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Synthesis of Some 3-Furylamine Derivatives

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A general and efficient method for the synthesis of 3-furylamines via Michael addition of amines to acyclic keto alkynol precursors has been achieved. The preparation of various 3-furylamines has been carried out using a flexible methodology which also allows modification of the substituent at the 5-position.

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Introduction

Furans serve as versatile building blocks in synthetic chemistry,^[1,2] and many biologically-active molecules^[3] and natural products^[4] incorporate the furan moiety. This has resulted in the continued development of many routes to furan derivatives.^[5] These compounds can be synthesized by functional group interconversions on the furan ring or by cyclization of acyclic precursors. Although the chemistry of furans permits ready functionalization at the 2- and 5-positions, similar operations at the 3- or 4-positions are difficult to achieve.

Electron-rich furan derivatives are exceptionally useful dienes for use in Diels–Alder reactions. Recently, in an attempt to significantly increase the electron density and hence the reactivity of furans, Padwa et al.^[6] prepared 2-aminofuran derivatives to be used in Diels–Alder reactions. These were subsequently used for preparing substituted anilines.

Research projects currently undertaken by our group have required the synthesis of a series of 5-alkyl-3-aminofurans as asymmetric precursors for the synthesis of bridged oxabicyclo compounds. Literature searches revealed numerous syntheses of 3-amino substituted furans from acyclic precursors. These include the base catalyzed [3,2]-sigmatropic rearrangement of a phenyl-(prop-2-ynyl) ammonium salt to give an allene intermediate, which spontaneously cyclizes to give the 2-methyl-5-phenyl-3-*N*-substituted furan.^[7] Reaction of diacetylenic glycols with amines under aqueous conditions has also proven to give 2,5-dialkyl-3-dialkylaminofurans in good yields.^[8] However, these approaches provide furans containing additional substitution at the 2- and 5-positions and removal or modification of these substituents while following the same synthetic methodology may be quite difficult. Syntheses by functional group interconversions on the 3-substituted furan ring included the preparation of the stable 3-acetamidofuran from commercially available 3-furoic acid,^[9] but methods of further substitution onto the

3-acetamidofuran may be complicated due to the presence of the amide functional group.

None of these well known or recently published preparations of 3-aminofuran derivatives^[7–10] provides a means of incorporating both a 5-alkyl group and a variety of 3-amino substituents.

Results and Discussion

Reports of 3-aminofuran derivatives are scarce in published literature and the chemical properties of these compounds remain largely unexplored. Numerous references^[11,12] imply that 3-aminofuran itself would be relatively unstable. Its enthalpy of tautomerization is remarkably low (0.061 eV)^[11] (Fig. 1), which suggests that the imine tautomer may be abundant and provide a facile pathway for unwanted side reactions.

In addition, *ab initio* molecular-orbital studies^[12] suggest that the presence of an amino group on the furan ring, especially in the 3- and 4-positions, has a considerably larger destabilizing effect than it does on a benzene ring.

Given the inherent instability of the unsubstituted 3-aminofuran, approaches to the preparation of mono and bis *N*-substituted 3-aminofurans were investigated. An exhaustive search of the literature revealed one reference for the preparation of 3-piperidino-2,5-dipropyl furan.^[13]

We have found that modification of this older and generally unutilized methodology provides a general and efficient route to a series of 3-*N*-substituted and 5-alkyl-3-*N*-substituted furan derivatives from acyclic precursors (Scheme 1).

Using literature procedures,^[14–16] propargyl alcohol (1) was first reacted with 3,4-dihydro-2*H*-pyran to form (2)

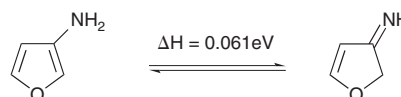
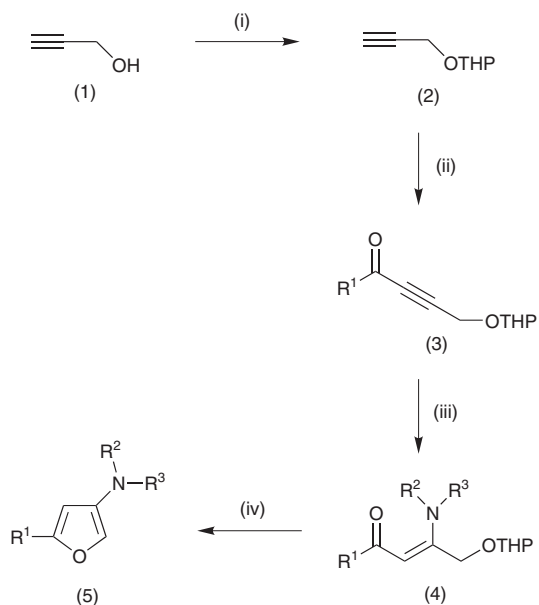


Fig. 1.



Scheme 1. (i) 3,4-Dihydro-2H-pyran, POCl₃; (ii) NaNH₂ (R¹CO)₂O, R¹ = Me, Et; BuⁿLi, DMF, R¹ = H; (iii) R²R³NH; (iv) TFA in 1,2-dichloroethane, NaOH.

(Scheme 1), which was then converted into the tetrahydropyran (THP)-protected keto alkynol (3) using sodamide and acetic or propanoic anhydride [R¹ = Me, Et], or BuⁿLi and dimethylformamide (DMF) [R¹ = H]. Michael addition reactions when R¹ = Me, Et were performed neat by the addition of equimolar amounts of the amine to (3). When R¹ = H, best yields were obtained when the reaction was performed in dry tetrahydrofuran (THF) at 5°C by the addition of (3) to the amine. Most amines reacted exothermically during the addition with the exception of the more hindered amines, diisopropylamine and dibenzylamine, which required mild heating and prolonged stirring in order to achieve optimal yields. Gas chromatography (GC) and ¹H nuclear magnetic resonance (NMR) analysis of the crude Michael-addition products indicated almost quantitative yields of enaminones (4). It is of interest to note that the Michael-addition products (4a)–(4k), where R¹ = Me, Et, gave the *E*-isomer, whereas products (4l) and (4m), where R¹ = H, gave the *Z*-isomer. The Michael-addition product of (4n) gave a 2 : 1 mixture of *E*- and *Z*-isomers. THP deprotection of (4) with trifluoroacetic acid (TFA) and aqueous alkaline reaction workup resulted in cyclization and dehydration to give the furans (5). Products which required no derivatization were directly isolated in >95% purity (Table 1).

3-Dialkylamino-substituted furans were stable as the free bases and could be stored for long periods at 0°C. 3-*N*-alkyl substituted furans (5) (R³ = H) were stable in solution at 0°C, and for characterization were isolated as their *N*-acetyl derivatives (6) (Scheme 2).

When R¹ = alkyl (a)–(k), higher product yields were obtained than for the unsubstituted R¹ = H (l)–(n) series of compounds. Amine substituents containing more hydrophilic groups gave higher yields of cyclized product compared with substituents containing bulkier organic groups. This may

Table 1. Yields of 3-*N*-substituted furans (5)

(5)	R ¹	R ² R ³ NH	% yield
a	Me	morpholine	96
b	Me	diethylamine	90
c	Me	diisopropylamine	95
d	Me	pyrrolidine	84
e	Me	dibenzylamine	73
f	Me	ethylenediamine	73 ^A
g	Me	<i>n</i> -butylamine	90 ^A
h	Me	cyclohexylamine	86 ^A
i	Et	morpholine	91
j	Et	diethylamine	88
k	Et	<i>n</i> -butylamine	84 ^A
l	H	morpholine	67
m	H	diethylamine	64
n	H	<i>n</i> -butylamine	65 ^A

^A The monosubstituted C₃-amines were isolated as *N*-acetyl derivatives.



Scheme 2. ^A Where R² = *n*-butyl, ethylene diamine. ^B Where R² = cyclohexylamine.

indicate that the aqueous workup is less efficient for more hydrophobic amine substituents.

Aniline underwent Michael addition with the protected keto alkynol (3) using the same general procedure as for amines (c) and (e), and was also successfully cyclized to the furan (5). An efficient derivatization method for the *N*-(furan-3-yl)aniline has not yet been found and the free amine is only stable for 1–2 h in ethereal solution at room temperature.

Conclusion

In this paper we have presented a versatile and high yielding synthesis of a range of 3-*N*-substituted and 5-alkyl-3-*N*-substituted furans.

The methodology described allows for the introduction of a variety of amine substituents in the 3-position, as well as the selective introduction of alkyl groups in the 5-position.

Experimental

Unless noted, materials were obtained from Aldrich Chemical Co. and used without further purification. Diethyl ether and THF were dried first with CaH₂, and then distilled from sodium/benzophenone before use. ¹H and ¹³C NMR spectra were recorded on a Varian Gemini 2000 (200 MHz) Fourier transform (FT) spectrometer, and were referenced to CHCl₃. FT-infrared (IR) spectra were recorded on a Perkin-Elmer Spectrum 2000 Fourier transform IR spectrometer. Gas chromatography mass spectra (GCMS) were recorded using a Hewlett Packard 5890 GC with a BPX-5 column and a Hewlett Packard 5970 mass selective detector.

3-(Tetrahydropyran-2-yloxy)prop-1-yne (2)^[14]

Phosphorus oxytrichloride (100 mg) was added to a mixture of propargyl alcohol (8.4 g) and 3,4-dihydro-2H-pyran (12.6 g), and stirred whilst

cooling in an ice bath until no more heat evolved. It was then stirred at room temperature for 2 h. Several NaOH pellets were added and the 3-(tetrahydropyran-2-yloxy)prop-1-yne was distilled directly from the reaction vessel under vacuum (19 g, 90% yield), b.p. 28°C/25 mmHg.

5-(Tetrahydropyran-2-yloxy)pent-3-yn-2-one (3, R¹ = Me)^[15]

3-(Tetrahydropyran-2-yloxy)prop-1-yne (28 g) was added dropwise under an inert atmosphere to a stirred mixture of sodamide (7.8 g) in anhydrous diethyl ether (150 mL). The mixture was then heated to reflux for 5 h. The suspension was diluted with anhydrous ether (200 mL) and poured into a vigorously stirred solution of acetic anhydride (20.4 g) in anhydrous ether (300 mL), the temperature being kept between –5 and –10°C. The mixture was allowed to reach room temperature and the white solid was separated by filtration. The solvent was evaporated under reduced pressure and any unreacted materials were removed using a high vacuum oil pump and gentle heating on a water bath (60°C). The product was obtained as a red oil (25 g, 70%).

The same method, as outlined above, was used to produce 6-(tetrahydropyran-2-yloxy)hex-4-yn-3-one (3, R¹ = Et), using propanoic anhydride.

4-(Tetrahydropyran-2-yloxy)but-2-ynal (3, R¹ = H)^[16]

3-(Tetrahydropyran-2-yloxy)prop-1-yne (7 g) was dissolved in dry THF (100 mL) and the solution cooled to –40°C under nitrogen. *n*-Butyllithium (1.6 M in hexane, 32 mL) was added dropwise and the solution was stirred at between –30°C and –40°C for 30 min. Anhydrous DMF (7.8 mL, 100 mmol) was added at once and the solution was allowed to warm to room temperature. Stirring was continued at room temperature for an additional 30 min, and the solution was then poured into a vigorously stirred biphasic solution of 10% KH₂PO₄ (250 mL) and diethyl ether (200 mL) at 5°C. The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 × 75 mL). The combined organic phases were dried, filtered, and concentrated to leave 4-(tetrahydropyran-2-yloxy)but-2-ynal (7 g, 84%) as a yellow viscous oil which was warmed on a water bath (60°C) under high vacuum to remove starting materials.

Michael Addition of Amines to Alkynone (3)

4-Morpholino-5-(tetrahydropyran-2-yloxy)pent-3-en-2-one (4a)

Morpholine (0.24 g) was added dropwise with stirring to neat 5-(tetrahydropyran-2-yloxy)pent-3-yn-2-one (3) (0.5 g) while cooling in a cold water bath (10°C). The viscous oil was then allowed to stir at room temperature for 2 h to afford *compound (4a)* (98%, GCMS). δ_{H} (200 MHz; CDCl₃) 1.90–1.40 (6H, m), 2.10 (3H, s), 3.35 (4H, m), 3.55 (1H, m), 3.73 (4H, t, *J* 5.0), 3.85 (1H, m), 4.68 (1H, m), 4.71 (1H, d, *J* 11.9), 5.20 (1H, s), 5.29 (1H, d, *J* 11.9). ^{13}C NMR (200 MHz; CDCl₃) 20.2, 25.5, 31.0, 32.3, 47.0, 60.8, 63.5, 66.6, 98.2, 100.0, 158.8, 195.9. Mass spectrum *m/z* 269 (M⁺, 3%), 210 (4), 186 (11), 185 (100), 184 (39), 170 (15), 169 (16), 168 (28), 167 (12), 166 (4), 157 (5), 156 (52), 154 (8), 152 (15), 150 (6), 143 (8), 142 (89), 140 (4), 138 (7), 137 (5), 136 (3), 127 (12), 126 (60), 124 (9), 114 (9), 112 (9), 110 (9), 109 (12), 108 (4), 98 (5), 97 (8), 96 (7), 92 (5), 86 (16), 85 (38), 84 (13), 83 (9), 82 (6), 81 (4), 80 (4), 70 (5), 69 (5), 68 (6), 67 (15), 57 (12), 56 (8), 55 (15), 54 (5), 43 (25), 42 (5), 41 (15).

Compounds (4b), (4d), (4f)–(4k) were also prepared using the procedure described above. Their characterization data are included in the Accessory material.

4-Dibenzylamino-5-(tetrahydropyran-2-yloxy)pent-3-en-2-one (4e)

Dibenzylamine (0.54 g) was added to 5-(tetrahydropyran-2-yloxy)pent-3-yn-2-one (3) (0.5 g) and stirred for 45 min in a warm water bath (70°C). The oil was allowed to stir for an additional 8 h at room temperature to give *compound (4e)* (97%, GCMS). δ_{H} (200 MHz; CDCl₃) 1.76–1.30 (6H, m), 1.95 (3H, s), 3.44 (1H, m), 3.78 (1H, m), 4.49 (4H, ABq, *J* 5.7), 4.74 (1H, m), 4.87 (1H, d, *J* 11.5), 5.20 (1H, s), 5.28 (1H, d, *J* 11.5), 7.40–7.07 (10H, m). ^{13}C NMR (200 MHz; CDCl₃) 19.9, 25.5, 30.8,

32.4, 52.8, 61.1, 63.1, 97.8, 99.9, 127.0, 127.6, 128.9, 136.7, 158.8, 195.6. Mass spectrum *m/z* 379 (M⁺, 1%), 336 (1), 296 (2), 295 (13), 294 (6), 288 (5), 280 (2), 279 (2), 278 (5), 277 (5), 276 (2), 262 (2), 252 (3), 236 (4), 234 (3), 232 (2), 205 (11), 204 (79), 189 (2), 188 (16), 186 (8), 162 (11), 160 (2), 158 (2), 146 (5), 144 (5), 143 (2), 132 (2), 117 (2), 115 (2), 106 (2), 105 (2), 104 (2), 92 (16), 91 (100), 85 (26), 67 (4), 65 (6), 57 (4), 55 (2), 43 (5), 41 (4).

Compound (4c) was also prepared using the procedure described above. Its characterization data is included in the Accessory material.

3-Diethylamino-4-(tetrahydropyran-2-yloxy)but-2-enal (4m)

4-(Tetrahydropyran-2-yloxy)but-2-ynal (0.5 g) was added dropwise over 15 min to a solution of diethylamine (0.22 g) in dry THF (40 mL) at 5°C. The solution was allowed to reach room temperature and was stirred for an additional 4 h. The solvent was removed under vacuum to afford *3-diethylamino-4-(tetrahydropyran-2-yloxy)but-2-enal (4m)* (94%, GCMS). δ_{H} (200 MHz; CDCl₃) 1.18 (6H, t, *J* 7.1), 1.90–1.40 (8H, m), 3.32 (4H, q, *J* 7.0), 3.53 (1H, m), 3.80 (1H, m), 4.58 (2H, s), 4.66 (1H, m), 5.24 (1H, d, *J* 8.3), 9.62 (1H, d, *J* 8.3). ^{13}C NMR (200 MHz; CDCl₃) 12.8, 19.5, 25.4, 30.5, 44.4, 59.8, 62.7, 98.1, 102.8, 159.7, 187.5. Mass spectrum *m/z* 241 (M⁺, 1%), 212 (1), 208 (2), 207 (5), 182 (2), 158 (3), 157 (9), 156 (28), 147 (2), 142 (5), 141 (18), 140 (30), 139 (3), 138 (3), 129 (6), 128 (75), 126 (10), 125 (2), 124 (23), 122 (8), 114 (3), 113 (13), 112 (52), 110 (14), 108 (2), 105 (2), 100 (6), 99 (4), 98 (18), 97 (6), 96 (14), 95 (2), 94 (4), 86 (9), 85 (88), 84 (33), 83 (19), 82 (18), 81 (4), 80 (3), 74 (4), 73 (10), 72 (19), 71 (19), 70 (55), 69 (24), 68 (19), 67 (28), 58 (21), 57 (57), 56 (42), 55 (44), 54 (22), 53 (8), 45 (4), 44 (28), 43 (54), 42 (65), 41 (100).

Compounds (4l) and (4n) were also prepared using the procedure described above. Their characterization data are included in the Accessory material.

Hydrolysis of THP-Protecting Group and Cyclization to Furan

4-(5-Methylfuran-3-yl)morpholine (5a)

Anhydrous trifluoroacetic acid (2 mL) was added to 4-morpholino-5-(tetrahydropyran-2-yloxy)pent-3-en-2-one (0.5 g) in 1,2-dichloroethane (20 mL). The solution was then stirred for 40 min at room temperature and gradually became deep red in colour. The organic layer was extracted with distilled H₂O (4 × 50 mL) and the combined aqueous extracts were extracted once with chloroform. Crushed ice (100 g) was added to the aqueous layer followed by an excess of conc. aq. NaOH. The aqueous solution was extracted while still cold with ether (3 × 75 mL), the organic layer dried with MgSO₄ and then evaporated to leave *4-(5-methylfuran-3-yl)morpholine (5a)* in high purity and yield. IR (neat)/cm^{–1} 3140w, 2960s, 2918s, 2855s, 2820s, 2760m, 1755m, 1681s, 1621s, 1555m, 1451s, 1397s, 1379s, 1359m, 1332m, 1302m, 1258s, 1228m, 1178m, 1161m, 1116s. δ_{H} (200 MHz; CDCl₃) 2.22 (3H, s), 2.87 (4H, m), 3.81 (4H, m), 5.86 (1H, s), 6.82 (1H, s). ^{13}C NMR (200 MHz; CDCl₃) 14.0, 50.8, 66.6, 100.2, 123.9, 141.7, 152.5. Mass spectrum *m/z* 169 (19%), 168 (56), 167 (M⁺, 78), 166 (6), 154 (3), 153 (8), 152 (12), 139 (4), 138 (10), 137 (6), 136 (8), 125 (3), 124 (8), 122 (8), 112 (7), 111 (34), 110 (83), 109 (100), 108 (12), 97 (2), 96 (4), 95 (4), 94 (6), 84 (4), 83 (4), 82 (11), 81 (15), 80 (16), 79 (4), 73 (3), 72 (2), 70 (4), 69 (4), 68 (4), 67 (6), 66 (5), 65 (3), 59 (2), 58 (2), 57 (5), 56 (4), 55 (9), 54 (8), 53 (8), 52 (3), 51 (4), 45 (9), 44 (49), 43 (15), 42 (10), 41 (18). High-resolution mass spectrum (HRMS) Found [M]⁺, 168.1019. C₉H₁₄NO₂ [M]⁺ requires 168.1025.

Cyclizations of all products (5b)–(5n) were performed using this procedure. Their characterization data are included in the Accessory material.

Accessory Material

Copies of the accessory material are available, until January 2008, from *Australian Journal of Chemistry— an International Journal for Chemical Science* (website: www.publish.csiro.au/journals/ajc/AcessMat.cfm).

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References

- [1] W. Eberbach, in *Houben-Weyl Methoden der Organischen Chemie* (5th Edn) **1994**, Vol. E6a, p. 16 (Thieme: Stuttgart).
- [2] Y. Kobayashi, M. Nakano, C. Biju Kumer, K. Kishihara, *J. Org. Chem.* **1998**, *63*, 7505.
- [3] T. H. Brown, M. A. Armitage, R. C. Blakemore, P. Blurton, G. J. Durant, C. R. Ganellin, R. J. Ife, M. E. Parsons, D. A. Rawlings, B. P. Slingsby, *Eur. J. Med. Chem.* **1990**, *25*, 217.
- [4] D. K. Barma, A. Kundu, R. Baati, C. Mioskowski, J. R. Falck, *Org. Lett.* **2002**, *4*, 1387.
- [5] (a) S. Ma, L. Li, *Org. Lett.* **2000**, *2*, 941; (b) C.-C. Pai, R.-S. Liu, *Org. Lett.* **2001**, *3*, 1295; (c) F. Stauffer, R. Neier, *Org. Lett.* **2000**, *2*, 3535.
- [6] A. Padwa, M. Dimitroff, A. G. Waterson, T. Wu, *J. Org. Chem.* **1997**, *62*, 4088.
- [7] S. Mageswaran, W. D. Ollis, D. A. Southam, I. O. Sutherland, Y. J. Thebtaranonth, *J. Chem. Soc., Perkin. Trans. 1* **1981**, 1969.
- [8] B. P. Gusev, V. F. Kucherov, *Izvestiya Akademii Nauk SSSR, Ser. Khim.* **1974**, *1*, 206.
- [9] (a) R. Kuhn, G. Krüger, *Chem. Ber.* **1957**, *90*, 264; (b) R. R. Burtner, *J. Am. Chem. Soc.* **1934**, *56*, 666; (c) M. C. Harris, S. L. Buchwald, *J. Org. Chem.* **2000**, *65*, 5327.
- [10] J. Ficini, M. Claeys, J. C. Depezau, *Tetrahedron Lett.* **1973**, 3353.
- [11] N. Bodor, M. J. S. Dewar, A. J. Harget, *J. Am. Chem. Soc.* **1970**, *92*, 2929.
- [12] I. G. John, L. Radom, *J. Am. Chem. Soc.* **1978**, *100*, 3981.
- [13] K. Bowden, E. A. Braude, E. R. H. Jones, B. C. L. Weedon, *J. Chem. Soc.* **1946**, 45.
- [14] H. B. Henbest, E. R. H. Jones, I. M. S. Walls, *J. Chem. Soc.* **1950**, 3646.
- [15] E. Duranti, C. Balsamini, *Synthesis* **1974**, 357.
- [16] M. Journet, D. Cai, L. M. DiMichele, R. D. Larsen, *Tetrahedron Lett.* **1998**, *39*, 6427.