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Reaction Pairing: A Diversity-Oriented Synthesis Strategy for the Synthesis of Diverse Benzofused Sultams

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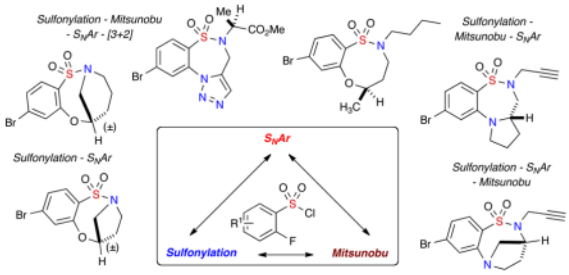
Abstract



A reaction pairing strategy centered on utilization of a reaction triad (sulfonylation, S_NAr addition and Mitsunobu alkylation) generating skeletally diverse benzofused tricyclic and bicyclic sultams is reported. Pairing sulfonylation and S_NAr reactions yields bridged, tricyclic and bicyclic benzofused sultams. Application of the Mitsunobu reaction in a sulfonylation–Mitsunobu–S_NAr pairing allows access to benzo-oxathiazocine-1,1-dioxides, while a simple change in the order of pairing to sulfonylation–S_NAr–Mitsunobu affords structurally different, benzofused bridged tricyclic sultams.

The development of new approaches to access diverse heterocycle collections for high throughput screening (HTS) is an important aspect in modern drug discovery. Diversity-oriented synthesis (DOS) has emerged in recent years as an enabling strategy for the production of diverse collections of heterocycles.[1] Key examples of DOS strategies include functional group pairing and build-couple-pair (BCP).[2] We herein report a reaction pairing strategy utilizing the ability of *o*-fluorobenzene sulfonamides to undergo nucleophilic aromatic substitution (S_NAr) for the facile generation of benzofused sultam scaffolds.

Sultams (cyclic sulfonamides) represent a class of non-natural chemotypes that have gained prominence in recent years due to their activity against a wide spectrum of biological targets.[3,4] Long–standing interest in the facile generation of sultam scaffolds has prompted the exploration of a reaction pairing strategy described herein. *o*-Halobenzene-sulfonyl chlorides and their corrsponding sulfonamides have emerged as highly versatile synthons for the generation of sultam scaffolds.[5] While sulfonylation and Mitsunobu alkyaltion are well precedented for sulfonamides,[6] the ability of these synthons to undergo facile nucleophilic

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Supporting Information Available: Experimental details and spectral charactization for all compounds, detailed in-silico analysis and crystal structure CIF files provided. This material is available free of charge via the Internet at http://pubs.acs.org.

aromatic substitution (S_NAr) is lesser known.[2f,5] Collectively, it was therefore envisioned that pairing of the reaction triad (sulfonylation, S_NAr addition and Mitsunobu alkylation) in varying order alongside the central *o*-fluorobenzenesulfonyl chloride building blocks could afford rapid access to both bridged-and fused-tricyclic sultams. This simple approach obviates the need for construction of elaborate multi-functional scaffolds and would merely require *o*-fluorobenzenesulfonyl chlorides, amines and alcohols as building blocks. Simple changes in the reaction pair sequence (eg. sulfonylation–S_NAr vs. sulfonylation–Mitsunobu–S_NAr) or changes in building blocks (1,2-amino alcohol vs 1,3-amino alcohol) allows access to skeletal and stereochemical diversity (Figure 1).

Investigations commenced with the exploration of pairing (*S*)-prolinol with 4-bromo-2-fluorobenzenesulfonyl chloride via a combination of sulfonylation, S_NAr and Mitsunobu methodologies (Scheme 1). Thus, (*S*)-prolinol was sulfonylated with 4- bromo-2-fluorobenzenesulfonyl chloride in CH_2Cl_2/H_2O, in the presence of $NaHCO_3$ to provide the β-hydroxy *o*-fluorobenzene sulfonamide **1** in 97% yield. Subjection of the sulfonamide to microwave (*m*W) irradiation at 150 °C for 30 minutes in DMF in the presence of Cs_2CO_3 gratifyingly produced the benzofused tricyclic sultam **2** in 88% yield. In contrast, S_NAr addition of (*S)*-prolinol to *n*-butyl-derived *o*-fluorobenzene sulfonamide **3** under *m*W irradiation in DMSO at 140 °C for 30 minutes afforded the desired S_NAr adduct **4** in 97% yield. Addition of PPh_3 to a stirring solution of the prolinol-derived S_NAr adduct in THF (0.05 M), followed by slow addition of DIAD, was found to proceed quickly (10 minutes) to furnish the desired tricyclic benzothiadiazepine-1,1-dioxde **5** in 91% yield. Overall, this approach rapidly furnishes different sultam skeletons implementing a single sulfonyl chloride in conjunction with an amino alcohol by merely changing the order of reaction pairing.

With these results in hand, the utilization of this reaction pairing strategy for the generation of benzofused sultams was explored. Thus, the use of (*S*)-prolinol alongside propargylamine derived *o*-fluorobenzene sulfonamides in the established S_NAr–Mitsunobu pairing afforded the desired tricycylic sultam **6** in good yield (Scheme 2). A simple switch in the amino alcohol component to (*R*)-(+)-3-hydroxypyrrolidine gratifyingly afforded the corresponding bridged, tricyclic benzofused sultams **7** and **8** in good moderate yield. Of notable importance, is the facile production of the unique bridged tricyclic sultam **7** containing a bridgehead nitrogen connected to an SO_2 moiety. It is proposed that this “bridged sultam”, like corresponding twisted amides, causes a deviation in the geometry of the sulfonamide group leading to proposed hybridization and geometry changes at nitrogen, ultimately affecting physical properties. [7,8] It has been reported that twisted amides (anti-Bredt’ amides) possess a distorted amide bond, which dramatically affect stability and reactivity in comparison to their standard planar amides while possessing a increased basicity of the nitrogen.[9]

Building on these results, utilization of 2-piperidinemethanol in the established reaction pairing protocol generated the corresponding benzofused tricyclic sultams **9** and **10** in good yield (Scheme 2). In contrast, use of 3-hydroxypiperidine allowed for the synthesis of the bridged benzofused sultams **11** and **12** in satisfactory yields (Figure 1), with **11** (see x-ray, SI) possessing similar bridged sultam’ structural characteristics as **7**. Overall, this reaction pairing sequence allowed for the rapid generation of a skeletally and stereochemically diverse collection of benzofused sultams by simple variation of the amine component.

Alternatively, it was envisioned that utilization of monoprotected diols, alongside *o*-fluorobenzene sulfonamides in a Mitsuonobu alkylation-intramolecular S_NAr *O*-arylation would allow access to oxygen-containing benzofused sultams **14a–c** (Scheme 3). Accordingly, 3-silyloxy-1-propanol was subjected to Mitsunobu alkylation with *n*-butyl-

derived *o*-fluorobenzene sulfonamide to furnish the 3° sulfonamide **3** in 97% yield. It was envisioned that deprotection of the TBS group under basic conditions would allow for an intramolecular S_NAr cyclization to take place. Accordingly, a THF solution of **13a** was stirred in the presence of TBAF for 30 minutes under *m*W irradiation at 150 °C to gratifyingly afford the desired sultam **14a** in 88% yield. Application of the enantiomers (*R*)- & (*S*)-3-((*tert*-butyldimethylsilyl)oxy)butan-1-ol in the above Mitsunobu–S_NAr pairing sequence was again found to cleanly furnish the corresponding benzothiazocine-1,1-dioxides **14b** and **14c** in good yields (Scheme 3). Overall, change in the order of the pairing of the S_NAr reaction with Mitsunobu alkylation to sulfonylation–Mitsunobu–S_NAr allows for face access to skeletally, as well stereochemically, diverse benzofused sultams.

Utilization of a [3+2] Huisgen cycloaddition reaction for the production of triazole-containing sultams was next explored. Hemming and coworkers have reported the elegent use of a one pot, tandem alkynylation-[3+2] cycloadditon approach to triazolosultams,[10] while a recent report by Yao and co-workers outline the utilization of a Cu catalyzed tandem [3+2] dipolar cycloadditio–N-arylation approach to these motifs utilizing *o*-bromo and *o*-iodobenzenesulfonamides. [11,12] However, there are no reports of the use of non-metal catalyzed, S_NAr–[3+2] Huisgen cycloaddition for the generation of benzofused sultams. Thus, a sulfonylation–Mitsunobu protocol using propargyl alcohol and *o*-fluorobenzene sulfonamide as the Mitsunobu partners produced the desired propargylated *o*-fluorobenzene sulfonamides **16a**–**d** in excellent overall yield (Scheme 4). Azidation of sulfonamides **16a**–**d** was carried out using NaN_3 in DMF at 90 °C in the presence of 18-crown-6 (1 equiv.) for 12 hours to afford the tricyclic triazole-containing sultams **17a**–**d**, which had participated in an intramolecular [3+2] Huisgen cycloaddition ring closure following intermolecular S_NAr azidation. To the best of our knowledge, this represents the first report of a one-pot tandem S_NAr-intramolecular [3+2] Huisgen cycloadditon for the synthesis of benzofused sultams.[13,14] Overall, the sulfonylation–Mitsunobu–S_NAr protocol is augmented by pairing with an intramolecular [3+2] cycloaddition protocol for the synthesis of triazol-containing benzofused sultams in 3 steps.

From chemical informatics analysis, utilizing a multifusion similarity (MFS) analysis,[15] it is apparent that sultams **2**–**12**, **14a–c** and **17a–d** (red) are fairly unique relative to the manifold of currently available analogs, and that there is a reasonable amount of structural diversity present.[16] Analysis was conducted against all 1198 compounds (blue) currently present in the NIH Molecular Libraries Probe Production Center Network (MLPCN) that contained the maximum common substructure (4-bromo-*N*-propylbenzenesulfonamide) evident within our own (Figure 2).

In conclusion, we have developed a reaction pairing strategy employing a reaction triad–sulfonylation, Mitsunobu, S_NAr for the rapid synthesis of a diverse collection of benzofused sultams. Simple changes to the order of the pairing sequence and/or building blocks, allows for access to skeletal and stereochemical diversity. Overall, this strategy affords a diverse set of heterocycles in 2–3 steps from commercially available building blocks. These results are highly amenable for library production to generate collections of skeletally diverse sultams for HTS screening.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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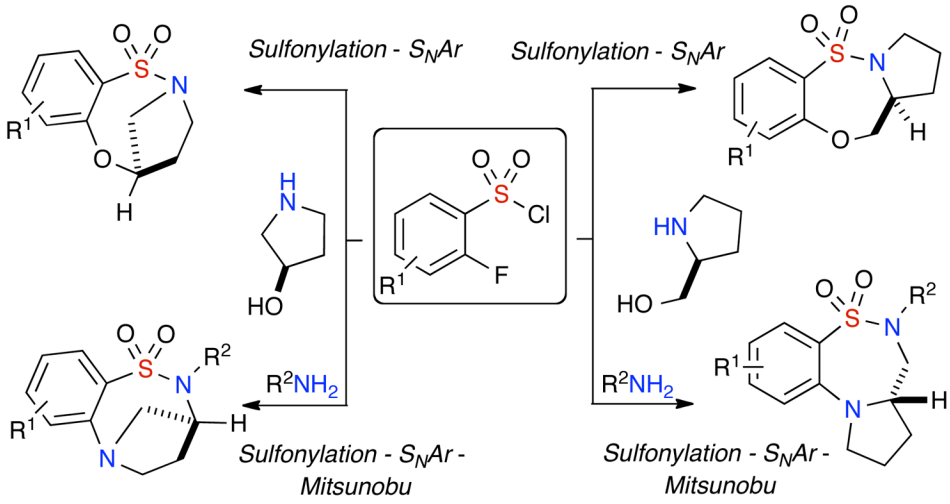


Figure 1.
Reaction pairing strategies to diverse benzofused sultams.

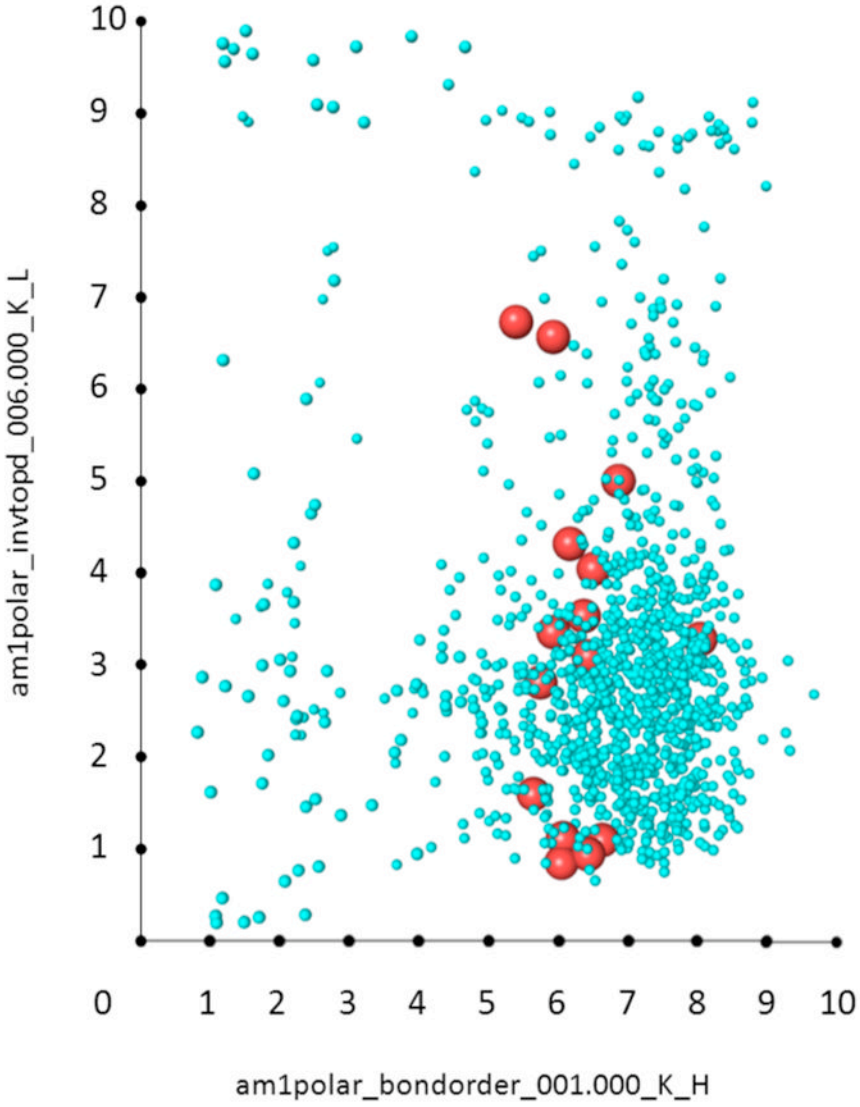
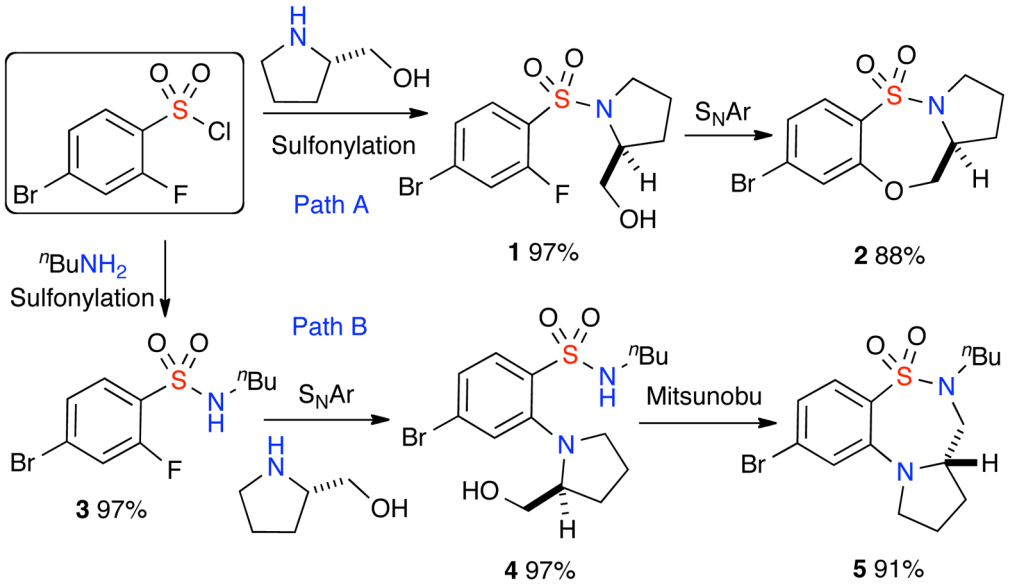


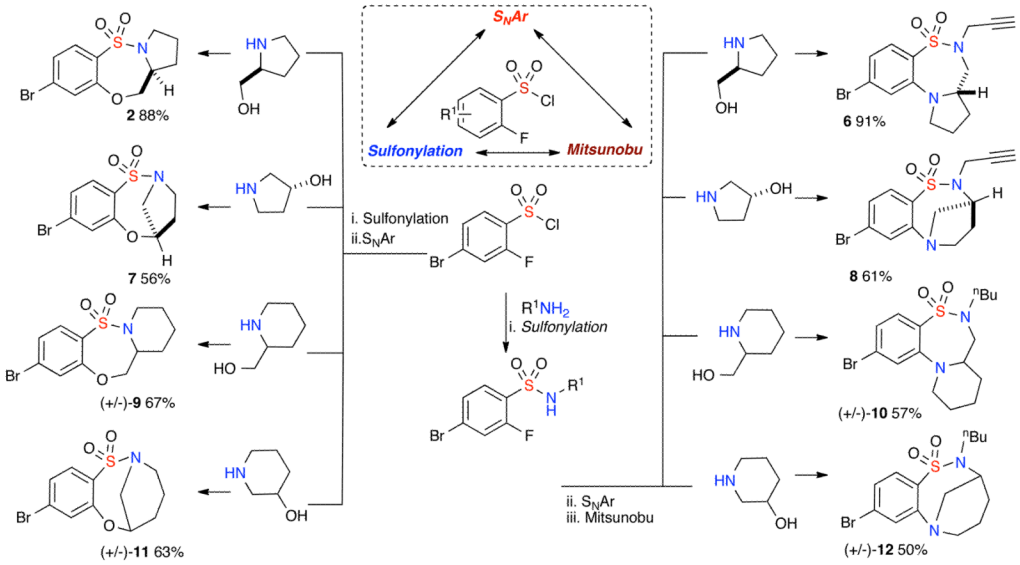
Figure 2.
Diversity distribution of sultams **2**–**12**, **14a–c** and **17a–d**, (red spheres) relative to analogous MLPCN compounds (blue) within a chemical space defined by BCUT polarizability metrics (x-axis reports values of an AM1 polarizability metric scaled by molecular bond-order profile; y-axis reports an AM1 polarizability metric scaled by an inverse topological distance profile).



Scheme 1.

Reaction pairing utilizing Sulfonylation–SNAr with amino alcohols.

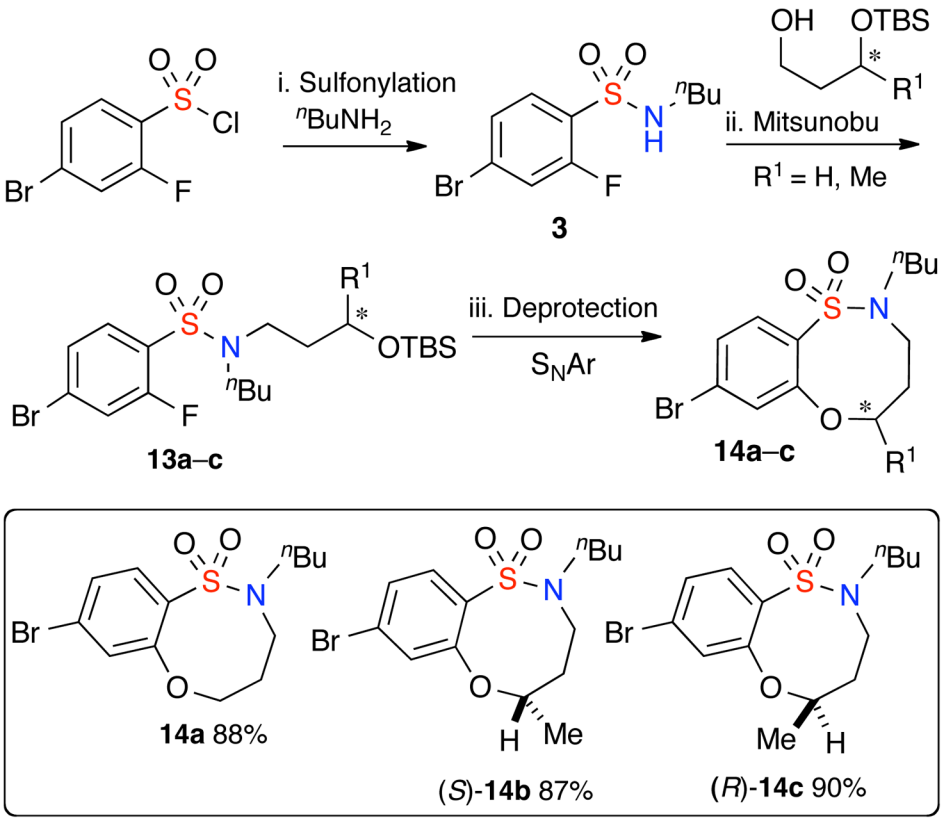
[a] **Sulfonylation**: $NaHCO_3$, CH_2Cl_2, H_2O, rt. **S_NAr**: Cs_2CO_3, DMF, 140 °C, *m*W. **Mitsunobu**: PPh_3, DIAD, THF, rt.



Scheme 2.

Reaction pairing strategy to access skeletally diverse sultams with an array of amino alcohols

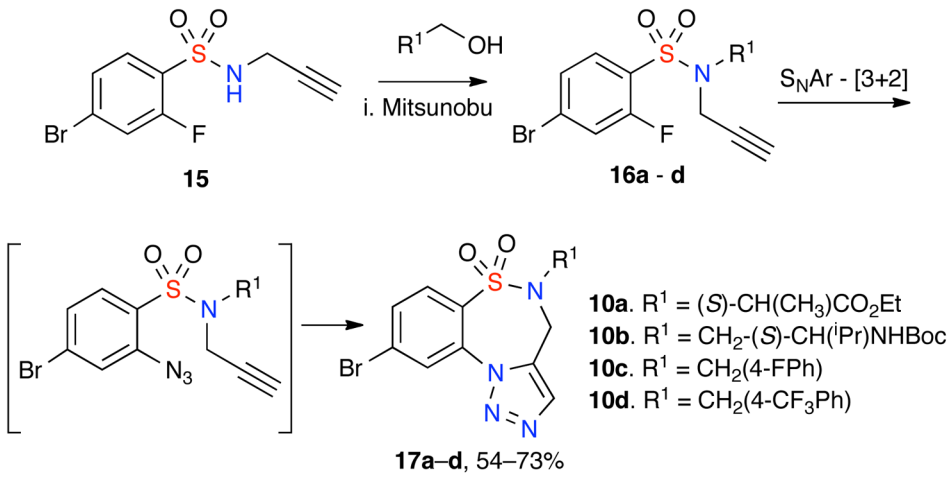
[a] **Sulfonylation**: R^1NH_2 [Compounds **6** & **8**, (R^1 = Propargyl) **10** and **12** (R^1 = $_n$Bu)], $NaHCO_3$, CH_2Cl_2, H_2O, rt. **S_NAr**: Cs_2CO_3, DMF, 140 °C, *m*W. **Mitsunobu**: PPh_3, DIAD, THF, rt.



Scheme 3.

Mitsunobu–Intramolecular S_NAr strategy to benzofused sultams.

[a] i. **Sulfonylation:** $NaHCO_3$, CH_2Cl_2, H_2O **ii. Mitsunobu**: PPh_3, DIAD, THF, rt. **iii. Deprotection-S_NAr cyclization:** TBAF, THF, 150 °C, *m*W.



Scheme 4.

Mitsunobu–azido S_NAr–[3+2] cyclization RP strategy to thiadiazepine 6,6-dioxides.

[a] **i. Mitsunobu**: PPh_3, DIAD, THF, rt. **ii Azido-S_NAr [3+2] Cyclization:** NaN_3, 18-c-6, DMF, 90 °C, 6–10 h