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Diels-Alder Reactions of 3-Furylamines in Organic and Aqueous Solvents.

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Abstract: Various 5-methyl-3-aminofurans have been shown to undergo facile Diels-Alder reactions with methyl acrylate in aqueous media. Reactions proceeded with exclusive regiochemistry, and enamine cycloadducts were readily hydrolysed to afford 7-oxabicyclo[2.2.1]heptanones in high yields.

Key words: Diels-Alder reaction, 3-furylamines, ionic solvents, 7-oxabicyclo[2.2.1]-heptanones.

Introduction

The Diels-Alder (D-A) reaction has become one of the most widely used synthetic tools in organic chemistry, providing a direct route to highly functionalized ring systems such as those found in carbohydrate and terpenoid structures.[1] It is often chosen in a synthetic pathway because of the predictability of its regiochemical outcomes and the ready accessibility of dienes and dienophiles.

The preparation of activated dienes has been achieved through the incorporation of heteroatom substituents onto the conjugated π system. The syntheses of heterosubstituted 1,3-butadienes[2] are well established, allowing access to specifically

functionalized reagents for the production of cyclic structures with complex substitution patterns. Furthermore, asymmetric activating substituents have shown remarkable success in achieving diastereoselectivity in [4π + 2π] cycloaddition reactions and, when labile, allow for the recovery of chiral auxiliaries[3, 4].

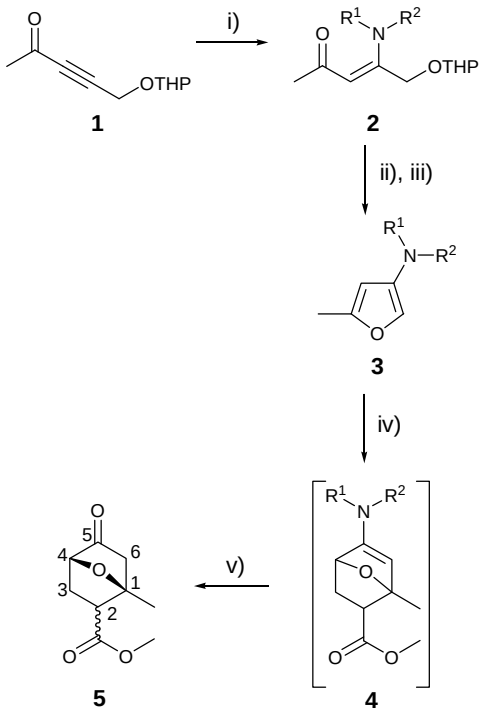
Furans are used in D-A reactions[5] as the general pathway to 7-oxabicyclo[2.2.1]heptenes and their derivatives. The low reactivity of furan dienes is often overcome by catalysis or by using elevated pressures and temperatures[6]. N-3'-furylbenzamide and 3-methylthiofuran[7, 8] undergo facile cycloaddition with mono-activated dienophiles, and Schlessinger *et al.* have demonstrated the preparation of oxabicycloheptanone adducts from chiral 3-furylamines for the construction of (+)-cyclophellitol[9, 10]. 2-Aminofurans have also been prepared by Padwa *et al.* and used in the preparation of substituted anilines and phenols[11, 12].

Bridged oxabicyclic products are useful building blocks for natural product synthesis[13] and were required for ongoing studies towards the ketone moiety of the biologically active neoclerodane diterpenoid salvinorin A[14]. Recent work undertaken by our group has focused on a general preparation of 3-furylamines as diene precursors to oxabicyclo[2.2.1]heptanones[15]. In this paper we wish to report our preliminary studies on the reactivity of 5-methyl-3-amino substituted furans in Diels-Alder cycloaddition reactions.

Results and Discussion

The chemistry of furans bearing amine substituents at the 3- or 4- position still remains largely unexplored. Preparation of 3-furylamines from tetrahydropyran-2-yloxy (THP)-protected alkynols has allowed the incorporation of a variety of amine substituents in these Diels-Alder substrates (Scheme 1).

Ab initio molecular-orbital studies suggest that the presence of an amino group on the furan ring has a destabilizing effect on the aromaticity of furan[16], as well as producing an increase in HOMO energy levels[12]. Both effects contribute to an increase in reactivity towards pericyclic reactions and promote exclusive selectivity in regiochemical outcomes.

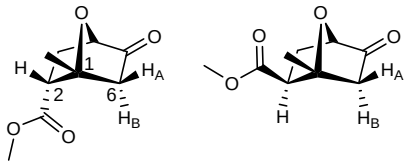


Scheme 1. (i) HNR^1R^2, neat or THF; (ii) TFA, DCE; (iii) Aq. NaOH; (iv) Methyl acrylate; (v) H_3O^+. NR^1R^2 = (a) morpholine, (b) diisopropylamine, (c) diethylamine, (d) dibenzylamine.

Preliminary D-A reactions were performed using various 5-methyl-3-furylamines and methyl acrylate (MAC) in a range of organic solvents. We were concerned to find that the reaction was unsuccessful using 4-(5-methylfuran-3-yl)morpholine **3a** in benzene, toluene and dioxane at room temperature and heating led to slow decomposition of the starting materials. However, cycloadduct **4a** was formed in moderate yield (60% via GCMS) in hexane at reflux and the reaction progressed cleanly to completion in dichloromethane (DCM) at ambient temperature. In DCM, decomposition accompanied reaction times longer than 12 hr for **3a-b** and no significant change in diastereomeric ratio was observed over time suggesting that the cycloaddition is under kinetic control. It should also be noted that the formation of by-products and decomposition create difficulties in differentiating changing diastereomeric ratios. The enamine **4** was labile to hydrolysis from traces of moisture and crude mixtures typically contained both **4** and **5**. Attempts to isolate **4** were unsuccessful and reversal to furylamine starting reagents

occurred during distillation and column chromatography on silica gel. Complete hydrolysis of the crude mixture was achieved under aqueous acidic conditions and the diastereomers of ketone **5** (Figure 1) were easily separated by flash column chromatography using pentane/EtOAc.

The regiochemistry of **5** was confirmed by NMR (COSY) analysis and was consistent with both FMO theory and the 'ortho/para' rule pertaining to D-A regioselectivity. Although the *endo*- adduct was found to be an oil, the *exo*- material was easily crystallized from Et_2O and **5b** was confirmed by x-ray crystal structure analysis (Figure 2) to establish the identity of each diastereomer. ^{1}H NMR analysis showed the expected 4 bond w-coupling of H-2 to H-6_A in the *endo*- isomer **5a** but not in the *exo*- isomer **5b**.



endo ***5a*** *exo* ***5b***

Figure 1. Diastereoisomers of methyl 1-methyl-5-oxo-7-oxa-bicyclo[2.2.1]heptane-2-carboxylate **5**.

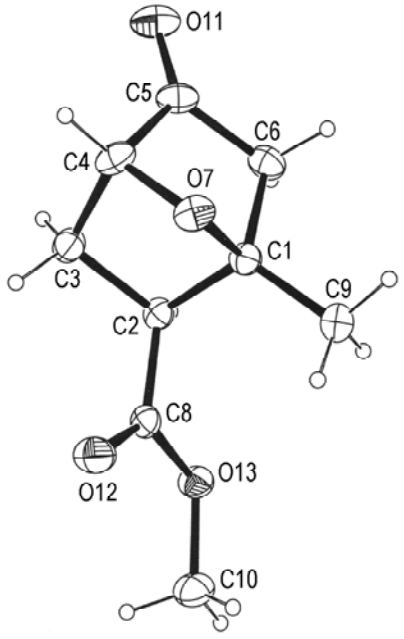


Figure 2. ORTEP drawing of *exo*-methyl 1-methyl-5-oxo-7-oxa-bicyclo[2.2.1]heptane-2-carboxylate **5b**.

The D-A studies were extended to the use of ionic solvents. Reactions in water gave impressive results with short reaction times using furans **3a**-**3c** provided all materials were freshly distilled (Table 1). Additional increases in ionic strength by the addition of lithium chloride shortened reaction times of furans **3b** and **3c** to less than 10 minutes at room temperature. Under aqueous conditions, the enamine intermediate **4** was hydrolysed *in situ* by continued stirring. It was interesting to note that although more hindered amines **3b** and **3d** gave poor yields in DCM, all furans studied were successfully transformed into products when the reaction was performed in water.

Table 1. Diels-Alder reactions of 3-furylamines (**3a-d**).

3	MAC (eq.)	Solvent	Temp. (^{o}C)	Time (hr.)	% Yield **5**[A]	*endo:exo*[C]
a	3.0	Toluene	111	12	0	-
a	3.0	Hexane	40	8	30	5:1
a	3.0	Hexane	50	8	45	7:1
a	3.0	Hexane	70	8	60[B]	9:1
a	3.0	Benzene	80	12	0[B]	-
a	3.0	Dioxane	100	24	0[B]	-
a	2.0	DCM	-78 to 0	8	4	2:1
a	2.0	DCM	4	8	69	2:1
a	2.0	DCM	r.t.	8	93	4:1
a	2.0	Water	r.t.	2	92	2:1
b	2.0	Toluene	60	8	0	-
b	2.0	Toluene	70	8	42[B]	1:1
b	1.5	DCM	r.t.	120	30[B]	1:1
b	1.0	DIMCARB	r.t.	1	>95	3:7
b	1.5	Water	r.t.	4	>95	1:2
b	1.5	Water/LiCl	r.t.	1	91	1:2
c	1.5	Water/LiCl	r.t.	1	>95	1:1
d	2.0	Water	r.t.	8	>95	4:1
d	2.5	DCM	r.t.	8	0	-

[A]Combined yields as determined by GC-MS.
[B]Significant decomposition.
[C]Ratio of diastereoisomers **5a**: **5b**.
Reactions in organic media performed using 1.2mmol of **3** in 10 mL solvent.

The increased rate of D-A reactions in aqueous solutions and aqueous salt solutions has been well documented since the discovery of the reaction itself and this has been attributed to hydrophobic packing and the increased internal pressure on hydrophobic substrates[17, 18]. The use of the ionic liquid DIMCARB[19] allowed reactions to be carried out under homogenous conditions, producing excellent results and offering an alternate benign solvent as a reaction medium.

In aqueous media gram quantities of racemic product **5** were made accessible using the furylamines **3a** and **3b**. Amines **3a** and **3d** required the addition of at least 2 equivalents of dienophile since the free amine consumed acrylate by 1,4-addition once hydrolysis had occurred. We also noticed that the longer reaction time of **3d,** bearing larger amine substituents, could be reduced to one hour when ultrasonic irradiation was employed as a means of enhancing the solubility of the furan in solution.

Further studies towards achieving enantioselectivity through the incorporation of non-racemic amines is currently under investigation. It is likely that chiral furylamines will allow access to enantioenriched mixtures of oxabicyclo[2.2.1]heptanes **5a** and **5b** as highly functionalized building blocks for the preparation of larger organic molecules. Provided both enantiomorphs of the chiral amine substituent are accessible, antipodes of both **5a** and **5b** can be prepared resulting in a general and flexible pathway to oxabicyclic structures with the desired stereo- and diastereo-chemical features.

Conclusion

In this paper we have described suitable reaction protocols for the Diels-Alder reaction of 5-methyl-3-aminofurans. General conditions have been realized using ionic reaction media to provide excellent yields and short reaction times. This methodology provides a convenient pathway to 7-oxabicyclo[2.2.1]heptanones, and diastereomers have been characterized by spectroscopic and crystallographic methods.

Experimental

Unless noted, materials were obtained from Aldrich Chemical Co. and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 (300MHz) NMR spectrometer and indirectly referenced to TMS *via* $CHCl_3$. FT-IR spectra were recorded on a Perkin-Elmer Spectrum 2000 Fourier transform IR spectrometer. GC-MS spectra were recorded using a Hewlett Packard 6890 GC with BPX-5 column, and Hewlett Packard 5973 Mass Selective Detector. Alkynone **1** and furylamines **3a-3d** were prepared by previously reported procedures[15].

^{1}H and ^{13}C NMR spectra reported for isolated compounds of purity >97%. Where ^{13}C data is included assignments are based on 2D experiments (DEPT, HMQC, HMBC, COSY) in each case.

General procedure for the Diels-Alder reaction of 3-furylamines in aqueous media.

Method 1. Freshly distilled 4-(5-methylfuran-3-yl)morpholine **3a** (100 mg, 0.60 mmol) was added to distilled water (20 mL) at ambient temperature, followed by MAC (103 mg, 1.20 mmol). The solution was allowed to stir at room temperature for 2 h then extracted with DCM (3 x 40 mL). The combined organic extracts were washed with HCl (0.5M, 2 x 20 mL), dried with $MgSO_4$ and evaporated to leave *methyl 1-methyl-5-oxo-7-oxa-bicyclo[2.2.1]heptane-2-carboxylate* **5** as a mixture of diastereomers (101 mg, combined yield 92%, d.r. 2:1). The diastereoisomers were separated by column chromatography in silica gel using 10:1 pentane:EtOAc, (**5a** R_f = 0.38, isolated yield 58%; **5b** R_f = 0.12, isolated yield 28%).

Method 2. Freshly distilled N,N-diisopropyl-5-methylfuran-3-amine **3b** (100 mg, 0.55 mmol) was added to a 3M solution of LiCl (20 mL) at ambient temperature, followed by MAC (71 mg, 0.83 mmol). The solution was allowed to stir at room temperature for 2 h then extracted with DCM (3 x 40 mL). The combined organic extracts were washed with HCl (0.5M, 2 x 20 mL), dried with $MgSO_4$ and evaporated to leave *methyl 1-methyl-5-oxo-7-oxa-bicyclo[2.2.1]heptane-2-carboxylate* **5** as a mixture of diastereomers (93 mg, Combined yield 91%, d.r. 1:2).

Procedure for the Diels-Alder reaction of 3-furylamines in organic media.

Example: Freshly distilled 4-(5-Methylfuran-3-yl)morpholine **3a** (200 mg, 1.2 mmol) was added to DCM (10ml) at ambient temperature, followed by MAC (210 mg, 2.4 mmol). The solution was allowed to stir at room temperature for 8hr then DCM (30 ml) was added and the reaction mixture vigorously shaken with HCl (0.5M, 3 x 20 ml). The aqueous acidic layers were re-extracted with DCM (2 x 20 ml) and the combined organic phases dried with Na_2SO_4 and evaporated to leave *methyl 1-methyl-5-oxo-7-oxa-bicyclo[2.2.1]heptane-2-carboxylate* **5** as a mixture of diastereomers (205 mg, Combined yield 93%, d.r. 4:1).

Endo-methyl 1-methyl-5-oxo-7-oxa-bicyclo[2.2.1]heptane-2-carboxylate **5a**. Pale yellow oil. IR (neat)/cm^{-1} 2956w, 1767s, 1733s, 1438w, 1388w, 1353w, 1320w, 1252w, 1203m, 1178m, 1149w, 1052w. ^{1}H (300MHz; $CDCl_3$) δ 4.37 (1H, d, *J* = 4.2 Hz, H-4), 3.72 (3H, s, H-10), 2.88 (1H, ddd, *J*1 = 11.4 Hz, *J*2 = 5.4 Hz, *J*3 = 2.1 Hz, H-2), 2.39 (1H, d, *J* = 17.8 Hz, H-6_A), 2.33 (1H, m, H-3_A), 2.17 (1H, apparent d, *J* = 18.4 Hz, H-6_B), 2.16 (1H, m, H-3_B), 1.7 (3H, s, H-9). ^{13}C (75MHz; $CDCl_3$) δ 210.3 (C-5), 172.2 (C-8), 86.0 (C-1), 81.4 (C-4), 52.5 (C-10), 51.0 (C-2), 46.0 (C-6), 30.9 (C-3), 21.5 (C-9). Mass Spectrum *m/z* 184 ($M^{+\cdot}$, 6.3%), 156 (7.9), 153 (14.3), 152 (12.7), 140 (7.1), 138 (11.1), 128 (13.5), 124 (12.7), 114 (11.7), 113 (42.1), 111 (41.3), 110 (7.9), 99 (15.9), 98 (100), 97 (24.6), 96 (27.0), 95 (18.3), 87 (9.5), 85 (9.5), 83 (46.0), 82 (17.5), 81 (14.3), 79 (7.9), 73 (7.9), 71 (9.5), 69 (50.8), 68 (37.3), 67 (30.2), 59 (23.8), 55 (51.6), 53 (22.2), 43 (84.1).

Exo-methyl 1-methyl-5-oxo-7-oxa-bicyclo[2.2.1]heptane-2-carboxylate **5b**. White crystalline solid, m.p. 104 – 105°C. IR (KBr disk)/cm^{-1} 3033m, 2961w, 1762s, 1731s, 1441m, 1431m, 1392s, 1362s, 1253m, 1222m, 1199s, 1171s, 1148m, 1077w, 1038m, 1006s. ^{1}H (300MHz; $CDCl_3$) δ 4.47 (1H, d, *J* = 6.4 Hz, H-4), 3.55 (3H, s, H-10), 2.80 (1H, dd, *J*1 = 8.7 Hz, *J*2 = 5.1 Hz, H-2), 2.52 (1H, dt, *J*1 = 13.4 Hz, *J*2 = 5.9 Hz, H-3_A), 2.25 (2H, m, AB quartet, H-6), 1.94 (1H, dd, *J*1 = 13.4 Hz, *J*2 = 8.7 Hz, H-3_B), 1.55 (3H, s, H-9). ^{13}C (75MHz; $CDCl_3$) δ 211.0 (C-5), 173.0 (C-8), 86.3 (C-1), 80.7 (C-4), 52.3 (C-10), 50.5 (C-6), 49.4 (C-2), 30.7 (C-3), 19.3 (C-9). Mass Spectrum *m/z* 184 ($M^{+\cdot}$, 9.5), 156 (17.5), 153 (27.8), 152 (15.9), 141 (7.1), 140 (14.3), 138 (22.2), 128 (27.0), 127 (7.9), 124 (27.0), 114 (18.3), 113 (65.1), 111 (59.5), 99 (15.9), 98 (98.4), 97 (39.7), 96 (41.3), 95 (17.5), 87 (10.3), 85 (11.1), 83 (66.7), 82 (23.0), 81 (21.4), 80 (9.5), 79 (11.9), 73 (11.1), 71 (7.9), 69 (68.3), 68 (44.4), 67 (51.6), 59 (30.2), 55 (63.5), 54 (8.7), 53 (18.3), 44 (11.1), 43 (100), 42 (19.0), 41 (85.7). High Resolution Mass Spectrum (HRESI) Found $[M]^{+\cdot}$, 207.0631. $C_9H_{12}O_4Na$ $[M]^{+\cdot}$ requires 207.0633.

Crystal Data for **5b**. $C_9H_{12}O_4$, MW = 184.19, T = 293(2) K, λ = 0.71073 Å, triclinic, space group *P*-1, *a* = 7.2235(10), *b* = 8.1158(11), *c* = 8.3058(12) Å, $\alpha = 75.273(2)^o$, $\beta = 74.540(3)^o$, $\gamma = 86.114(2)^o$, *V* = 453.89(11) $Å^3$, Z = 2, D_c = 1.348 Mg/m^3, μ(Mo Kα) = 0.106 mm^{-1}, F(000) = 196, crystal size 0.50 x 0.15 x 0.10 mm^3, 2428 reflections measured, 1583 independent reflections (R_{int} = 0.0587); the final *w*R(F^2) was 0.1414 (all data) and final R was 0.0529 for 1311 unique data [$I > 2\sigma(I)$]. Goodness of fit on F^2 = 1.029. Crystallographic data for the structure reported has been deposited with the Cambridge Crystallographic Data Centre as deposition No. 288600. Copies of the data can be obtained, free of charge, via www.ccdc.ca.ac.uk or on application to Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB@ 1EZ, UK (fax: +44 1233 336033).

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References

[1] K. C. Nicolaou, S. A. Snyder, T. Montagnon, G. Vassilikogiannakis, *Agnew. Chem. Int. Ed. Engl.* **2002**, 41, 1668.

[2] M. Petrzilka, J. I. Grayson, *Synthesis*. **1981**, 10, 753.

[3] J. Barluenga, F. Anzar, C. Ribas, C. Valdés, *J. Org. Chem*. **1997**, 62, 6746.

[4] S. A. Kozmin, V. H. Rawal, *J. Am. Chem. Soc*. **1997**, 119, 7165.

[5] L. F. Tietze, G. Kettschaw, *Top. Curr. Chem.* **1997**, 189, 1.

[6] U. Pindur, G. Lutz, C. Otto, *Chem. Rev*. **1993**, 93, 741.

[7] I. Yamamoto, K. Narasaka, *Chem. Lett.* **1995**, 1129.

[8] J. N. Bridson, *Can. J. Chem.* **1979**, 57, 314.

[9] R. H. Schlessinger, T. R. R. Pettus, J. P. Springer, K. Hoogsteen, *J. Org. Chem.* **1994**, 59, 3246.

[10] R. H. Schlessinger, C. P. Bergstrom, *J. Org. Chem.* **1995**, 60, 16.

[11] J. E. Cochran, T. Wu, A. Padwa, *Tetrahedron Lett.* **1996**, 37, 2903.

[12] A. Padwa, M. Dimitroff, A. G. Waterson, T. Wu, *J. Org. Chem.* **1997**, 62, 4088.

[13] D. Josien-Lefebvre, C. Le Drain, *Helv. Chim. Acta.* **2003**, 86, 661.

[14] (a) L. J. Valdés III, *J. Psych. Drugs* **1994**, 26, 277; (b) D. J. Siebert, *J. Ethnopharmacol.* **1994**, 43, 53.

[15] A. R. Lingham, T. J. Rook, H. M. Hügel, *Aust. J. Chem.* **2002**, 55, 795.

[16] I. G. John, L. Radom, *J. Am. Chem. Soc.* **1978**, 100, 3981.

[17] L. Chao-Jun, C. Tak-Hang, in *Organic Reactions in Aqueous Media*. **1997**, Ch. 1-2, pp. 6-17 (John Wiley & Sons: New York).

[18] A. Kumar, *Chem. Rev.* **2001**, 101, 1.

[19] U. P. Kreher, A. E. Rosamilia, C. L. Raston, J. L. Scott, C. R. Strauss, *Molecules.* **2004**, 9, 387.