 (31), 151 (64), 125 (53), 79 (25), 41 (35).

4.1.3. (3aR,4R,5R,6aS)-4-(iodomethyl)-2-oxohexahydro-2H-cyclopenta [b]furan-5-yl biphenyl-4-carboxylate (5)

To a solution of alcohol **4** (2.0 g, 5.68 mmol), triphenylphosphine (3.72 g, 14.19 mmol), and imidazole (0.96 g, 14.19 mmol) in anhydrous acetonitrile (35.0 mL) was added I_2 (2.88 g, 11.35 mmol). The solution was stirred for 3 h at 80 °C under nitrogen atmosphere. After this time, the reaction mixture was added to brine (~150 mL) and washed with EtOAc (3 × 30 mL). The organic layer was dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The crude was purified by flash column chromatography to afford the white solid **5** (2.2 g, 85%). m.p. 142–145 °C. R_f: 0.4 (Hex/EtOAc 6:4). ^{1}H NMR: (300 MHz, $CDCl_3$) δ = 8.06 (d, *J* = 8.4 Hz, 2 Ar—H), 7.76–7.33 (m, 7 Ar—H), 5.33–5.23 (m, 1 H), 5.07 (td, *J* = 6.4, 1.8 Hz, 1 H), 3.36 (dd, *J* = 10.3, 5.2 Hz, 1 H), 3.22 (dd, *J* = 10.3, 7.7 Hz, 1 H), 2.95 (dd, *J* = 17.8, 10.1 Hz, 1 H), 2.87–2.76 (m, 1 H), 2.66–2.49 (m, 2 H), 2.46–2.27 (m, 2 H) ppm.

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 176.11 (C═O), 165.65 (C═O), 146.02 (C), 139.72 (C), 130.19 (2 CH), 128.90 (2 CH), 128.20 (CH), 127.99 (C), 127.21 (2 CH), 127.12 (2 CH), 83.71 (CH), 79.45 (CH), 54.05 (CH), 44.28 (CH), 37.86 (CH_2), 35.72 (CH_2), 7.03 (CH_2-I) ppm. MS-EI$^+$ *m/z* (%): 463 [M+1]$^+$ (78), 335 (21), 277 (74), 200 (76), 180 (100), 154 (77), 127 (41), 109 (40), 91 (89), 77 (87), 54 (73), 39 (56).

4.1.4. (3aR,4S,5R,6aS)-4-((4-acetyl-5-methyl-1H-1,2,3-triazol-1-yl) methyl)-2-oxohexahydro-2H-cyclopenta[b]furan-5-yl biphenyl-4-carboxylate (6a)

The alkyl halide **5** (1.0 g, 2.16 mmol) and sodium azide (0.16 g, 2.38 mmol) were added to anhydrous dimethylformamide (17.0 mL). The reaction mixture was stirred at 60 °C for 6 h under nitrogen atmosphere. After this time, TLC indicated the disappearance of the starting material. Then, acetylacetone (0.24 mL, 2.38 mmol) and DBU (0.36 mL, 2.38 mmol) were added to the reaction mixture which was stirred for 12 h at 60 °C. Brine (~100.0 mL) was added to the reaction mixture and washed with EtOAc (3 × 30 mL). The organic layer was dried (Na_2SO_4) and the solvent evaporated under reduced pressure. Flash column chromatography afforded the yellow solid **6a** (0.71 g, 72%). m.p. 56–60 °C. R_f: 0.4 (Hex/EtOAc 3:7). ^{1}H NMR: (300 MHz, $CDCl_3$) δ = 8.05–7.95 (m, 2 Ar—H), 7.72–7.56 (m, 4 Ar—H), 7.54–7.35 (m, 3 Ar—H), 5.32–5.20 (m, 1 H), 5.18–5.07 (m, 1 H), 4.55–4.30 (m, 2 H), 3.07–2.95 (m, 1 H), 2.93–2.78 (m, 1 H), 2.77–2.52 (m, 8 H), 2.45–2.21 (m, 2 H), 1.45–1.11 (m, 1 H), 0.97–0.82 (m, 1 H) ppm. ^{13}C NMR: (75 MHz, $CDCl_3$) δ = 194.03 (C═O), 175.66 (C═O), 165.69 (C═O), 146.27 (C), 143.67 (C), 139.61 (C), 136.81 (C), 130.11 (2 CH), 128.91 (2 CH), 128.26 (CH), 127.48 (C), 127.19 (2 CH), 127.15 (2 CH), 83.26 (CH), 77.13 (CH), 51.66 (CH_2), 48.57 (CH), 41.21 (CH), 37.68 (CH_2), 35.33 (CH_2), 27.58 (CH_3), 9.09 (Ar-CH_3) ppm. MS-EI$^+$ *m/z* (%): 459 [M$^+$], 181 (15), 149 (14), 91 (12), 71 (22), 57 (42), 48 (100), 41 (50).

4.1.5. (3aR,4S,5R,6aS)-4-((4-benzoyl-5-phenyl-1H-1,2,3-triazol-1-yl) methyl)-2-oxohexahydro-2H-cyclopenta[b]furan-5-yl biphenyl-4-carboxylate (6b)

The alkyl halide **5** (1.0 g, 2.16 mmol) and sodium azide (0.16 g, 2.38 mmol) were added to anhydrous dimethylformamide (17.0 mL). The reaction mixture was stirred at 60 °C for 6 h under nitrogen atmosphere. After this time, TLC indicated the disappearance of the starting material. Then, 2-benzoylacetophenone (0.54 g, 2.38 mmol) and DBU (0.36 mL, 2.38 mmol) were added to the reaction mixture which was stirred for 12 h at 60 °C. Brine (~100.0 mL) was added to the reaction mixture and washed with EtOAc (3 × 30 mL). The organic layer was dried (Na_2SO_4) and the solvent evaporated under reduced pressure. Flash column chromatography afforded the slightly yellow solid **6b** (0.84 g, 67%). m.p. 71–76 °C. R_f: 0.55 (Hex/EtOAc 3:7). ^{1}H NMR: (500 MHz, $CDCl_3$) δ = 8.24–8.22 (m, 1 Ar—H), 8.22–8.21 (m, 1 Ar—H), 7.93 (d, *J* = 2.0 Hz, 1 Ar—H), 7.91 (d, *J* = 2.0 Hz, 1 Ar—H), 7.65–7.64 (m, 1 Ar—H), 7.63–7.62 (m, 1 Ar—H), 7.61–7.59 (m, 1 Ar—H), 7.61–7.56 (m, 1 Ar—H), 7.58–7.55 (m, 1 Ar—H), 7.53–7.49 (m, 3 Ar—H), 7.50–7.45 (m, 2 Ar—H), 7.48–7.43 (m, 2 Ar—H), 7.46–7.39 (m, 3 Ar—H), 5.16–5.12 (m, 1 H), 5.01 (td, *J* = 6.5, 2.2 Hz, 1 H), 4.53 (dd, *J* = 14.1, 6.9 Hz, 1 H), 4.44 (dd, *J* = 14.2, 7.7 Hz, 1 H), 2.84–2.79 (m, 2 H), 2.63–2.52 (m, 2 H), 2.28–2.21 (m, 1 H), 2.19–2.13 (m, 1 H) ppm. ^{13}C NMR: (125 MHz, $CDCl_3$) δ = 186.10 (C═O), 175.55 (C═O), 165.50 (C═O), 146.22 (C), 143.82 (C), 141.93 (C), 139.71 (C), 136.83 (C), 133.14 (C), 130.61 (2 CH_2), 130.37 (CH), 130.15 (2 CH_2), 129.54 (2 CH_2), 129.16 (2 CH_2), 128.93 (2 CH_2), 128.28 (C), 128.25 (2 CH_2), 127.58 (CH), 127.27 (2 CH_2), 127.14 (2 CH_2), 125.90 (CH), 82.91 (CH), 77.21 (CH), 51.59 (CH_2), 49.21 (CH), 41.11 (CH), 37.61 (CH_2), 35.12 (CH_2) ppm.

*4.1.6. (3aR,4S,5R,6aS)-4-((4-acetyl-5-methyl-1H-1,2,3-triazol-1-yl) methyl)-5-hydroxyhexahydro-2H-cyclopenta[b]furan-2-one (**7a**)*

To a solution of ester **6a** (0.6 g, 1.31 mmol) in MeOH (5.0 mL) was added a catalytic amount of DBN (0.008 mL, 0.065 mmol). The reaction mixture was stirred at room temperature for 12 h. Then solvent was removed under reduced pressure. The crude was purified by flash column chromatography to give the thick yellow oil **7a** (0.32 g, 87%). **R_f**: 0.3 (Hex/EtOAc 5:95). **^{1}H NMR**: (500 MHz, $CDCl_3$) δ = 4.94 (td, *J* = 6.8, 3.1 Hz, 1 H), 4.42–4.29 (m, 2 H), 4.03 (q, *J* = 6.8 Hz, 1 H), 2.79–2.72 (m, 2 H), 2.69 (s, 3 H), 2.61 (s, 3 H), 2.51 (dt, *J* = 14.9, 6.8 Hz, 1 H), 2.30 (p, *J* = 7.0 Hz, 1 H), 2.26–2.17 (m, 2 H), 2.05 (ddd, *J* = 14.9, 6.8, 3.2 Hz, 1 H) ppm. **^{13}C NMR**: (125 MHz, $CDCl_3$) δ = 194.17 (C═O), 176.19 (C═O), 143.68 (C), 137.03 (C), 82.13 (CH), 74.36 (CH), 52.68 (CH_2), 48.08 (CH), 40.51 (CH_2), 40.34 (CH), 34.66 (CH_2), 27.72 (CH_3), 9.13 (CH_3) ppm. **MS-EI$^+$ *m/z* (%)**: 279 [M$^+$] (20), 167 (77), 148 (35), 127 (84), 112 (32), 85 (85), 70 (87), 55 (81), 41 (83).

4.1.7. (3aR,4S,5R,6aS)-4-((4-benzoyl-5-phenyl-1H-1,2,3-triazol-1-yl) methyl)-5-hydroxyhexahydro-2H-cyclopenta[b]furan-2-one (7b)

This compound was prepared from **6b** (0.7 g, 1.2 mmol) according to the synthetic procedure for **7a**. The crude was purified by flash column chromatography to afford the thick yellow oil **7b** (0.392 g, 81%). R_f: 0.35 (Hex/EtOAc 1:9). ^{1}H NMR: (500 MHz, $CDCl_3$) δ = 7.96–7.93 (m, 3 Ar—H), 7.69–7.66 (m, 1 Ar—H), 7.64–7.61 (m, 1 Ar—H), 7.50–7.42 (m, 5 Ar—H), 3.57–3.51 (m, 2 H), 3.48–3.41 (m, 3 H), 3.40–3.35 (m, 3 H), 2.63–2.57 (m, 2 H), 2.18 (s, 1 OH), 1.80–1.75 (m, 1 H) ppm. ^{13}C NMR: (125 MHz, $CDCl_3$) δ = 177.34 (C═O), 166.93 (C═O), 143.88 (C), 140.33 (C), 134.53 (C), 131.16 (2 CH), 128.84 (2 CH), 128.47 (2 CH), 127.60 (C), 127.20 (CH), 127.16 (CH), 127.07 (2 CH), 77.42 (CH), 77.22 (CH), 49.62 (CH_2), 45.00 (CH), 37.15 (CH), 35.31 (2 CH), 29.96 (CH_2) ppm. MS-EI$^+$ *m/z* (%): 351 [$C_{19}H_{17}N_3O_4^{\cdot}$] (38), 52 [$C_4H_4^{\cdot}$] (14), 183 [$C_8H_4N_2O^{\cdot}$] (72), 276 (80), 246 (22), 199 (90), 152 (88), 127 (100), 99 (60), 69 (80), 55 (97).

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bioorg.2016.09.003.

References

[1] (a)P. Merino (Ed.), Chemical Synthesis of Nucleoside Analogues, John Wiley & Sons, Inc, Hoboken, NJ, USA, 2013, http://dx.doi.org/10.1002/9781118498088;
(b)L.H. Zhang, Z. Xi, J. Chattopadhyaya (Eds.), Medicinal Chemistry of Nucleic Acids, John Wiley & Sons, Inc, Hoboken, NJ, USA, 2011, http://dx.doi.org/10.1002/9781118092804;
(c) C. Simons, Nucleoside Mimetics: Their Chemistry and Biological Properties, Taylor & Francis Ltd, 2000. ISBN-13: 9789056993245.;
(d)C.K. Chu (Ed.), Recent Advances in Nucleosides: Chemistry and Chemotherapy, Elsevier Science B.V., 2002. ISBN: 978-0-444-50951-2.
[2] (a) U. Pradere, E.C. Garnier-Amblard, S.J. Coats, F. Amblard, R.F. Schinazi, Chem. Rev. 114 (2014) 9154–9218;
(b) P. Clivio, S. Coantic-Castex, D. Guillaume, Chem. Rev. 113 (2013) 7354–7401;
(c) T. Pathak, Chem. Rev. 102 (2002) 1623–1667;
(d) A. Mieczkowski, V. Roy, L.A. Agrofoglio, Chem. Rev. 110 (2010) 1828–1856;
(e) J. Štambaský, M. Hocek, P. Kočovský, Chem. Rev. 109 (2009) 6729–6764;

(f) L.A. Agrofoglio, I. Gillaizeau, Y. Saito, Chem. Rev. 103 (2003) 1875–1916;
(g) J.S. Cooperwood, G. Gumina, F.D. Boudinot, C.K. Chu, Nucleoside and nucleotide prodrugs, in: C.K. Chu (Ed.), Recent Advances in Nucleosides: Chemistry and Chemotherapy, Elsevier Science B.V, 2002, http://dx.doi.org/10.1016/B978-044450951-2/50005-9.

[3] (a) E.S. Matyugina, A.L. Khandazhinskaya, Russ. Chem. Bull. Int. Ed. 63 (2014) 1069–1080;
(b) O. Boutureira, M.I. Matheu, Y. Díaz, S. Castillón, Chem. Soc. Rev. 42 (2013) 5056–5072;
(c) E. Leclerc, Chemical synthesis of carbocyclic analogues of nucleosides, in: P. Merino (Ed.), Chemical Synthesis of Nucleoside Analogues, John Wiley & Sons Inc, Hoboken, NJ, USA, 2013, http://dx.doi.org/10.1002/9781118498088.ch12;
(d) J. Wang, R.K. Rawal, C.K. Chu, Recent advances in carbocyclic nucleosides: synthesis and biological activity, in: L.H. Zhang, Z. Xi, J. Chattopadhyaya (Eds.), Medicinal Chemistry of Nucleic Acids, John Wiley & Sons Inc, Hoboken, NJ, USA, 2011, http://dx.doi.org/10.1002/9781118092804.ch1;
(d) S.W. Wang, K.L. Seley, V.R. Hegde, V.P. Rajappan, 5′-Norcarbanucleosides in L-like configurations, in: C.K. Chu (Ed.), Recent Advances in Nucleosides: Chemistry and Chemotherapy., Elsevier Science B.V., 2002, http://dx.doi.org/10.1016/B978-044450951-2/50009-6;
(f) M. Ferrero, V. Gotor, Chem. Rev. 100 (2000) 4319–4347.

[4] (a) F. de Carvalho da Silva, M.F. do Carmo Cardoso, P. Garcia-Ferreira, V.F. Ferreira, Biological Properties of 1*H*–1,2,3- and 2*H*–1,2,3-Triazoles, in: W. Dehaen, V.A. Bakulev (Eds.), Chemistry of 1,2,3-Triazoles, Springer International Publishing, Switzerland, 2015, http://dx.doi.org/10.1007/7081_2014_124;
(b) A. Massarotti, S. Aprile, V. Mercalli, E. Del Grosso, G. Grosa, G. Sorba, G.C. Tron, ChemMedChem 9 (2014) 2497–2508;
(c) S.G. Agalave, S.R. Maujan, V.S. Pore, Chem. Asian J. 6 (2011) 2696–2718;
(d) A. Lauria, R. Delisi, F. Mingoia, A. Terenzi, A. Martorana, G. Barone, A.M. Almerico, Eur. J. Org. Chem. (2014) 3289–3306;
(e) P. Thirumurugan, D. Matosiuk, K. Jozwiak, Chem. Rev. 113 (2013) 4905–4979;
(f) J.F. Lutz, Z. Zarafshani, Adv. Drug Deliv. Rev. 60 (2008) 958–970.

[5] (a) F. Amblard, J.H. Cho, R.F. Schinazi, Chem. Rev. 109 (2009) 4207–4220;
(b) W. Zou, M. Bhasin, K. Vembaiyan, D.T. Williams, Carbohydrate Res. 344 (2009) 1024–1027;
(c) V. Aragao-Leoneti, V.L. Campo, A.S. Gomes, R.A. Field, I. Carvalho, Tetrahedron 66 (2010) 9475–9492.

[6] (a) L. Kiss, E. Forró, R. Sillanpää, F. Fülöp, Tetrahedron 66 (2010) 3599–3607;
(b) N. Joubert, R.F. Schinazi, L.A. Agrofoglio, Tetrahedron 61 (2005) 11744–11750;
(c) J.H. Cho, D.L. Bernard, R.W. Sidwell, E.R. Kern, C.K. Chu, J. Med. Chem. 49 (2006) 1140–1148;
(d) I. Pérez-Castro, O. Caamaño, F. Fernández, M.D. García, C. López, E. De Clercq, Org. Biomol. Chem. 5 (2007) 3805–3813;
(e) Y. Saito, V. Escuret, D. Durantel, F. Zoulim, R.F. Schinazi, L.A. Agrofoglio, Bioorg. Med. Chem. 11 (2003) 3633–3639.

[7] (a) U. Chiacchio, M.G. Saita, L. Crispino, G. Gumina, S. Mangiafico, V. Pistarà, G. Romeo, A. Piperno, E. De Clercq, Tetrahedron 62 (2006) 1171–1181;
(b) C.L. Scremin, J.H. Boal, A. Wilk, L.R. Phillips, S.L. Beaucage, Bioorg. Med. Chem. Lett. 6 (1996) 207–212;
(c) J.H. Boal, A. Wilk, C.L. Scremin, G.N. Gray, L.R. Phillips, S.L. Beaucage, J. Org. Chem. 61 (1996) 8617–8626;
(d) N. Hossain, N. Blaton, O. Peeters, J. Rozenski, P.A. Herdewijn, Tetrahedron 52 (1996) 5563–5578;
(e) M.W. Winkley, Carbohydrate Res. 31 (1973) 245–254.

[8] (a) V.P. Rajappan, X. Yin, S.W. Schneller, Tetrahedron 58 (2002) 9889–9895;
(b) F. Abad, F. Álvarez, F. Fernández, X. García-Mera, J.E. Rodríguez-Borges, Nucleos. Nucleot. Nucleic Acids 20 (2001) 1127–1128;
(c) U. Dhuppad, V. Aravat, S. Navhat, A. Thomas, S. Kadam, (Glenmark Pharmaceuticals S.A., Switzerland). Pharmaceutical Containing Melogliptin Dipeptidyl Peptidase-IV Inhibitor. U.S. Pat. Appl. Publ. 2010, US 2010-683696; US 20100173964 A1, July 8, 2010; SciFinder Scholar: AN 2010:85194.

[9] C. Lamberth, Org. Prep. Proc. Int. 34 (2002) 149–167.

[10] (a) A. Kayet, D. Datta, G. Kumar, A. Sundar, A.S. Ghosh, T. Pathak, RSC Adv. 4 (2014) 63036–63038;
(b) A. Kayet, T. Pathak, J. Org. Chem. 78 (2013) 9865–9875;
(c) B. Bhatt, R.J. Thompson, M. von Itsztein, Tetrahedron Lett. 52 (2011) 2741–2743;
(d) R.P. Tripathi, A.K. Yadav, A. Ajay, S.S. Bisht, V. Chaturvedi, S.K. Sinha, Eur. J. Med. Chem. 45 (2010) 142–148;
(e) R.V. Somu, H. Boshoff, C. Qiao, E.M. Bennett, C.E. Barry III, C.C. Aldrich, J. Med. Chem. 49 (2006) 31–34;
(f) A. Goeminne, M. McNaughton, G. Bal, G. Surpateanu, P. Van der Veken, S. De Prol, W. Versées, J. Steyaert, S. Apers, A. Haemers, K. Augustyns, Bioorg. Med. Chem. Lett. 17 (2007) 2523–2526;
(g) P. Norris, D. Horton, B.R. Levine, Heterocycles 43 (1996) 2643–2655;
(h) N. Singh, S.K. Pandey, R.P. Tripathi, Carbohydrate Res. (2010) 1641–1648;
(i) D.R. da Rocha, W.C. Santos, E.S. Lima, V.F. Ferreira, Carbohydrate Res. 350 (2012) 14–19;
(j) T.M. Potewar, K.T. Petrova, M.T. Barros, Carbohydrate Res. 379 (2013) 60–67.

[11] (a) S. Hanessian, S. Marcotte, R. Machaalani, G. Huang, Org. Lett. 5 (2003) 4277–4280;
. For a complete Review about synthetic bicyclic nucleosides see:(b) J. Lebreton, J.M. Escudier, L. Arzel, C. Len, Chem. Rev. 110 (2010) 3371–3418.

[12] (a) K. Sakata, A. Bakurai, S. Tamura, Agric. Biol. Chem. 37 (1973) 697–699;
(b) K. Sakata, A. Sakurai, S. Tamura, Agric. Biol. Chem. 39 (1975) 885–892.

[13] K. Isono, P.F. Crain, J.A. McCloskey, J. Am. Chem. Soc. 97 (1975) 943–945.

[14] (a) S. Hanessian, G. Huang, C. Chenel, R. Machaalani, O. Loiseleur, J. Org. Chem. 70 (2005) 6721–6734;
(b) A. Datta, Synthetic studies on antifungal peptidyl nucleoside antibiotics, in: P. Merino (Ed.), Chemical Synthesis of Nucleoside Analogues, John Wiley & Sons Inc, Hoboken, NJ, USA, 2013, http://dx.doi.org/10.1002/9781118498088.ch18.

[15] (a) D.C. Pryde, D.S. Middleton, P.T. Stephenson, P. Wainwright, A. Maddaford, X. Zhang, D. Leese, R. Glen, J. Hart, N. Forrest, T. Guyot, Tetrahedron Lett. 52 (2011) 6415–6419;
(b) M.J. Comin, D.A. Parrish, J.R. Deschamps, V.E. Marquez, Org. Lett. 8 (2006) 705–708;
(c) B. Richichi, S. Cicchi, U. Chiacchio, G. Romeo, A. Brandi, Tetrahedron 59 (2003) 5231–5240.

[16] N.R. Swamy, N. Suryakiran, P.P. Naidu, Y. Venkateswarlu, Carbohydrate Res. 352 (2012) 191–196.

[17] (a) A. Santana, J.M.G. Molinillo, F.A. Macías, Eur. J. Org. Chem. (2015) 2093–2110;
(b) B.M. Fraga, Nat. Prod. Rep. 29 (2012) 1334–1366.

[18] M.I. Choudhary, S.G. Musharraf, A. Sami, Atta-ur-Rahman, Helv. Chim. Acta 87 (2004) 2685–2694.

[19] M. Kassou, S. Castillón, J. Org. Chem. 62 (1997) 3696–3701.

[20] M. Ikbal, C. Cerceau, F. Le Goffic, S. Sicsic, Eur. J. Med. Chem. 24 (1989) 415–420.

[21] L.V.R. Reddy, P.V. Reddy, N.N. Mishra, P.K. Shukla, G. Yadav, R. Srivastava, A.K. Shaw, Carbohydr. Res. 345 (2010) 1515–1521.

[22] (a) C.S. Stauffer, A.W. Fothergill, M.G. Rinaldi, A. Dutta, Future Med. Chem. 1 (2009) 379–389;
(b) X. Yin, G. Zhao, S.W. Schneller, Tetrahedron Lett. 48 (2007) 4809–4811;
(c) C.S. Stauffer, P. Bhaket, A.W. Fothergill, M.G. Rinaldi, A. Datta, J. Org. Chem. 72 (2007) 9991–9997;
(d) M. Winn, R.J.M. Goss, K. Kimura, T.D.H. Bugg, Nat. Prod. Rep. 27 (2010) 279–304;
(e) R. Srivastava, A. Bhargava, R.K. Singh, Bioorg. Med. Chem. Lett. 17 (2007) 6239–6244;
(f) C.S. Stauffer, A. Datta, J. Org. Chem. 73 (2008) 4166–4174.

[23] (a) C.G.S. Lima, A. Ali, S.S. van Berkel, B. Westermann, M.W. Paixão, Chem. Commun. 51 (2015) 10784–10796;
(b) J. John, J. Thomas, W. Dehaen, Chem. Commun. 51 (2015) 10797–10806;
(c) S.S.V. Ramasastry, Angew. Chem. Int. Ed. 53 (2014) 14310–14312.

[24] C.A. González-González, A. Fuentes-Benítes, E. Cuevas-Yañez, D. Corona-Becerril, C. González-Romero, D. González-Calderón, Tetrahedron Lett. 54 (2013) 2726–2728.

[25] D. González-Calderón, L.J. Benitez-Puebla, C.A. González-González, M.E. García-Eleno, A. Fuentes-Benítes, E. Cuevas-Yañez, D. Corona-Becerril, C. González-Romero, Synth. Commun. 44 (2014) 1258–1265.

[26] P.J. Garegg, B.J.C.S. Samuelsson, J. Chem. Soc., Chem. Commun. (1979) 978–980.

[27] D. González-Calderón, J.G. Aguirre-De Paz, C.A. González-González, A. Fuentes-Benítes, C. González-Romero, Tetrahedron Lett. 56 (2015) 1713–1715.

[28] (a) National Committee for Clinical Laboratory Standards Institute (CLSI), Document M38-A2: Reference Method for Broth Dilution Antifungal Susceptibility Testing of Filamentous Fungi, Approved Standarde, Second Edition, Clinical and Laboratory Standards Institute, Wayne, PA, 2002.;
(b) A.L. Barry, An overview of the Clinical and Laboratory Standards Institute (CLSI) and its impact on antimicrobial susceptibility tests, in: R. Schwalbe, L. Steele-Moore, A.C. Goodwin (Eds.), Antimicrobial Susceptibility Testing Protocols, CRC Press Taylor & Francis Group, Florida, 2007, pp. 1–6.. ISBN: 9780824741006 pp. 209-241;
(c) A. Espinel-Ingroff, E. Canton, Antifungal susceptibility testing of filamentous fungi, in: R. Schwalbe, L. Steele-Moore, A.C. Goodwin (Eds.), Antimicrobial Susceptibility Testing Protocols, CRC Press Taylor & Francis Group, Florida, 2007 (9780824741006).

[29] (a) National Committee for Clinical and Laboratory Standards Institute (CLSI), M27–A3: Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts, Approved Standard, third ed., Clinical and Laboratory Standards Institute, Wayne, PA, 2008. pp. 173–208, ISBN: 1-56238-666-2.;
(b) A. Espinel-Ingroff, E. Canton, Antifungal susceptibility testing of yeasts, in: R. Schwalbe, L. Steele-Moore, A.C. Goodwin (Eds.), Antimicrobial Susceptibility Testing Protocols, CRC Press Taylor & Francis Group, Florida, 2007 (9780824741006);
(c) A.W. Fothergill, Antifungal susceptibility testing: Clinical Laboratory and Standards Institute (CLSI) methods, in: G.S. Hall (Ed.), Interactions of Yeasts, Moulds, and Antifungal Agents. How to Detect Resistance, Springer Science-Business Media, 2012, pp. 65–74, http://dx.doi.org/10.1007/978-1-59745-134-5_2.

[30] W.L.F. Armarego, C. Chai, Purification of Laboratory Chemicals, seventh ed., Elsevier, Oxford, UK, 2013. ISBN-13: 978-0123821614.

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Short communication

Azide-enolate 1,3-dipolar cycloaddition in the synthesis of novel triazole-based miconazole analogues as promising antifungal agents

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ABSTRACT

Seven miconazole analogs involving 1,4,5-tri and 1,5-disubstituted triazole moieties were synthesized by azide-enolate 1,3-dipolar cycloaddition. The antifungal activity of these compounds was evaluated *in vitro* against four filamentous fungi, including *Aspergillus fumigatus*, *Trichosporon cutaneum*, *Rhizopus oryzae*, and *Mucor hiemalis* as well as three species of *Candida* spp. as yeast specimens. These pre-clinical studies suggest that compounds **4b**, **4d** and **7b** can be considered as drug candidates for future complementary biological studies due to their good/excellent antifungal activities.

1. Introduction

Miconazole is an azole-type drug with a broad spectrum of antifungal activity [1]. Due to the development of fungal resistance to this drug [2], the medicinal chemistry of anti-fungal agents has become an important field of study in organic synthesis [3]. To design new agents free of antibiotic resistance, the modification of functional groups in lead molecules has been an efficient strategy [4].

The triazole ring system, is a very well-recognized pharmacophore [5], this nitrogen heterocycle is prominent among U.S. FDA approved pharmaceuticals [6]. In particular, the 1,2,3-triazole core has been an increasingly important heterocycle with successful application in medicinal chemistry [7]. There are reports in literature about the biological activity of 1,2,3-triazole derivatives against cancer [8], malaria [9], tuberculosis [10], trypanosomiasis [11], leishmaniasis [12], HIV [13], influenza [14], dengue [15], pain (analgesic) [16], epilepsy [17], obesity [18], inflammation [19] and bacterial infection [20]. On the other hand, the study of 1,2,3-triazole scaffolds for the synthesis of antifungals [21], and particularly for miconazole analogs [22] has represented an ongoing and promising field of research in the last few years.

Cu-catalyzed azide-alkyne cycloaddition (CuAAC) represents the conventional method for obtaining 1,2,3-triazole moieties [23]. In recent years, azide-enolate 1,3-dipolar cycloaddition has emerged as a novel and potent tool for the synthetic approach to these valuable heterocycles [24]. Its application in medicinal chemistry has already been demonstrated [25].

We previously reported the antifungal activity of *benzyloxy* derivatives of miconazole [26]. As part of our ongoing research, we herein describe the synthesis/evaluation of *triazolic* analogs (1,4,5- and 1,5-substituted derivatives) that maintain the 1-(2-phenylethyl)imidazole core responsible for the biological activity of this compound [27] (Fig. 1).

2. Chemistry

From 2,4-dichlorobenzaldehyde **1** [Eq. (1)], the 1-(2,4-

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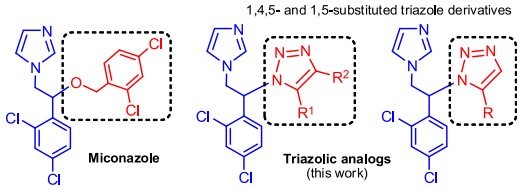
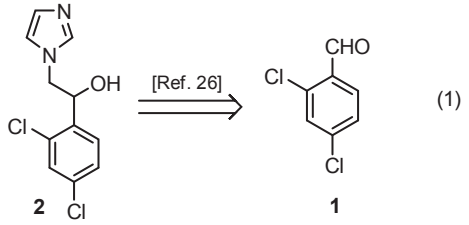
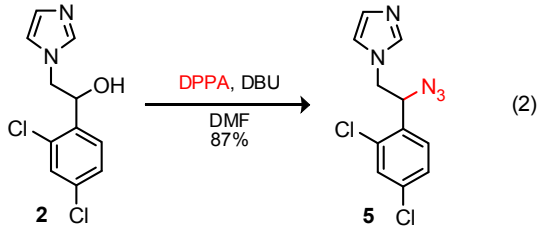


Fig. 1. Proposed triazolic analogs of miconazole.

dichlorophenyl)-2-(1*H*-imidazol-1-yl)ethanol **2** (key precursor) was obtained in two steps according to our previous report [26]. Previously we published a novel method for preparing 1,4,5-trisubstituted 1,2,3-triazoles from benzylic alcohols *via* an azide-enolate 1,3-dipolar cycloaddition [28]. For this purpose we used diphenylphosphoryl azide (DPPA) as an azidating agent, followed by an efficient cycloaddition in the presence of active ketones. Miconazole analogs **4a**–**d** (1,4,5-trisubstituted derivatives) were synthesized in good yields (Table 1) by coupling acetylacetone **3a**, 2-benzoylacetophenone **3b**, benzoylacetonitrile **3c** and 1-(phenylsulfonyl)heptan-2-one **3d** under the aforementioned protocol.



Recently [29] we reported a novel method for obtaining 1,5-disubstituted triazoles from azides by coupling them with β-keto-phosphonates. Therefore, we decided to begin with the synthesis of benzyl azide **5** [Eq. (2)] as a precursor. The azidation of benzyl alcohol **2** was achieved using DPPA and DBU in dry DMF with good yields [30]. The synthesis of alkyl (**7a** and **7b**) and aryl (**7c**) 1,5-disubstituted triazole derivatives was carried out *via* an azide-enolate 1,3-dipolar cycloaddition (Table 2).



An outstanding aspects for compounds **7a**–**c** is a singlet signal in the range δ 7.6–7.4 ppm (^{1}H NMR spectra) attributable to the triazolic hydrogen [Eq. (3)]. Likewise, for all final compounds, the hydrogens H^a, H^b and H^c on the imidazole moiety can be observed in the ranges δ 7.7–7.4, 7.0–6.9 and 6.9–6.6 ppm respectively.

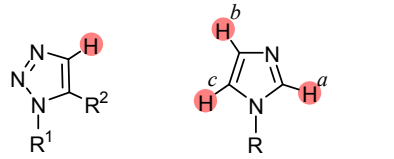
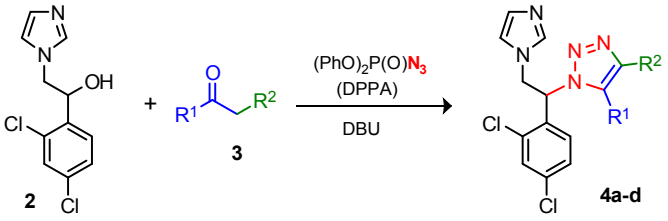


Table 1
Synthesis of 1,4,5-trisubstituted 1,2,3-triazole **4a**–**d** (miconazole analogs) from alcohol 2 by coupling with active ketones 3.



Entry[a]	Ketone	Triazole[b] (Yield%)[c]
1	**3a**: R^1 = CH_3, R^2 = $COCH_3$	**4a** (75%)
2	**3b**: R^1 = Ph, R^2 = COPh	**4b** (67%)
3	**3c**: R^1 = Ph, R^2 = CN	**4c** (63%)
4	**3d**: R^1 = $CH_3(CH_2)_4$–, R^2 = SO_2Ph	**4d** (78%)

[a] *Reaction conditions*: A mixture of compound **2** (1.0 eq), DPPA (1.1 eq), and DBU (2.0 eq) in DMF was stirred at r.t. for 3 h. Then **3** (1.0 eq) was added and the reaction continued at 60 °C for 3 h.
[b] Confirmed by ^{1}H NMR, ^{13}C NMR, and MS.
[c] Yields refer to chromatographically pure isolated compounds.

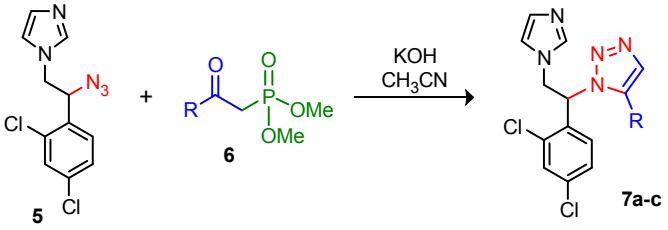
3. Microbiology

Compounds **4a-d** and **7a-c** were evaluated for their *in vitro* antifungal activity against four filamentous fungi (*Aspergillus fumigatus* ATCC-16907, *Trichosporon cutaneum* ATCC-28592, *Rhizopus oryzae* ATCC-10329 and *Mucor hiemalis* ATCC-8690) as well as three yeast specimens (*Candida utilis* ATCC-9226, *Candida albicans* ATCC-10231 and *Candida tropicalis* ATCC-13803).

CLSI standardized methods were adopted to carry out the microbiological tests. The M38-A microdilution method [31] was used to determine the sensitivity of filamentous fungi, and the M27-A3 method [32] for *Candida* yeasts.

The antifungal activity of compounds **4a**–**d** and **7a**–**c** was compared with itraconazole, a standard antifungal drug. The minimum inhibitory concentration (MIC) values of the compounds and standard drugs, expressed in micrograms per millilitre, were determined in 96-well plates by using RPMI 1640 medium buffered with MOPS (3-[N-morpholino]propane sulfonic acid; Sigma-Aldrich).

Table 2
Synthesis of 1,5-disubstituted 1,2,3-triazole **7a**–**c** (miconazole analogs) from azide 5 by coupling with β-ketophosphonates 6.



Entry[a]	Ketone	Triazole[b] (Yield%)[c]
1	**6a**: R = cyclohexyl	**7a** (64%)
2	**6b**: R = $CH_3(CH_2)_3C(CH_3)_2$–	**7b** (70%)
3	**6c**: R = *p*-(CH_3S)phenyl	**7c** (72%)

[a] *Reaction conditions*: A mixture of compound **5** (1.0 eq), **6** (1.0 eq), and KOH (3.0 eq), in CH_3CN was stirred at 60 °C for 5 h.
[b] Confirmed by ^{1}H NMR, ^{13}C NMR, and MS.
[c] Yields refer to chromatographically pure isolated compounds.

Table 3
In vitro antifungal activities of synthetized compounds (MIC, μg/mL).

Compound	Yeast fungi			Filamentous fungi			
	C. uti.	*C. alb.*	*C. trop.*	*A. fum.*	*T. cut.*	*R. ory.*	*M. hie*
4a	16	16	16	16	16	8	16
4b	16	0.03	0.06	16	16	8	16
4c	16	16	16	16	16	16	16
4d	0.25	0.06	0.06	2	0.12	0.5	0.25
7a	16	16	8	16	16	2	0.12
7b	2	0.03	0.03	0.5	8	8	16
7c	16	4	1	16	16	16	16
Standard[a]	0.06	0.03	0.03	0.25	1	0.5	1

Abbreviations: *C. uti., Candida utilis; C. alb., Candida albicans; C. trop., Candida tropicalis; A. fum., Aspergillus fumigatus; T. cut., Trichosporon cutaneum; R. ory., Rhizopus oryzae; M. hie., Mucor hiemalis.*
[a] Itraconazole.

Table 4
Determination of the sensitivity of yeast (according to document M27-A3): Susceptible (S), dose-dependent sensitive (SDD) and resistant (R).

Compound	*C. uti.*	*C. alb.*	*C. trop.*
4a	R	R	R
4b	R	S	S
4c	R	R	R
4d	SDD	S	S
7a	R	R	R
7b	R	S	S
7c	R	R	SDD
Standard[a]	S	S	S

[a] Itraconazole. Interpretive criteria: Breakpoints (MIC, μg/mL) = 0.12 [S], 0.25–0.5 [SDD], 1 [R].

4. Results and discussion

The antifungal activity of the evaluated compounds is summarized in Table 3. Compounds **4b**, **4d** and **7b** showed good activity against *C. albicans* and *C. tropicalis* (MIC 0.03–0.06 μg/mL) as compared to itraconazole (MIC 0.03 μg/mL). Such compounds proved to be 'sensitive'[1] according to the sensitivity parameters of document M27-A3 (Table 4). On the other hand, the antifungal screening of compound **4d** showed that it was either better than or comparable to itraconazole against filamentous fungi *T. cutaneum, R. oryzae,* and *M. hiemalis* (MIC 0.12 versus 1.0, 0.5 versus 0.5, and 0.25 versus 1.0 μg/mL respectively). Compound **7b** demonstrated moderate growth inhibition of *A. fumigatus* (MIC 0.5 μg/mL) compared with the standard drug (MIC 0.25 μg/mL). In contrast with the results observed for an aryl substituent, these outcomes clearly indicate that an alkyl group in the 5-substituted triazole promotes the biological activity of this type of compound. Additionally, substituent probably allows for a better interaction with the 14-α-demethylase ($P450_{14DM}$, CYP51) enzyme [33], leading to its selective inhibition and therefore the growth inhibition of the fungal cell.

5. Conclusion

In summary, azide-enolate 1,3-dipolar cycloaddition allowed for the synthesis of seven miconazole analogs with 1,4,5-tri and 1,5-disubstituted triazole moieties. The pre-clinical studies showed that compounds **4b**, **4d** and **7b** have a good scope against *C. albicans* and *C. tropicalis*. A broader spectrum of **4d** against filamentous fungi (*T. cutaneum, R. oryzae,* and *M. hiemalis*) has been demonstrated. Due to their good/excellent activity, these miconazole analogs can be considered as drug candidates for future complementary biological studies.

6. Experimental section

6.1. General

Flash column chromatography: SiO_2 60 (230–400 mesh). *TLC*: Silica-gel plates (SiO_2; 0.20-mm thickness); visualization with UV light at 254 nm *m.p.*: Fischer-Johns Scientific melting point apparatus; uncorrected. ^1H and ^{13}C-NMR spectra: Bruker Avance 300 MHz and Varian 500 MHz; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. *MS*: Shimadzu GCMS-QP2010 Plus; in *m*/*z* (rel. %).

6.2. Experimental procedures

6.2.1. 1-(1-(1-(2,4-Dichlorophenyl)-2-(1H-imidazol-1-yl)ethyl)-5-methyl-1H-1,2,3-triazol-4-yl)ethanone **4a**

To a cold solution (0 °C) of benzylic alcohol **2** (0.35 g, 1.36 mmol) and diphenylphosphoryl azide (0.32 mL, 1.5 mmol) in anhydrous DMF (3.5 mL) was added DBU (0.4 mL, 2.72 mmol). The solution was stirred for 15 min at 0 °C under nitrogen atmosphere, and then brought to room temperature with continuous stirring for 3 h. At this time, TLC indicated the disappearance of the starting material. Acetylacetone **3a**, (0.14 mL, 1.36 mmol) was then added to the reaction mixture, which was stirred for 3 h at 60–70 °C. Brine (~40 mL) was added and then the reaction mixture was washed with EtOAc (3 × 10 mL). The organic layer was dried (Na_2SO_4) and the solvent evaporated under reduced pressure. The crude extract was purified by flash column chromatography, eluting with DCM/MeOH 95/5 to afford the thick yellow oil **4a** (0.37 g, 75%). R_f: 0.3 (DCM/MeOH 95/5). ^1H NMR: (500 MHz, $CDCl_3$) δ = 7.51 (d, *J* = 1.7 Hz, 1Im-H), 7.33–7.26 (m, 3Ar–H), 7.01 (s, 1Im–H), 6.86 (s, 1Im–H), 6.03 (dd, *J* = 9.9, 4.0 Hz, 1H), 5.25 (dd, *J* = 14.7, 10.0 Hz, 1H), 4.62 (dd, *J* = 14.7, 3.9 Hz, 1H), 2.69 (s, 3H), 2.31 (s, 3H) ppm. ^{13}C NMR: (125 MHz, $CDCl_3$) δ = 193.91 (C=O), 143.86 (C), 137.94 (C–Cl), 136.42 (C), 133.09 (C), 131.03 (CH), 130.91 (C–Cl), 130.20 (CH), 129.94 (CH), 129.18 (CH), 128.78 (CH), 128.72 (CH), 59.52 (CH), 49.25 (CH_2), 27.77 (CH_3), 8.56 (Ar–CH_3) ppm. MS-EI$^+$ *m*/*z* (%): 364 [M^++1], 212 (100), 203 (45), 149 (63), 81 (20), 57 (19), 43 (83).

6.2.2. (1-(1-(2,4-Dichlorophenyl)-2-(1H-imidazol-1-yl)ethyl)-5-phenyl-1H-1,2,3-triazol-4-yl)(phenyl)methanone **4b**

Following the synthetic procedure for **4a**, compound **2** (0.35 g, 1.36 mmol) and **3b** (0.305 g, 1.36 mmol) were coupled in the presence of diphenylphosphoryl azide (0.32 mL, 1.5 mmol) and DBU (0.4 mL, 2.72 mmol). The crude extract was purified by flash column chromatography, eluting with DCM/MeOH 95/5 to afford the thick yellow oil **4b** (0.445 g, 67%). R_f: 0.35 (DCM/MeOH 95/5). ^1H NMR: (500 MHz, $CDCl_3$) δ = 8.28–8.20 (m, 2Ar–H), 7.73 (d, *J* = 8.5 Hz, 1Im–H), 7.64–7.56 (m, 1Ar–H), 7.53–7.32 (m, 8Ar–H), 7.01 (s, 1Im–H), 6.87–6.80 (m, 2Ar–H), 6.71 (s, 1Im–H), 5.98 (dd, *J* = 10.6, 3.7 Hz, 1H), 5.18 (dd, *J* = 14.6, 10.6 Hz, 1H), 4.48 (dd, *J* = 14.6, 3.8 Hz, 1H) ppm. ^{13}C NMR: (125 MHz, $CDCl_3$) δ = 185.81 (C=O), 143.73 (C), 143.37 (C–Cl), 137.31 (C), 136.77 (C), 136.23 (C), 133.23 (C), 132.93 (C–Cl), 131.34 (CH), 130.57 (2CH), 130.40 (CH), 130.13 (C), 129.89 (CH), 129.59 (CH), 129.57 (CH), 129.39 (CH), 129.35 (2CH), 128.92 (2CH), 128.58 (CH), 128.28 (2CH), 60.02 (CH), 49.84 (CH_2) ppm. MS-EI$^+$ *m*/*z* (%): 487 [M^+], 105 [$C_7H_5O^\bullet$] (100), 84 (25), 77 [$C_6H_5^\bullet$] (61), 43 (47).

[1] 'S', 'SDD' and 'R' are represented by standardized values (breakpoints) used to appreciate the clinical value of the *in vitro* antifungal testing result and predicting the response of patients infected. Sensitivity is dependent on achieving the maximum dosages in plasma (breakpoints) to obtain optimal response. For itraconazole, an MIC within the susceptible-dose dependent (SDD) range indicates the need for plasma concentrations 0.25–0.5 μg/mL for an optimal response. Actual breakpoints are described in Table 4 (See Ref. [32b]).

*6.2.3. 1-(1-(2,4-Dichlorophenyl)-2-(1H-imidazol-1-yl)ethyl)-5-phenyl-1H-1,2,3-triazole-4-carbonitrile **4c***

Following the synthetic procedure for **4a**, compound **2** (0.35 g, 1.36 mmol) and **3c** (0.197 g, 1.36 mmol) were coupled in the presence of diphenylphosphoryl azide (0.32 mL, 1.5 mmol) and DBU (0.4 mL, 2.72 mmol). The crude extract was purified by flash column chromatography, eluting with DCM/MeOH 95/5 to afford the thick yellow oil **4c** (0.35 g, 63%). R_f: 0.3 (DCM/MeOH 95/5). ^{1}H NMR: (500 MHz, $CDCl_3$) δ = 7.68 (d, J = 8.5 Hz, 1Ar–H), 7.59–7.55 (m, 1Ar–H), 7.52–7.47 (m, 3Ar–H), 7.39 (dd, J = 8.5, 2.1 Hz, 1Ar–H), 7.34 (s, 1Ar–H), 7.01 (s, 1Ar–H), 6.95–6.90 (m, 2Ar–H), 6.64 (s, 1Ar–H), 6.07 (dd, J = 10.5, 3.7 Hz, 1H), 5.13 (dd, J = 14.7, 10.5 Hz, 1H), 4.52 (dd, J = 14.7, 3.8 Hz, 1H) ppm. ^{13}C NMR: (125 MHz, $CDCl_3$) δ = 145.35 (C), 136.76 (C–Cl), 132.92 (C), 131.73 (CH), 130.57 (C), 130.23 (C–Cl), 130.15 (CH), 129.79 (2CH), 129.59 (CH), 129.43 (CH), 128.83 (CH), 128.75 (2CH), 124.73 (CH), 121.97 (CH), 120.89 (C), 111.21 (C≡N), 60.97 (CH), 49.99 (CH_2) ppm. MS-EI$^+$ m/z (%): 409 [M^+], 373 (20), 299 (30), 229 (31), 203 (100), 149 (36), 81 (85).

*6.2.4. 1-(1-(2,4-Dichlorophenyl)-2-(1H-imidazol-1-yl)ethyl)-5-pentyl-4-(phenylsulfonyl)-1H-1,2,3-triazole **4d***

Following the synthetic procedure for **4a**, compound **2** (0.35 g, 1.36 mmol) and **3d** (0.346 g, 1.36 mmol) were coupled in the presence of diphenylphosphoryl azide (0.32 mL, 1.5 mmol) and DBU (0.4 mL, 2.72 mmol). The crude extract was purified by flash column chromatography, eluting with DCM/MeOH 95/5 to afford the thick yellow oil **4d** (0.54 g, 78%). R_f: 0.4 (DCM/MeOH 9/1). ^{1}H NMR: (500 MHz, $CDCl_3$) δ = 8.07–8.01 (m, 2Ar–H), 7.68–7.63 (m, 1Im–H), 7.60–7.54 (m, 2Ar–H), 7.51 (dd, J = 1.6, 0.8 Hz, 1Ar–H), 7.39 (s, 1H), 7.31–7.29 (m, 2Ar–H), 6.92 (s, 1Im–H), 6.70 (s, 1Im–H), 6.03 (dd, J = 9.7, 4.2 Hz, 1H), 5.15 (dd, J = 14.7, 9.7 Hz, 1H), 4.56 (dd, J = 14.9, 4.3 Hz, 1H), 2.88–2.68 (m, 2H), 1.23–1.09 (m, 6H), 0.78 (t, J = 6.9 Hz, 3H) ppm. ^{13}C NMR: (125 MHz, $CDCl_3$) δ = 145.12 (C–Cl), 141.44 (C), 140.43 (C), 137.25 (C), 136.62 (C), 134.00 (C), 132.82 (CH), 130.90 (C–Cl), 129.91 (CH), 129.35 (2CH), 129.21 (CH), 128.91 (CH), 128.79 (CH), 127.90 (2CH), 118.76 (CH), 60.31 (CH), 49.52 (CH_2), 31.29 (CH_2), 28.49 (CH_2), 22.50 (CH_2), 22.02 (CH_2), 13.70 (CH_3) ppm. MS-EI$^+$ m/z (%): 518 [M^+], 376 (13), 280 (19), 203 (64), 172 (36), 159 (37), 149 (49), 125 (58), 77 (100), 41 (49).

*6.2.5. 1-(2-Azido-2-(2,4-dichlorophenyl)ethyl)-1H-imidazole **5***

To a cold solution (0 °C) of benzylic alcohol **2** (1.5 g, 5.83 mmol) and diphenylphosphoryl azide (1.25 mL, 5.83 mmol) in anhydrous DMF (13.0 mL), was added DBU (0.872 mL, 5.83 mmol). The solution was stirred for 15 min at 0 °C under nitrogen atmosphere, and then brought to room temperature with continuous stirring for 3 h. Brine (~100 mL) was added to the reaction mixture and washed with EtOAc (3 × 30 mL). The organic layer was dried (Na_2SO_4) and the solvent evaporated under reduced pressure. The crude extract was purified by flash column chromatography, eluting with DCM/MeOH 95/5 to afford the thick yellow oil **5** (1.43 g, 87%). R_f: 0.4 (DCM/MeOH 95/5). ^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.46 (d, J = 2.0 Hz, 1Im–H), 7.38–7.20 (m, 3Ar–H), 7.05 (s, 1Im–H), 6.91 (s, 1Im–H), 5.26 (dd, J = 7.6, 3.5 Hz, 1H), 4.22 (dd, J = 14.4, 3.5 Hz, 1H), 4.01 (dd, J = 14.4, 7.6 Hz, 1H) ppm. ^{13}C NMR: (75 MHz, $CDCl_3$) δ = 137.62 (C–Cl), 135.46 (C), 133.03 (CH), 132.32 (C–Cl), 129.81 (CH), 129.68 (CH), 128.81 (CH), 128.14 (CH), 119.45 (CH), 62.65 (CH–N_3), 50.51 (CH_2) ppm.

*6.2.6. 5-Cyclohexyl-1-(1-(2,4-dichlorophenyl)-2-(1H-imidazol-1-yl)ethyl)-1H-1,2,3-triazole **7a***

To a solution of benzyl azide **5** (0.35 g, 1.24 mmol) and β-ketophosphonate **6a** (0.29 g, 1.24 mmol) in acetonitrile grade reagent (3.5 mL) was added potassium hydroxide (0.2 g, 3.73 mmol). The solution was stirred for 5 h at 60 °C. Brine (~40 mL) was added to the reaction mixture and washed with EtOAc (3 × 30 mL). The organic layer was dried (Na_2SO_4) and the solvent evaporated under reduced pressure. The crude extract was purified by flash column chromatography, eluting with DCM/MeOH 95/5 to afford the thick yellow oil **7a** (0.31 g, 64%). R_f: 0.3 (DCM/MeOH 95/5). ^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.50 (d, J = 2.0 Hz, 1Im–H), 7.45 (s, 1Ar–H), 7.42 (s, 1Ar–H), 7.31–7.29 (m, 2Ar–H), 6.96 (s, 1Im–H), 6.76 (s, 1Im–H), 6.03 (dd, J = 9.9, 3.9 Hz, 1H), 5.22 (dd, J = 14.5, 9.9 Hz, 1H), 4.55 (dd, J = 14.5, 3.9 Hz, 1H), 2.64–2.50 (m, 1H), 1.90–1.47 (m, 5H), 1.43–1.01 (m, 5H) ppm. ^{13}C NMR: (75 MHz, $CDCl_3$) δ = 143.80 (C–Cl), 135.94 (C), 132.75 (C), 132.19 (CH), 131.23 (C–Cl), 129.80 (CH), 129.67 (CH), 129.58 (CH), 128.64 (CH), 122.56 (CH), 118.99 (CH), 59.41 (CH), 51.56 (CH_2), 33.22 (CH), 32.37 ($2CH_2$), 25.71 (CH), 25.44 ($2CH_2$) ppm.

*6.2.7. 1-(1-(2,4-Dichlorophenyl)-2-(1H-imidazol-1-yl)ethyl)-5-(2-methylhexan-2-yl)-1H-1,2,3-triazole **7b***

Following the synthetic procedure for **7a**, compound **5** (0.35 g, 1.24 mmol) and **6b** (0.311 g, 1.24 mmol) were coupled in the presence of KOH (0.2 g, 3.73 mmol). The crude extract was purified by flash column chromatography, eluting with DCM/MeOH 95/5 to afford the thick yellow oil **7b** (0.35 g, 70%). R_f: 0.3 (DCM/MeOH 9/1). ^{1}H NMR: (500 MHz, $CDCl_3$) δ = 7.54–7.53 (m, 1Im–H), 7.44 (s, 1Ar–H), 7.28–7.27 (m, 1Ar–H), 7.27–7.25 (m, 2Ar–H), 6.96 (s, 1Im–H), 6.78 (s, 1Im–H), 6.23 (dd, J = 10.6, 3.0 Hz, 1H), 5.29 (dd, J = 14.6, 10.6 Hz, 1H), 4.50 (dd, J = 14.6, 3.0 Hz, 1H), 1.37–1.21 (m, 2H), 1.10 (s, 3H), 1.03 (s, 3H), 0.97–0.82 (m, 2H), 0.75–0.64 (m, 1H), 0.61–0.54 (m, 3H), 0.43–0.31 (m, 1H) ppm. ^{13}C NMR: (75 MHz, $CDCl_3$) δ = 145.93 (C–Cl), 137.33 (C), 135.81 (CH), 133.29 (CH), 132.53 (C–Cl), 132.26 (CH), 130.90 (C), 129.73 (CH), 129.50 (CH), 128.45 (CH), 118.89 (CH), 62.20 (CH), 49.80 (CH_2), 41.07 (CH_2), 33.47 (C), 27.77 (CH_3), 27.67 (CH_3), 26.73 (CH_2), 22.76 (CH_2), 13.65 (CH_3) ppm. MS-EI$^+$ m/z (%): 406 [M^+], 296 (11), 240 (28), 203 (53), 172 (25), 159 (33), 124 (34), 81 (45), 57 (100), 41 (71).

*6.2.8. 1-(1-(2,4-Dichlorophenyl)-2-(1H-imidazol-1-yl)ethyl)-5-(4-(methylthio)phenyl)-1H-1,2,3-triazole **7c***

Following the synthetic procedure for **7a**, compound **5** (0.35 g, 1.24 mmol) and **6c** (0.341 g, 1.24 mmol) were coupled in the presence of KOH (0.2 g, 3.73 mmol). The crude extract was purified by flash column chromatography, eluting with DCM/MeOH 95/5 to afford the thick yellow oil **7c** (0.385 g, 72%). R_f: 0.3 (DCM/MeOH 9/1). ^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.69 (m, 1Im–H), 7.68 (s, 1Ar–H), 7.47 (d, J = 2.1 Hz, 2Ar–H), 7.36–7.19 (m, 4Ar–H), 6.96 (s, 1Im–H), 6.75 (d, J = 8.4 Hz, 2Ar–H), 6.64 (s, 1Im–H), 6.01 (dd, J = 10.5, 3.5 Hz, 1H), 5.15 (dd, J = 14.5, 10.5 Hz, 1H), 4.48 (dd, J = 14.5, 3.6 Hz, 1H), 2.49 (s, 3H) ppm. ^{13}C NMR: (75 MHz, $CDCl_3$) δ = 141.81 (C), 139.43 (C–Cl), 136.05 (C–S), 133.21 (C), 132.72 (CH), 131.83 (CH), 130.91 (C–Cl), 129.83 (CH), 129.77 (C), 129.40 (CH), 128.94 (2CH), 128.79 (CH), 128.55 (CH), 126.14 (2CH), 118.83 (CH), 59.98 (CH), 50.20 (CH_2), 15.05 (CH_3) ppm.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2016.02.013

References

[1] M. Grudzień, A. Król, G. Paterek, K. Stępień, F. Pluciński, A.P. Mazurek, The structure–bioavailability approach in antifungal agents, Eur. J. M. Chem. 44 (2009) 1978–1981.

[2] (a) Z.A. Kanafani, J.R. Perfect, Resistance to antifungal agents: mechanisms and clinical impact, Clin. Infect. Dis. 46 (2008) 120–128;
(b) Michael A. Pfaller, Antifungal drug resistance: mechanisms, epidemiology, and consequences for treatment, Am. J. Med. 125 (2012) S3–S13;
(c) Giulia Morace, Federica Perdoni, Elisa Borghi, Antifungal drug resistance in Candida species, Am. J. Med. 2 (2014) 254–259;
(d) G. Morace, F. Perdoni, E. Borghi, Antifungal drug resistance in Candida species, J. Glob. Antim. Resis 2 (2014) 254–259;
(e) J.B. Anderson, Evolution of antifungal-drug resistance: mechanisms and pathogen fitness, Nat. Rev. Microbiol. 3 (2005) 547–556.

[3] For complete Reviews about this issue see: (a) M.K. Kathiravan, A.B. Salake, A.S. Chothe, P.B. Dudhe, R.P. Watode, M.S. Mukta, S. Gadhwe, The biology and chemistry of antifungal agents: a review, Bioorg. Med. Chem. 20 (2012) 5678–5698;
(b) A.B. Petersen, M.H. Rønnest, T.O. Larsen, M.H. Clausen, The chemistry of griseofulvin, Chem. Rev. 114 (2014) 12088–12107;
(c) J. Heeres, L. Meerpoel, P. Lewi, Conazoles, Molecules 15 (2010) 4129–4188.

[4] W.R.J.D. Galloway, A. Bender, M. Welch, D.R. Spring, The discovery of anti-bacterial agents using diversity-oriented synthesis, Chem. Commun. (2009) 2446–2462.

[5] (a) A. Massarotti, S. Aprile, V. Mercalli, E. Del Grosso, G. Grosa, G. Sorba, G.C. Tron, Are 1,4- and 1,5-disubstituted 1,2,3-triazoles good pharmacophoric groups? ChemMedChem 9 (2014) 2497–2508;
(b) S.G. Agalave, S.R. Maujan, V.S. Pore, Click Chemistry: 1,2,3-Triazoles as Pharmacophores, 6, 2011, pp. 2696–2718;
(c) C.H. Zhou, Y. Wang, Recent researches in triazole compounds as medicinal drugs, Curr. Med. Chem. 19 (2012) 239–280.

[6] (a) E. Vitaku, D.T. Smith, J.T. Njardarson, Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among U.S. FDA approved pharmaceuticals, J. Med. Chem. 57 (2014) 10257–10274;
(b) H.X. Ding, C.A. Leverett, R.E. Kyne, K.K.C. Liu, S.J. Fink, A.C. Flick, C.J. O'Donnell, Synthetic approaches to the 2013 new drugs, Bioorg. Med. Chem. 23 (2015) 1895–1922.

[7] For concise Reviews about this issue see: (a) F. de Carvalho da Silva, M.F. do Carmo Cardoso, P. Garcia-Ferreira, V.F. Ferreira, Biological properties of 1*H* -1,2,3- and 2*H* -1,2,3-triazoles, in: W. Dehaen, V.A. Bakulev (Eds.), Chemistry of 1,2,3-triazoles, Springer International Publishing, Switzerland, 2015, pp. 117–165, http://dx.doi.org/10.1007/7081_2014_124;
(b) A. Lauria, R. Delisi, F. Mingoia, A. Terenzi, A. Martorana, G. Barone, A.M. Almerico, 1,2,3-Triazole in heterocyclic compounds, endowed with biological activity, through 1,3-dipolar cycloadditions, Eur. J. Org. Chem. (2014) 3289–3306;
(c) P. Thirumurugan, D. Matosiuk, K. Jozwiak, Click chemistry for drug development and diverse chemical–biology applications, Chem. Rev. 113 (2013) 4905–4979;
(d) J.F. Lutz, Z. Zarafshani, Efficient construction of therapeutics, bioconjugates, biomaterials and bioactive surfaces using azide–alkyne "click" chemistry, Adv. Drug Deliv. Rev. 60 (2008) 958–970;
(e) F. Amblard, J.H. Cho, R.F. Schinazi, Cu(I)-Catalyzed Huisgen azide-alkyne 1,3-dipolar cycloaddition reaction in nucleoside, nucleotide, and oligonucleotide Chemistry, Chem. Rev. 109 (2009) 4207–4220.

[8] (a) L.Y. Ma, L.P. Pang, B. Wang, M. Zhang, B. Hu, D.Q. Xue, K.P. Shao, B.L. Zhang, Y. Liu, E. Zhang, H.M. Liu, Design and synthesis of novel 1,2,3-triazole-pyrimidine hybrids as potential anticancer agents, Eur. J. Med. Chem. 86 (2014) 368–380;
(b) L.Y. Ma, B. Wang, L.P. Pang, M. Zhang, S.Q. Wang, I.C. Zheng, K.P. Shao, D.Q. Xue, H.M. Liu, Design and synthesis of novel 1,2,3-triazole–pyrimidine–urea hybrids as potential anticancer agents, Bioorg. Med. Chem. Lett. 25 (2015) 1124–1128;
(c) B.E. Gryder, M.J. Akbashev, M.K. Rood, E.D. Raftery, W.M. Meyers, P. Dillard, S. Khan, A.K. Oyelere, Selectively targeting prostate cancer with antiandrogen equipped histone deacetylase inhibitors, ACS Chem. Biol. 8 (2013) 2550–2560.

[9] (a) K. Kumar, B. Pradines, M. Madamet, R. Amalvict, N. Benoit, V. Kumar, 1H-1,2,3-triazole tethered isatin-ferrocene conjugates: synthesis and in vitro antimalarial evaluation, Eur. J. Med. Chem. 87 (2014) 801–804;
(b) R. Raj, J. Gut, P.J. Rosenthal, V. Kumar, 1H-1,2,3-Triazole-tethered isatin-7-chloroquinoline and 3-hydroxy-indole-7-chloroquinoline conjugates: Synthesis and antimalarial evaluation, Bioorg. Med. Chem. Lett. 24 (2014) 756–759.

[10] (a) T. Yempala, J.P. Sridevi, P. Yogeeswari, D. Sriram, S. Kantevari, Rational design and synthesis of novel dibenzo[b,d]furan-1,2,3-triazole conjugates as potent inhibitors of Mycobacterium tuberculosis, Eur. J. Med. Chem. 71 (2014) 160–167;
(b) M.H. Shaikh, D.D. Subhedar, L. Nawale, D. Sarkar, F.A. Kalam Khan, J.N. Sangshetti, B.B. Shingate, 1,2,3-Triazole derivatives as antitubercular agents: synthesis, biological evaluation and molecular docking study, Med. Chem. Commun. 6 (2015) 1104–1116.

[11] P. de Andrade, O.A. Galo, M.R. Carvalho, C.D. Lopes, Z.A. Carneiro, R. Sesti–Costa, E.B. de Melo, J.S. Silva, I. Carvalho, 1,2,3-Triazole-based analogue of benznidazole displays remarkable activity against Trypanosoma cruzi, Bioorg. Med. Chem. 23 (2015) 6815–6826.

[12] T.T. Guimarães, M.C.F.R. Pinto, J.S. Lanza, M.N. Melo, R.L. do Monte-Neto, I.M.M. de Melo, E.B.T. Diogo, V.F. Ferreira, C.A. Camara, W.O. Valença, R.N. de Oliveira, F. Frézard, E.N. da Silva Jr., Potent naphthoquinones against antimony-sensitive and -resistant Leishmania parasites: Synthesis of novel α- and nor-α-lapachone-based 1,2,3-triazoles by copper-catalyzed azide–alkyne cycloaddition, Eur. J. Med. Chem. 63 (2013) 523–530.

[13] (a) S.K.V. Vernekar, L. Qiu, J. Zacharias, R.J. Geraghty, Z. Wang, Synthesis and antiviral evaluation of 4′-(1,2,3-triazol-1-yl)thymidines, Med. Chem. Commun. 5 (2014) 603–608;
(b) R. Aneja, A.A. Rashad, H. Li, R.V.K. Sundaram, C. Duffy, L.D. Bailey, I. Chaiken, Peptide triazole inactivators of HIV-1 utilize a conserved two-cavity binding site at the junction of the inner and outer domains of Env gp120, J. Med. Chem. 58 (2015) 3843–3858.

[14] B.H. Fraser, S. Hamilton, A.M. Krause-Heuer, P.J. Wright, I. Greguric, S.P. Tucker, A.G. Draffan, V.V. Fokin, K.B. Sharpless, Synthesis of 1,4-triazole linked zanamivir dimers as highly potent inhibitors of influenza A and B, Med. Chem. Commun. 4 (2013) 383–386.

[15] S.K.V. Vernekar, L. Qiu, J. Zhang, J. Kankanala, H. Li, R.J. Geraghty, Z. Wang, 5′-Silylated 3′-1,2,3-triazolyl thymidine analogues as inhibitors of West Nile virus and dengue virus, J. Med. Chem. 58 (2015) 4016–4028.

[16] J.L. Díaz, U. Christmann, A. Fernández, A. Torrens, A. Port, R. Pascual, I. Álvarez, J. Burgueño, X. Monroy, A. Montero, A. Balada, J.M. Vela, C. Almansa, Synthesis and structure–activity relationship study of a new series of selective σ1 receptor ligands for the treatment of pain: 4-aminotriazoles, J. Med. Chem. 58 (2015) 2441–2451.

[17] (a) S.K. Kessler, A. McCarthy, A. Cnaan, D.J. Dlugos, Retention rates of rufinamide in pediatric epilepsy patients with and without Lennox–Gastaut Syndrome, Epilepsy Res. 112 (2015) 18–26;
(b) J. Gilchrist, S. Dutton, M. Diaz-Bustamante, A. McPherson, N. Olivares, J. Kalia, A. Escayg, F. Bosmans, Nav1.1 Modulation by a novel triazole compound attenuates Epileptic seizures in rodents, ACS Chem. Biol. 9 (2014) 1204–1212.

[18] H.H. Kinfe, Y.H. Belay, J.S. Joseph, E. Mukwevho, Evaluation of the influence of thiosemicarbazone–triazole hybrids on genes implicated in lipid oxidation and accumulation as potential anti-obesity agents, Bioorg. Med. Chem. Lett. 23 (2013) 5275–5278.

[19] S. Shafi, M.M. Alam, N. Mulakayala, C. Mulakayala, G. Vanaja, A.M. Kalle, R. Pallu, M.S. Alam, Synthesis of novel 2-mercapto benzothiazole and 1,2,3-triazole based bis-heterocycles: their anti-inflammatory and anti-nociceptive activities, Eur. J. Med. Chem. 49 (2012) 324–333.

[20] (a) M.R. El Sayed Aly, H.A. Saad, M.A.M. Mohamed, Click reaction based synthesis, antimicrobial, and cytotoxic activities of new 1,2,3-triazoles, Bioorg. Med. Chem. Lett. 25 (2015) 2824–2830;
(b) H. Kuhn, D. Gutelius, E. Black, C. Nadolny, A. Basu, C. Reid, Anti-bacterial glycosyl triazoles – identification of an N-acetylglucosamine derivative with bacteriostatic activity against Bacillus, Med. Chem. Commun. 5 (2014) 1213–1217.

[21] (a) S.Z. Ferreira, H.C. Carneiro, H.A. Lara, R.B. Alves, J.M. Resende, H.M. Oliveira, L.M. Silva, D.A. Santos, R.P. Freitas, Synthesis of a new peptide–coumarin conjugate: A potential agent against cryptococcosis, ACS Med. Chem. Lett. 6 (2015) 271–275;
(b) M. Irfan, B. Aneja, U. Yadava, S.I. Khan, N. Manzoor, C.G. Daniliuc, M. Abid, Synthesis, QSAR and anticandidal evaluation of 1,2,3-triazoles derived from naturally bioactive scaffolds, Eur. J. Med. Chem. 93 (2015) 246–254;
(c) Z. Jiang, J. Gu, C. Wang, S. Wang, N. Liu, Y. Jiang, G. Dong, Y. Wang, Y. Liu, J. Yao, Z. Miao, W. Zhang, C. Sheng, Design, synthesis and antifungal activity of novel triazole derivatives containing substituted 1,2,3-triazole-piperdine side chains, Eur. J. Med. Chem. 82 (2014) 490–497.

[22] (a) K. Pericherla, P. Khedar, B. Khungar, A. Kumar, Click chemistry inspired structural modification of azole antifungal agents to synthesize novel 'drug like' molecules, Tetrahedron Lett. 53 (2012) 6761–6764;
(b) S. Kim, S.N. Cho, T. Oh, P. Kim, Design and synthesis of 1H-1,2,3-triazoles derived from econazole as antitubercular agents, Bioorg. Med. Chem. Lett. 22 (2012) 6844–6847.

[23] For complete Reviews about this issue see: (a) S. Hassan, T.J.J. Müller, Multicomponent syntheses based upon copper-catalyzed alkyne-azide cycloaddition, Adv. Synth. Catal. 357 (2015) 617–666;
(b) J. Totobenazara, A.J. Burke, New click-chemistry methods for 1,2,3-triazoles synthesis: recent advances and applications, Tetrahedron Lett. 56 (2015) 2853–2859;
(c) B. Dervaux, F.E. Du Prez, Heterogeneous azide–alkyne click chemistry: towards metal-free end products, Chem. Sci. 3 (2012) 959–966;
(d) M. Meldal, C.W. Tornøe, Cu-catalyzed azide–alkyne cycloaddition, Chem. Rev. 108 (2008) 2952–3015;
(e) V.D. Bock, H. Hiemstra, J.H. van Maarseveen, Cu^{I}-catalyzed alkyne–azide "Click" cycloadditions from a mechanistic and synthetic perspective, Eur. J. Org. Chem. (2006) 51–68.

[24] For complete Reviews about this issue see: (a) C.G.S. Lima, A. Ali, S.S. van Berkel, B. Westermann, M.W. Paixão, Emerging approaches for the synthesis of triazoles: beyond metal-catalyzed and strain-promoted azide–alkyne cycloaddition, Chem. Commun. 51 (2015) 10784–10796;
(b) J. John, J. Thomas, W. Dehaen, Organocatalytic routes toward substituted 1,2,3-triazoles, Chem. Commun. 51 (2015) 10797–10806;
(c) S.S.V. Ramasastry, Enamine/Enolate-mediated organocatalytic azide–carbonyl [3+2] cycloaddition reactions for the synthesis of densely functionalized 1,2,3-triazoles, Angew. Chem. Int. Ed. 53 (2014) 14310–14312.

[25] (a) D.V. Demchuk, A.V. Samet, N.B. Chernysheva, V.I. Ushkarov, G.A. Stashina, L.D. Konyushkin, M.M. Raihstat, S.I. Firgang, A.A. Philchenkov, M.P. Zavelevich, L.M. Kuiava, V.F. Chekhun, D.Y. Blokhin, A.S. Kiselyov, M.N. Semenova, V.V. Semenov, Synthesis and antiproliferative activity of conformationally restricted 1,2,3-triazole analogues of combretastatins in the sea urchin embryo model and against human cancer cell lines, Bioorg. Med. Chem. 22 (2014) 738–755;
(b) J.B. He, L.L. Feng, J. Li, R.J. Tao, Y.L. Ren, J. Wan, H.W. He, Design, synthesis and molecular modeling of novel N-acylhydrazone derivatives as pyruvate dehydrogenase complex E1 inhibitors, Bioorg. Med. Chem. 22 (2014) 89–94.

[26] A. Ramírez-Villalva, D. González-Calderón, C. González-Romero, M. Morales-Rodríguez, B. Jauregui-Rodríguez, E. Cuevas-Yañez, A. Fuentes-Benítes, A facile synthesis of novel miconazole analogues and the evaluation of their antifungal activity, Eur. J. Med. Chem. 97 (2015) 275–279.

[27] (a) G. La Regina, F.D. D'Auria, A. Tafi, F. Piscitelli, S. Olla, F. Caporuscio, L. Nencioni, R. Cirilli, F. La Torre, N. Rodrigues De Melo, S.L. Kelly, D.C. Lamb, M. Artico, M. Botta, A.T. Palamara, R. Silvestri, 1-[(3-Aryloxy-3-aryl)propyl]-1H-imidazoles, new imidazoles with potent activity against Candida albicans and dermatophytes. Synthesis, structure–activity relationship, and molecular modeling studies, J. Med. Chem. 51 (2008) 3841–3855;
(b) A. Davood, M. Iman, Molecular docking and QSAR study on imidazole derivatives as 14α-demethylase inhibitors, Turk. J. Chem. 37 (2013) 119–133.

[28] D. González-Calderón, I. Santillán-Iniesta, C.A. González-González, A. Fuentes-Benítes, C. González-Romero, A novel and facile synthesis of 1,4,5-trisubstituted 1,2,3-triazoles from benzylic alcohols through a one-pot, three-component system, Tetrahedron Lett. 56 (2015) 514–516.

[29] D. González-Calderón, A. Fuentes-Benítes, E. Díaz-Torres, C.A. González-González, C. González-Romero, An azide–enolate 1,3-dipolar cycloaddition as an efficient approach for the synthesis of 1,5-disubstituted 1,2,3-triazoles from alkyl/aryl azides and β-ketophosphonates, Eur. J. Org. Chem. (2016) 668–672.

[30] A.S. Thompson, G.R. Humphrey, A.M. DeMarco, D.J. Mathre, E.J.J. Grabowski, Direct conversion of activated alcohols to azides using diphenyl phosphorazidate. A practical alternative to Mitsunobu conditions, J. Org. Chem. 58 (1993) 5886–5888.

[31] (a) National Committee for Clinical Laboratory Standards Institute (CLSI), Document M38–A2: Reference Method for Broth Dilution Antifungal Susceptibility Testing of Filamentous Fungi, Approved Standard–Second Edition, Clinical and Laboratory Standards Institute, Wayne, PA, 2002;
(b) A.L. Barry, An overview of the Clinical and Laboratory Standards Institute (CLSI) and its impact on antimicrobial susceptibility tests, in: R. Schwalbe, L. Steele-Moore, A.C. Goodwin (Eds.), Antimicrobial Susceptibility Testing Protocols, CRC Press Taylor & Francis Group, Florida, 2007, pp. 1–6. ISBN: 9780824741006;
(c) A. Espinel-Ingroff, E. Cantón, Antifungal susceptibility testing of filamentous fungi, in: R. Schwalbe, L. Steele-Moore, A.C. Goodwin (Eds.), Antimicrobial Susceptibility Testing Protocols, CRC Press Taylor & Francis Group, Florida, 2007, pp. 209–241. ISBN: 9780824741006.

[32] (a) National Committee for Clinical and Laboratory Standards Institute (CLSI), M27–A3: Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts, Approved Standard–Third Edition, Clinical and Laboratory Standards Institute, Wayne, PA, 2008. ISBN: 1-56238-666-2;
(b) A. Espinel-Ingroff, E. Cantón, Antifungal susceptibility testing of yeasts, in: R. Schwalbe, L. Steele-Moore, A.C. Goodwin (Eds.), Antimicrobial Susceptibility Testing Protocols, CRC Press Taylor & Francis Group, Florida, 2007, pp. 173–208. ISBN: 9780824741006;
(c) A.W. Fothergill, Antifungal Susceptibility Testing: Clinical Laboratory and Standards Institute (CLSI) methods, in: G.S. Hall (Ed.), Interactions of Yeasts, Moulds, and Antifungal Agents. How to Detect Resistance, Springer Science-Business Media, 2012, pp. 65–74, http://dx.doi.org/10.1007/978-1-59745-134-5_2.

[33] (a) C. Sheng, W. Zhang, H. Ji, M. Zhang, Y. Song, H. Xu, J. Zhu, Z. Miao, Q. Jiang, J. Yao, Y. Zhou, J. Zhu, J. Lü, Structure-based optimization of azole antifungal agents by CoMFA, CoMSIA, and molecular docking, J. Med. Chem. 49 (2006) 2512–2525;
(b) H. Ji, W. Zhang, Y. Zhou, M. Zhang, J. Zhu, Y. Song, J. Lü, J. Zhu, A three-dimensional model of lanosterol 14α-demethylase of Candida albicans and its interaction with azole antifungals, J. Med. Chem. 43 (2000) 2493–2505.

RSC Advances

COMMUNICATION

A straightforward and versatile protocol for the direct conversion of benzylic azides to ketones and aldehydes†

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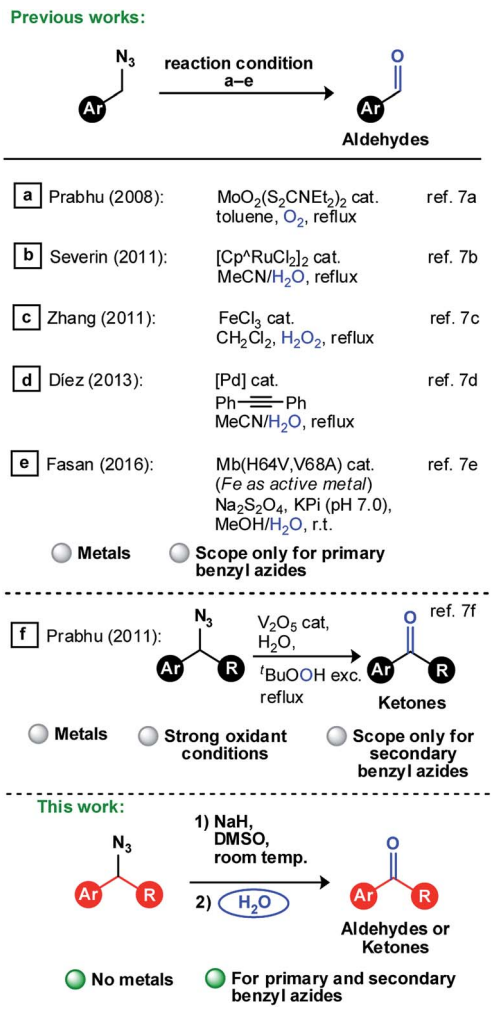
The synthesis of carbonyl compounds from benzylic azides through benzylideneamides is described for the first time. NaH-mediated activation of benzyl azides allows a rapid water-promoted oxidation under a facile protocol with good yields.

The chemistry of organic azides is very well-known. Books[1] and reviews[2] have compiled the role of these valuable nitrogen compounds as mediators between chemistry, medicine, biology and materials science. As synthetic intermediates, organic azides can be coupled to other substrates (*e.g.* 1,3-dipolar cycloaddition)[3] or directly converted to other functional groups, for example by reduction (*e.g.* Staudinger reaction)[4] or by an oxidation process. Regarding the latter, there are reports on obtaining nitro compounds[5] (oxidation of the $-N_3$ moiety) as well as synthesizing nitriles[6] (oxidation of benzylic carbon). In this context, synthetic strategies to achieve carbonyls from azido groups (Scheme 1)[7] (an inverse reaction as proposed by Ghorai)[8] are still challenging and attractive for organic chemists. Unfortunately, all such strategies developed to date [eqn (a)–(f)] suffer from serious drawbacks, including the use of metals as reagents that are very expensive and/or unconventional and require the use of peroxides, as well as cumbersome experimental procedures or high temperatures that are particularly disadvantageous for large-scale reactions.

Synthetic strategies involving the acidic hydrolysis of enamines [Scheme 2, eqn (g)] or imines [eqn (h)] generated *in situ* from azide compounds have been reported in literature. Hendrickson (1977)[9a] and Hassner (1979)[9b] published the direct conversion of vinyl azides to carbonyls *via* enamines in good yields. Although the thermal, photolytic and acidic decomposition of organic azides to imines has been studied extensively[10,12g] their applications for obtaining carbonylic compounds[11] are rather limited. The high temperatures (*ca.* 300 °C) required for a thermal process in the synthesis of alde-hydes from alkylic azides[12a] (inefficient for benzylic azides)[12b] preclude the use of



Scheme 1 Recent advances in the synthesis of carbonyl derivatives from azide compounds.

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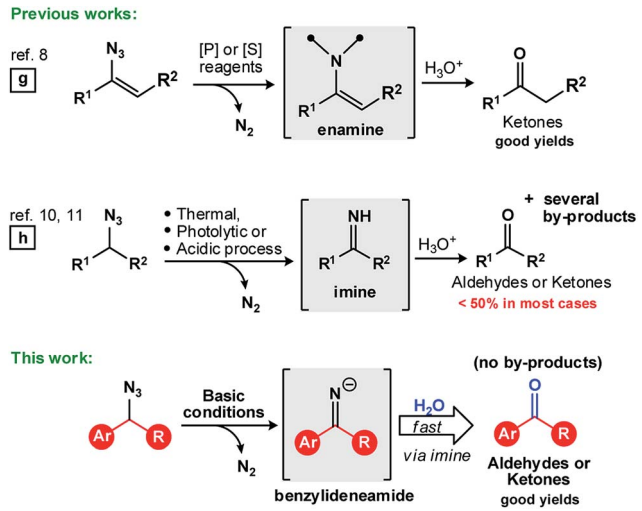
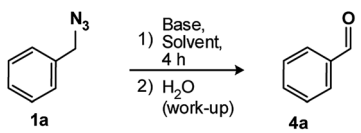
† Electronic supplementary information (ESI) available: Characterization data and copies of ^{1}H-NMR/^{13}C-NMR of all compounds. See DOI: 10.1039/c6ra13088g



Scheme 2 Acidic hydrolysis of enamines (efficient) or imines (inefficient) generated *in situ* from azide derivatives representing synthetic strategies for the attainment of carbonyls.

this type of reaction for most substrates. In contrast, a photolytic process using primary alkyl azides[12c–f] occurs at or below room temperature. However, its use is limited by very low yields (18–50%) from a complex reaction mixture. Finally, trace amounts of carbonyls have been observed under strong acid conditions.[12g–i] The evident inefficiency of all these methods as synthetic strategies to afford carbonyls from azides *via* imines has led to complete disinterest and abandonment of their use, a fact that has been demonstrated by the absence of studies in contemporary literature.[13]

Table 1 Optimization of reaction conditions: [a]Effect of solvent and base



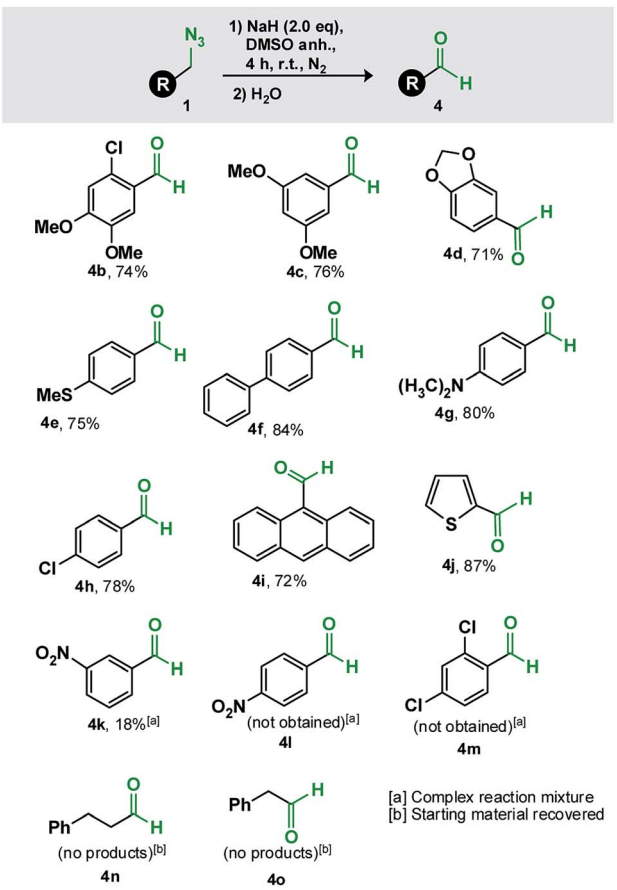
Entry	Solvent	Base[b]	Yield[c] (%)
1	DMF anh.	NaH	70
2	DMF anh.	K_2CO_3	NR[e]
3[d]	DMF anh.	K_2CO_3	NR[e]
4	DMF anh.	^{t}BuOK	60
5	DMF anh.	KOH	Trace[e]
6[d]	DMF anh.	KOH	45
7	MeCN anh.	NaH	35
8	DMSO anh.	^{t}BuOK	72
9	DMSO anh.	NaH	80
10	DMSO anh.	NaH (1.5 eq.)	74[f]
11	DMSO anh.	NaH (1.0 eq.)	70[f]

[a] Unless otherwise stated, reactions were run at room temperature for 8 h. [b] Unless otherwise stated, reactions were performed using 2.0 eq. [c] Yields refer to chromatographically pure isolated compounds. [d] These experiments were carried out at 60 °C. [e] Starting material was recovered. [f] Along with the corresponding starting material (~15% recovered).

Previously Manetsch[14a] and Wu/Pan[14b] demonstrated the ^{t}BuOK-promoted attainment of PhCH=N$^-$ (benzylideneamide) from $PhCH_2N_3$ as well as its inefficient use for coupling the latter with carbonyl compounds. We herein describe the utility of benzylideneamides for directly converting benzyl azides to carbonyl derivatives with good yields.

During one of our current research programs, focused on the development of novel methodologies for the construction of 1,2,3-triazole moieties through base-promoted azide-ketone cycloadditions[15] we observed that when NaH was subjected to our study, benzaldehyde was isolated as by-product along with the corresponding triazole. Intrigued by this outcome, we decided to do follow-up investigation this fact in greater detail.

Firstly, in absence of ketones (in order to avoid the formation of the corresponding triazole) good yields were observed at room temperature with a reaction time of 4 h. Secondly, the effects of solvents and bases on compound **1a** were observed in optimization studies (Table 1). The best performance was found for NaH (entry 9) in dimethyl sulfoxide using 2.0 equivalents of the base. The optimized conditions were then used to study the direct conversion of a variety of azides‡ to aldehydes (Scheme 3).§ In order to evaluate the scope of our protocol, both benzylic and aliphatic azides were subjected to the optimized



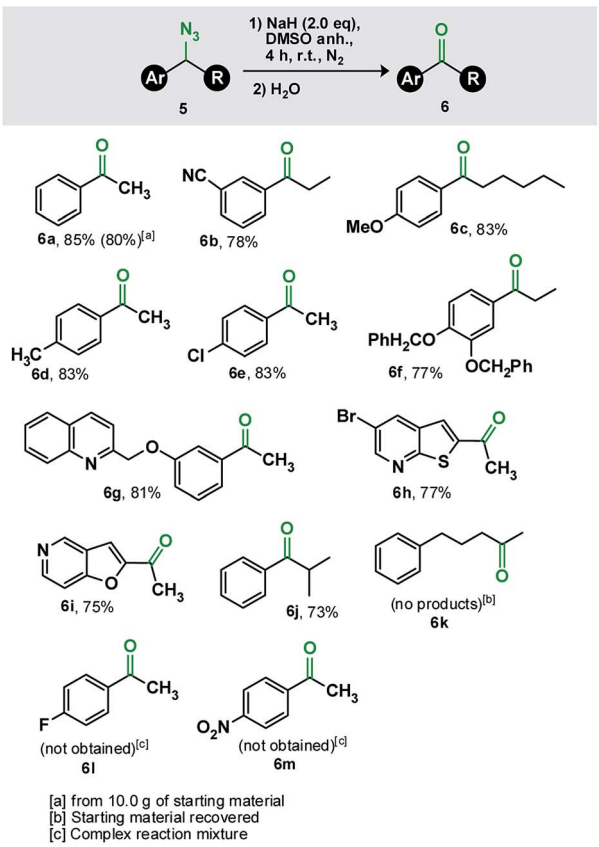
Scheme 3 Direct conversion of primary azides (**1**) to aldehydes (**4**) under optimized conditions. Reaction conditions: NaH (0.2 mmol) was added to a solution of compound **1** (0.1 mmol) in DMSO anh. Then, water was added in excess.

reaction conditions. Unfortunately, aliphatic compounds (**4n** and **4o**) did not react to such conditions remaining intact in the flask even under thermal conditions (60 °C). Therefore, only benzylic azides were considered for the present study. An effective approach to the aldehyde derivatives was carried out with heterocycles (**4j**), strongly (**4c**, **4d**, **4e**, **4g** and **4i**) and weakly (**4f**) activated rings as well as weakly deactivated (**4h**) rings. The exception was strongly deactivated rings (**4k**, **4l** and **4m**).

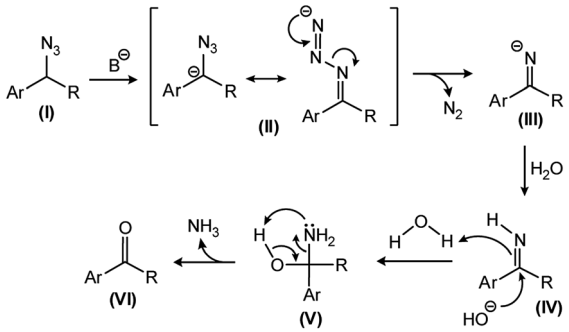
Encouraged by these outcomes, we decided to investigate another possibility: the synthesis of ketones using secondary azido groups. We therefore submitted the (1-azidoethyl)benzene [$PhCH(N_3)CH_3$] to the current protocol achieving the synthesis of the corresponding acetophenone (**6a**, Scheme 4) with good yields (85%). Therefore, a series of compounds containing secondary azides‡ were studied under the same reaction conditions.§

At this stage we found the behavior similar to that observed for primary azides including the lack of reaction for aliphatic (**6k**) and strongly deactivated aromatic rings (**6m**). Two interesting exceptions were N=C– [a strongly deactivating derivative (**6b**)] and F-substituted [a weakly deactivating derivative (**6l**)].

Finally, in order to demonstrate the scalability of such protocol, acetophenone (**6a**) was efficiently obtained (80%) from 10.0 g of the corresponding starting material [$PhCH(N_3)CH_3$]. The use of ice bath was necessary due to the exothermic reaction



Scheme 4 Direct conversion of secondary azides (**5**) to ketones (**6**) under optimized condicions. Reaction conditions: NaH (0.2 mmol) was added to a solution of compound **5** (0.1 mmol) in DMSO anh. Then, water was added in excess.



Scheme 5 Proposed plausible mechanism for direct conversion of benzyl azido groups to carbonyl derivatives.

observed along with the intense bubbling ($N_2\uparrow$) during the addition (in five portions) of the hydride.

According to these results, a plausible mechanism is proposed in Scheme 5. The generation of benzylideneamide (**III**) by a base-promoted deprotonation of the benzyl azide (**I**) is supported by previous studies (Manetsch[14a] and Wu/Pan[14b]). We propose that this was followed by a rapid hydrolysis under basic conditions leading to the corresponding carbonyl group (**VI**).

Conclusions

In summary, we report that the benzyl azido group is directly converted to carbonyls in good yields through a rapid hydrolysis (basic conditions) of benzylideneamides generated readily/efficiently *in situ*. We are convinced that this synthesis is the most versatile reported so far as its scope includes both primary azides (affording aldehydes) and secondary azides (affording ketones) reacted with conventional reagents under a very simple procedure.

Acknowledgements

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Notes and references

‡ Azide compounds (starting materials) were obtained from the corresponding alcohols,[16] halides[17] or tosylates[18] according to synthetic protocols described in literature.

§ General experimental procedure for the direct conversion of azides to carbonyls: NaH (0.4 mmol, 60% dispersion in mineral oil) was added to a solution of the azide derivative (0.2 mmol) in anhydrous dimethyl sulfoxide (*ca.* 2.0 mL $mmol^{-1}$). The solution was stirred at room temperature for 4 h under an inert atmosphere. Brine (*ca.* 20.0 mL) was added to the reaction stirring vigorously for 15 min. Then, the mixture was washed with ethyl acetate (3 × 8 mL). The organic layer was dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. The crude extract was purified by flash column chromatography to afford the corresponding carbonyl derivative.

1 (*a*) *Organic Azides: Syntheses and Applications*, ed. S. Bräse and K. Banert, John Wiley & Sons, Ltd, Chichester, England, UK, 2010, DOI: 10.1002/9780470682517; (*b*) *Supplement F2: The Chemistry of Amino, Nitroso, Nitro and Related Groups*, ed. S. Pata, John Wiley & Sons, Ltd, Chichester, England, 1996, ISBN: 0-471-95171-4.

2 (*a*) S. Bräse, C. Gil, K. Knepper and V. Zimmermann, *Angew. Chem., Int. Ed.*, 2005, **44**, 5188–5240; (*b*) W. P. Fehlhammer and W. Beck, *Z. Anorg. Allg. Chem.*, 2015, **641**, 1599–1678; (*c*) W. P. Fehlhammer and W. Beck, *Z. Anorg. Allg. Chem.*, 2013, **639**, 1053–1082; (*d*) S. Chiba, *Synlett*, 2012, **23**, 21–44; (*e*) T. M. Klapötke, *Chem. Ber.*, 1997, **130**, 443–452; (*f*) E. F. V. Scriven and K. Turnbull, *Chem. Rev.*, 1988, **88**, 297–368.

3 For complete reviews about this issue see: (*a*) M. Meldal and C. W. Tornøe, *Chem. Rev.*, 2008, **108**, 2952–3015; (*b*) C. G. S. Lima, A. Ali, S. S. van Berkel, B. Westermann and M. W. Paixão, *Chem. Commun.*, 2015, **51**, 10784–10796; (*c*) J. John, J. Thomas and W. Dehaen, *Chem. Commun.*, 2015, **51**, 10797–10806; (*d*) S. S. V. Ramasastry, *Angew. Chem., Int. Ed.*, 2014, **53**, 14310–14312.

4 For a complete review about this issue see: S. Liu and K. J. Edgar, *Biomacromolecules*, 2015, **16**, 2556–2571.

5 (*a*) M. Carmeli and S. Rozen, *J. Org. Chem.*, 2006, **71**, 4585–4589; (*b*) G. K. Surya Prakash and M. Etzkorn, *Angew. Chem., Int. Ed.*, 2003, **43**, 26–28.

6 (*a*) J. He, K. Yamaguchi and N. Mizuno, *J. Org. Chem.*, 2011, **76**, 4552–4553; (*b*) M. Lamani, P. Devadig and K. R. Prabhu, *Org. Biomol. Chem.*, 2012, **10**, 2753–2759.

7 (*a*) M. Maddani and K. R. Prabhu, *Tetrahedron Lett.*, 2008, **49**, 4526–4530; (*b*) J. Risse, R. Scopelliti and K. Severin, *Organometallics*, 2011, **30**, 3412–3418; (*c*) H. P. Zhang, Y. Z. Dai and L. M. Tao, *J. Chem. Res.*, 2011, **35**, 720–722; (*d*) L. Martínez-Sarti and S. Díez-González, *ChemCatChem*, 2013, **5**, 1722–1724; (*e*) S. Giovani, R. Singh and R. Fasan, *Chem. Sci.*, 2016, 234–239; (*f*) K. Alagiri and K. R. Prabhu, *Tetrahedron*, 2011, **67**, 8544–8551.

8 S. Pramanik and P. Ghorai, *Org. Lett.*, 2014, **16**, 2104–2107.

9 (*a*) J. B. Hendrickson, K. W. Bair and P. M. Keehn, *J. Org. Chem.*, 1977, **42**, 2935–2936; (*b*) B. A. Belinka and A. Hassner, *J. Org. Chem.*, 1979, **44**, 4712–4713. Also see: (*c*) A. Hassner, E. S. Ferdinandi and R. J. Isbister, *J. Am. Chem. Soc.*, 1970, **92**, 1672–1675.

10 G. L'abbe, *Chem. Rev.*, 1969, **69**, 345–363.

11 A. H. Haines, 5–Oxidation of Amines, Nitro Compounds and Azides, in *Methods for Oxidation of Organic Compounds. Alcohols, Alcohol Derivatives, Alky Halides, Nitroalkanes, Alkyl Azides, Carbonyl Compounds Hydroxyarenes and Aminoarenes*, Academic Press, United Kingdom, 1988, pp. 199–239, DOI: 10.1016/B978-0-12-315502-3.50010-8, see specially, pp. 233–234.

12 (*a*) W. Pritzkow and D. Timm, *J. Prakt. Chem.*, 1966, **32**, 178–189; (*b*) R. Kreher and D. Kühling, *Angew. Chem.*, 1964, **76**, 272; (*c*) H. F. G. Beving, A. E. Luetzow and O. Theander, *Carbohydr. Res.*, 1975, **41**, 105–115; (*d*) D. M. Clode and D. Horton, *Carbohydr. Res.*, 1971, **17**, 365–373; (*e*) D. C. Baker and D. Horton, *Carbohydr. Res.*, 1972, **21**, 393–405; (*f*) A. Reiser and H. M. Wagner, Photochemistry of the azido group, in *The Azido Group*, ed. S. Patai, John Wiley & Sons, Ltd, Chichester, UK, 1971, pp. 441–501, DOI: 10.1002/9780470771266.ch8; (*g*) P. A. S. Smith, *J. Am. Chem. Soc.*, 1948, **70**, 320–323; (*h*) R. A. Abramovitch and E. P. Kyba, Decomposition of organic azides, in *The Azido Group*, ed. S. Patai, John Wiley & Sons, Ltd, Chichester, UK, 1971, pp. 221–329, DOI: 10.1002/9780470771266.ch5; (*i*) J. H. Boyer and F. C. Canter, *Chem. Rev.*, 1954, **54**, 1–57, see specially p. 26 and references therein.

13 Under this tenor, during the correction of the manuscript, an interesting work was published involving the synthesis of α-fluoroketones from vinyl azides: S. W. Wu and F. Liu, *Org. Lett.*, 2016, **18**, 3642–3645.

14 (*a*) S. S. Kulkarni, X. Hu and R. Manetsch, *Chem. Commun.*, 2013, **49**, 1193–1195; (*b*) Z. M. Yan, N. Wu, D. Liang, H. S. Wang and Y. M. Pan, *Org. Lett.*, 2014, **16**, 4048–4051.

15 (*a*) D. González-Calderón, A. Fuentes-Benítes, E. Díaz-Torres, C. A. González-González and C. González-Romero, *Eur. J. Org. Chem.*, 2016, 668–672; (*b*) D. González-Calderón, I. Santillán-Iniesta, C. A. González-González, A. Fuentes-Benítes and C. González-Romero, *Tetrahedron Lett.*, 2015, **56**, 514–516; (*c*) D. González-Calderón, J. G. Aguirre-De Paz, C. A. González-González, A. Fuentes-Benítes and C. González-Romero, *Tetrahedron Lett.*, 2015, **56**, 1713–1715.

16 A. S. Thompson, G. R. Humphrey, A. M. DeMarco, D. J. Mathre and E. J. J. Grabowski, *J. Org. Chem.*, 1993, **58**, 5886–5888.

17 D. Enders and D. Klein, *Synlett*, 1999, 719–720.

18 C. A. González-González, A. Fuentes-Benítez, E. Cuevas-Yáñez, D. Corona-Becerril, C. González-Romero and D. González-Calderón, *Tetrahedron Lett.*, 2013, **54**, 2726–2728.

Anexo 2

Este manuscrito ha sido aceptado (05/Agosto/2017) para su publicación en la revista Synlett

Rapid Continuous Ru-Catalysed Transfer Hydrogenation of Aromatic Nitriles to Primary Amines

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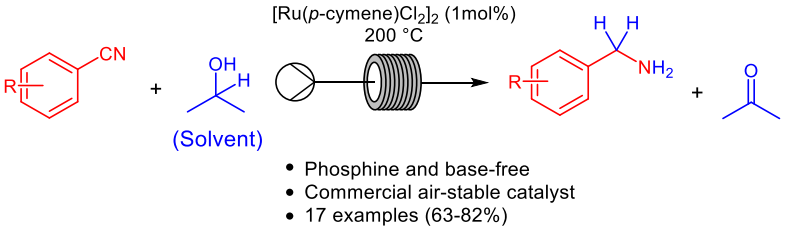
Dedicated to our friend Vic Snieckus on the occasion of his 80th birthday.



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Abstract A continuous flow method for the selective reduction of aromatic nitriles is reported. The method is based on a Ruthenium catalysed transfer hydrogenation process, requires no additives, which uses isopropanol as both solvent and reducing agent. The process utilizes 1 mol% of the commercially available [Ru(*p*-cymene)Cl_2]$_2$, with a residence time of *ca.* 9 min, and a throughput of 50 mmol/h. The method was successfully applied to a range of aromatic nitriles providing the corresponding primary amines in good yields.

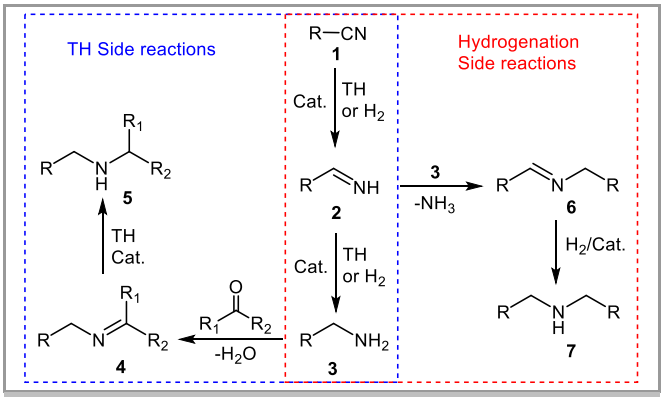
Key words Nitrile reduction, transfer hydrogenation, Ruthenium, primary amine, continuous flow.

Amines are key intermediates in the production of fine chemicals, active pharmaceutical ingredients (APIs), agro-chemicals, as well as many natural products.[1]

Primary amines are of particular importance as synthetic building blocks, and used in many processes such as the Buchwald–Hartwig coupling reactions,[2] hydroaminations[3] and alcohol amination by hydrogen borrowing strategies[4–7] for example.

The reduction of nitriles is among the most common route to generate the corresponding primary amines.[8] The use of stoichiometric amounts of hydrides such as $LiAlH_4$ is effective for the transformation, but catalytic hydrogenation methods while for example Raney nickel are often preferred, but are not without problems. Despite being known for decades,[9] transfer hydrogenation processes (TH) have gained more interest recently[10] also with application to nitrile reduction.[11–14] Transfer hydrogenations are attractive as they eliminate the need for pressurized hydrogen gas typical of many catalytic methods.

Both direct hydrogenation (employing H_2), and TH methodologies can however suffer from selectivity issues and lead to several by-products being formed (Scheme 1).



Scheme 1 Side reactions for the transfer hydrogenation and hydrogenation of nitriles.

Several recent attempts have been reported to solve these selectivity problems for the reduction of nitriles to primary amines employing catalysis and H_2 gas,[8] and selective TH reactions.[11–13]

To the best of our knowledge, while hydrogenation reactions have been thoroughly investigated in continuous flow,[15,16] including nitrile reductions to the correspondent primary amine[17] and direct reductive amination,[18] no continuous transfer hydrogenation of nitriles to primary amines has been reported so far. However, we could expect to see distinct advantages from a safety perspective and the ability to control the dynamics of the reaction, hopefully leading to improved selectivity.

Beller's group has reported the use of 2-butanol in the transfer hydrogenation of nitriles to obtain the corresponding primary amine while simultaneously reducing the formation of by-products.[11] The same group also noted the use of 2-propanol with NaOH to afford the alkylated secondary amines, [19] and a

heterogeneous TH using Pd/C and ammonium formate as hydrogen source.[12] On the other hand Zhou and Liu assessed two Cobalt catalysts for TH of nitriles that led to the selective preparation of primary, secondary or tertiary products. Here the solvent choice played a crucial role on the outcome of the reaction.[13]

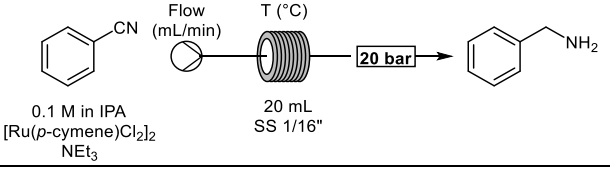
Notably also three recent reports using transfer hydrogenation to reduce nitriles with a Ruthenium catalyst led to the *N*-isopropylidene derivatives (**4**, Scheme 1) as the main product through a further coupling and reductio. These reports use KO^{t}Bu as base and relatively long reaction times.[14,20,21] Recently the use of a Nickel catalyst, and 1,4-butanediol as hydrogen source, to afford *N*-benzylidenes as main products of the transfer hydrogenation nitrile reduction have been observed.[22]

Even with all these advances, we felt there was a need for a practical, safe and selective method for the transfer hydrogenation of nitriles tolerant to a wide aromatic functionality.

Inspired by our recent studies towards the chemoselective continuous Ru-catalysed hydrogen-transfer oxidation of secondary alcohols,[23] we became interested in expanding the application scope of our system. Among other advantages of using a continuous flow system is the precise control of residence times and heating regimes.

By analogy with our previous approach to continuous transfer hydrogenation we devised a simple system comprising of a pump, a heated coil and a backpressure regulator (BPR). Initial screening was performed using a Uniqsis FlowSyn[24] unit equipped with a 20 mL stainless-steel coil reactor operating at the temperature indicated (Table 1).

Table 1 Initial optimization for the continuous TH of nitriles



Entry	Residence time (min)	T (°C)	Cat. (mol%)	NEt_3 (Equiv.)	Yield[a]
1	40	100	0	2	0
2	40	100	1	2	50
3	40	125	1	2	75
4	40	150	1	2	85
5	40	150	1	0	85
6[b]	40	150	1	2	0
7	40	150	0.5	0	80
8	40	150	5	0	66
9	20	150	1	0	85
10	10	150	1	0	85

[a] Yield of primary amine by ^{1}H NMR analysis (1,4-dinitrobenzene as internal standard) of the crude mixture after solvent removal.
[b] Using $(Ph_3P)_3RuCl_2$ as catalyst.

Our study began employing triethylamine as it proved to be beneficial in our previous work employing the same catalyst.[23] It was quickly realized that triethylamine was not necessary for this transformation to proceed (Table 1)

Interestingly, Beller's report suggests that no conversion was observed using the same catalyst $[Ru(p\text{-cymene})Cl_2]_2$ and 2-butanol at 120 °C for 10 min in batch.[11] We were pleasantly surprised to find that under the conditions described, even at 100 °C (Table 1, Entry 2), the expected primary amine could be observed in flow. By increasing the temperature to 150 °C the yield increased to 85% in the absence of phosphine ligands or base (Table 1, Entry 5). Concentration of the substrate in IPA was substantial to the outcome of the reaction. By increasing either the concentration of substrate or the amount of ruthenium catalyst, the amount of alkylated byproduct (**5**) also increased. Residence time could be reduced to 10 min maintaining the primary amine yield. By reducing the residence time we diminished the amount of alkylated by-product (**5**) but on the other hand we could now see some unreacted imine (**2**), while the overall yield of primary amine was unchanged.

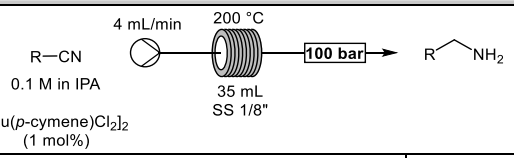
The reaction system then moved onto a Phoenix reactor platform,[25] equipped with a 1/8'' 35 mL stainless steel coil. This gave us the opportunity to work at even higher temperatures and pressures.

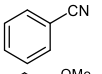
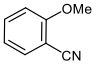
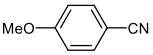
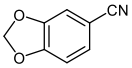
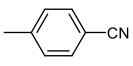
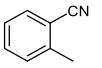
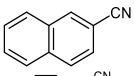
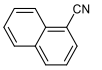
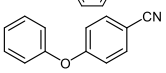
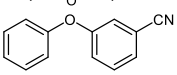
By precisely controlling the residence time of the solution we could halt the reaction at a specific equilibrium point between **1-5** (Scheme 1). The residence time was then optimized using benzonitrile as a model substrate.

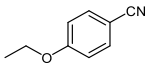
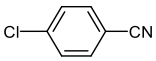
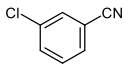
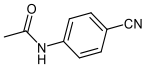
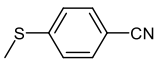
To enable a suitable downstream product isolation we opted to isolate the primary amines as their hydrochloride salts, as those could be easily separated by filtration and in doing so removed any ruthenium residues.

The general method was then applied to different nitriles (Table 2).

Table 2 Substrate scope for the continuous TH of nitriles



Entry	Substrate	Yield[a]
1		78
2		71[b]
3		80
4		69
5		76
6		71
7		69
8		70
9		72
10		82
11		70

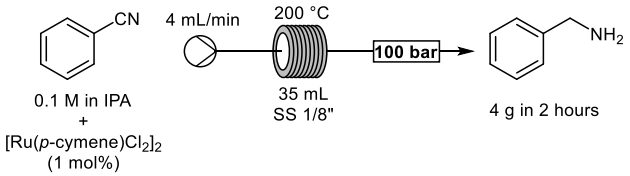
12		78
13		72
14		63
15		77
16		71[b]
17		70

[a] Isolated yield as hydrochloride salts.
[b] Yield of primary amine by ^{1}H NMR analysis (1,4-dinitrobenzene as internal standard).

Notably aromatic nitriles bearing ether, thioether, chloride and amide functionalities were all successfully selectively reduced in good yields. The pyridine derivative (Table 2, Entry 16) was also converted to the desired primary amine in good yield. The nitrile compound containing an amide group (Table 2, Entry 15) selectively afforded the corresponding primary amine, however substrates bearing more reactive carbonyl groups as in ketones or aldehydes led to a mixture of products.

Attempts to reduce aliphatic nitriles also led to poor yields due to reduced reactivity of these substrates.[26] This expected lower reactivity has been observed by others.[12,14]

To further evaluate the robustness of the methodology, the system was operated continuously for 2 hours and afforded 4 g of benzylamine (Scheme 2).



Scheme 2 TH of nitriles, 2 hours continuous operation.

To conclude we developed a fast, continuous ruthenium-catalysed transfer hydrogenation of aromatic nitriles to afford primary amines. The system uses a commercial Ruthenium catalyst and IPA as solvent and hydrogen donor. This system was applied to 17 different nitriles affording their correspondent primary amines in good yields.

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Acknowledgment

Click here to insert acknowledgment text. Funding sources and grant numbers should be given above in the Funding Information section.

Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO (this text will be deleted prior to publication)

References and Notes

(1) Hayes, K. S. *Appl. Catal. A Gen.* **2001**, *221*, 187.
(2) Ruiz-Castillo, P.; Buchwald, S. L. *Chem. Rev.* **2016**, *116*, 12564.
(3) Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795.
(4) Leonard, J.; Blacker, A. J.; Marsden, S. P.; Jones, M. F.; Mulholland, K. R.; Newton, R. *Org. Process Res. Dev.* **2015**, *19*, 1400.
(5) Bähn, S.; Imm, S.; Neubert, L.; Zhang, M.; Neumann, H.; Beller, M. *ChemCatChem* **2011**, *3*, 1853.
(6) Gunanathan, C.; Milstein, D. *Angew. Chemie Int. Ed.* **2008**, *47*, 8661.
(7) Imm, S.; Bähn, S.; Zhang, M.; Neubert, L.; Neumann, H.; Klasovsky, F.; Pfeffer, J.; Haas, T.; Beller, M. *Angew. Chemie Int. Ed.* **2011**, *50*, 7599.
(8) Bagal, D. B.; Bhanage, B. M. *Adv. Synth. Catal.* **2015**, *357*, 883.
(9) Brieger, G.; Nestrick, T. J. *Chem. Rev.* **1974**, *74*, 567.
(10) Wang, D.; Astruc, D. *Chem. Rev.* **2015**, *115*, 6621.
(11) Werkmeister, S.; Bornschein, C.; Junge, K.; Beller, M. *Chem. – A Eur. J.* **2013**, *19*, 4437.
(12) Vilches-Herrera, M.; Werkmeister, S.; Junge, K.; Borner, A.; Beller, M. *Catal. Sci. Technol.* **2014**, *4*, 629.
(13) Shao, Z.; Fu, S.; Wei, M.; Zhou, S.; Liu, Q. *Angew. Chemie Int. Ed.* **2016**, *55*, 14653.
(14) Mai, V. H.; Nikonov, G. I. *Organometallics* **2016**, *35*, 943.
(15) Irfan, M.; Glasnov, T. N.; Kappe, C. O. *ChemSusChem* **2011**, *4*, 300.
(16) Cossar, P. J.; Hizartzidis, L.; Simone, M. I.; McCluskey, A.; Gordon, C. P. *Org. Biomol. Chem.* **2015**, *13*, 7119.
(17) Saito, Y.; Ishitani, H.; Ueno, M.; Kobayashi, S. *ChemistryOpen* **2017**, *6*, 211.
(18) Sharma, S. K.; Lynch, J.; Sobolewska, A. M.; Plucinski, P.; Watson, R. J.; Williams, J. M. J. *Catal. Sci. Technol.* **2013**, *3*, 85.
(19) Werkmeister, S.; Bornschein, C.; Junge, K.; Beller, M. *European J. Org. Chem.* **2013**, *2013*, 3671.
(20) Paul, B.; Chakrabarti, K.; Kundu, S. *Dalt. Trans.* **2016**, *45*, 11162.
(21) Lee, S.-H.; Nikonov, G. I. *ChemCatChem* **2015**, *7*, 107.
(22) Garduño, J. A.; García, J. J. *ACS Omega* **2017**, *2*, 2337.
(23) Labes, R.; Battilocchio, C.; Mateos, C.; Cumming, G. R.; Frutos, O. de; Rincón, J. A.; Binder, K.; Ley, S. V. *Submitted*.
(24) Uniqsis FlowSyn http://www.uniqsis.com/paFlowSystem.aspx (accessed Jun 7, 2017).
(25) ThalesNano. Phoenix Reactor http://thalesnano.com/phoenix-flow-reactor (accessed Jun 2, 2017).
(26) Under the conditions in Table 1 - Entry 5 cyclohexanecarbonitrile was not sucessfully converted to considerable amounts of the desired product. .