Synthesis of highly functionalised 2-aminofurans

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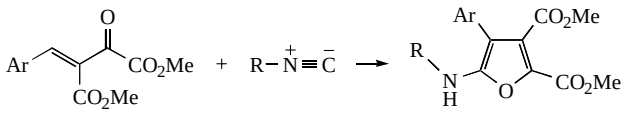
The reaction of alkyl isocyanides and dimethyl 2-oxo-3-arylidenesuccinates leads to highly functionalised aminofuran derivatives in good yields.

Furans are common substructures in numerous natural products, such as kallolides[1] and combranolides.[2] Polysubstituted furans play an important role in organic chemistry not only due to their presence as key structural units in many natural products and in important pharmaceuticals,[3] but also they can be employed as building blocks in synthetic organic chemistry. Many strategies have been developed for the preparation of furans.[4] As part of our current studies[5] on the development of new routes to heterocyclic systems, we now report an efficient synthetic route to aminofurans using alkyl isocyanides and 2-oxo-3-arylidenesuccinates **1**. Thus, the reaction between alkyl isocyanides and **1** at ambient temperature in dichloromethane leads to 2-aminofuran derivatives **3a**–**g** in 70–90% yields (Scheme 1). Compound **1**, which is readily available,[6] possesses a highly polarised carbon–carbon double bond.[7,8] Therefore, it is expected to be a strong Michael acceptor.



1a–f **2a,b** **3a–g**

1 **a** Ar = phenyl
b Ar = 3-nitrophenyl
c Ar = 4-nitrophenyl
d Ar = 4-chlorophenyl
e Ar = 1-naphthyl
f Ar = 2-furyl

2 **a** R = Bu^t
b R = Bz

3		Yield
a	Ar = phenyl, R = Bu^t	70%
b	Ar = 3-nitrophenyl, R = Bu^t	85%
c	Ar = 4-nitrophenyl, R = Bu^t	88%
d	Ar = 4-chlorophenyl, R = Bu^t	75%
e	Ar = 1-naphthyl, R = Bu^t	70%
f	Ar = 1-naphthyl, R = Bz	90%
g	Ar = 2-furyl, R = Bu^t	70%

Scheme 1

The reaction of dimethyl 2-oxo-3-arylidenesuccinates **1** with *tert*-butyl or benzyl isocyanide proceeded spontaneously at room temperature in dichloromethane and produced dimethyl 5-alkylamino-4-aryl-2,3-furandicarboxylates **3a**–**g**.† The structures of compounds **3a**–**g** were deduced from their elemental analyses, mass spectra, ^{1}H and ^{13}C NMR and IR spectroscopic data.‡ The ^{1}H NMR spectrum of **3a** exhibited three single sharp lines readily recognised as arising from *tert*-butyl (δ 1.52 ppm) and methoxy (δ 3.79 and 3.97 ppm) protons. A singlet (δ 6.92 ppm) is observed for the NH group, and the phenyl moiety gave rise to characteristic signals in the aromatic region of the spectrum. The proton-decoupled ^{13}C NMR spectrum of **3a** showed 13 distinct resonances in agreement with the proposed structure.

A plausible mechanism for the formation of 2-aminofuran derivatives **3a**–**g** is indicated in Scheme 2. On the basis of the well-established chemistry of isocyanides,[9–13] it is reasonable to assume that compounds **3a**–**g** result from the addition of alkyl isocyanides to the polarised olefinic system of **1**. Then, the carbon atom of the isocyanide moiety is attacked by the oxygen atom of enolate ion **4** to form compound **5**. Such an

† When the reaction of **1a** and **2a** was carried out in the presence of dimethyl acetylenedicarboxylate or dibenzoylacetylene, compound **3a** and the unchanged acetylenic compound were isolated.

‡ ^{1}H and ^{13}C NMR spectra were measured with a Bruker DRX-500 AVANCE instrument with $CDCl_3$ as a solvent at 500.1 and 125.7 MHz, respectively. Mass spectra were recorded on a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 70 eV.

Typical experimental procedure for the preparation of **3a**–**g**: to a magnetically stirred solution of 0.49 g of dimethyl 2-oxoarylidenesuccinate (2 mmol) in 10 ml of CH_2Cl_2 was added dropwise at –10 °C for 10 min 0.16 g of *tert*-butyl isocyanide (2 mmol). The reaction mixture was then allowed to warm up to room temperature and stand for 24 h. The solvent was removed under a reduced pressure, and the residue was separated by silica gel column chromatography (Merck 230-400 mesh) using *n*-hexane–ethyl acetate (5:1) as an eluent.

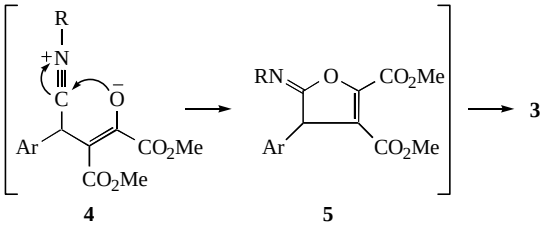
3a: yield 0.23 g (70%), yellow oil. ^{1}H NMR ($CDCl_3$) δ: 1.50 (s, CMe_3), 3.71 and 3.92 (2s, 2OMe), 6.90 (s, NH), 7.32–7.72 (m, Ph). ^{13}C NMR ($CDCl_3$) δ: 29.12 (CMe_3), 50.69 and 51.97 (2OMe), 52.01 (*C*Me_3), 88.23 (C^3 furan), 124.30 and 128.65 (5CH), 127.55 (C^4 furan), 129.10 (C_{ipso}), 141.27 (C^5 furan), 162.02 (N–C–O), 165.17 and 166.18 (2C=O, ester). IR (KBr, ν/cm^{-1}): 3325 (NH), 1728 and 1671 (C=O). MS, *m*/*z* (%): 331 (M^+, 60), 275 (75), 243 (30), 211 (25), 105 (90), 77 (30), 57 (30), 41 (30). Found (%): C, 65.30; H, 6.41; N, 4.25. Calc. for $C_{18}H_{21}NO_5$ (%):C, 65.24; H, 6.39; N, 4.23.

3b: yield 0.32 g (85%), mp 148–150 °C. ^{1}H NMR ($CDCl_3$) δ: 1.52 (s, CMe_3), 3.79 and 3.97 (2s, 2OMe), 6.92 (s, NH), 7.53 (t, CH, $^3J_{HH}$ 8.1 Hz), 7.81 (t, CH, $^3J_{HH}$ 7.9 Hz), 8.07 (dd, CH, $^3J_{HH}$ 8.1 Hz, $^4J_{HH}$ 1.2 Hz), 8.35 (d, CH, $^4J_{HH}$ 1.6 Hz). ^{13}C NMR ($CDCl_3$) δ: 29.84 (CMe_3), 51.31 and 52.90 (2OMe), 53.00 (*C*Me_3), 88.87 (C^3 furan), 115.79 (C^4 furan), 118.92, 121.64, 129.45 and 129.80 (4CH), 130.75 (C_{ipso}), 138.53 (C^5 furan), 148.65 (C–NO_2), 161.71 (N–C–O), 164.71 and 165.38 (2C=O, ester). IR (KBr, ν/cm^{-1}): 3300 (NH), 1727 and 1667 (C=O). MS, *m*/*z* (%): 376 (M^+, 25), 320 (80), 288 (75), 256 (60), 150 (75), 134 (30), 104 (30), 76 (25), 57 (90), 41 (75). Found (%): C, 57.51; H, 5.39; N, 7.46. Calc. for $C_{18}H_{20}N_2O_7$ (%): C, 57.44; H, 5.36; N, 7.44.

3c: yield 0.33 g (88%), mp 174–176 °C. ^{1}H NMR ($CDCl_3$) δ: 1.52 (s, CMe_3), 3.79 and 3.96 (2s, 2OMe), 6.97 (s, NH), 7.60 (d, CH, $^3J_{HH}$ 8.5 Hz), 8.21 (d, CH, $^3J_{HH}$ 8.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 29.78 (CMe_3), 51.43 and 53.04 (2OMe), 53.13 (*C*Me_3), 89.63 (C^3 furan), 117.51 (C^4 furan), 123.93 and 124.39 (4CH), 134.98 (C_{ipso}), 138.33 (C^5 furan), 145.96 (C–NO_2), 161.92 (N–C–O), 164.56 and 165.50 (2C=O, ester). IR (KBr, ν/cm^{-1}): 3420 (NH), 1721 and 1676 (C=O). MS, *m*/*z* (%): 376 (M^+, 25), 320 (80), 288 (80), 256 (30), 151 (80), 134 (25), 104 (25), 57 (50), 41 (30). Found (%): C, 57.48; H, 5.40; N, 7.45. Calc. for $C_{18}H_{20}N_2O_7$ (%): C, 57.44; H, 5.36; N, 7.44.

3d: yield 0.25 g (75%), mp 91–93 °C. ^{1}H NMR ($CDCl_3$) δ: 1.48 (s, CMe_3), 3.77 and 3.90 (2s, 2OMe), 6.83 (s, NH), 7.33 (d, CH, $^3J_{HH}$ 8.4 Hz), 8.45 (d, CH, $^3J_{HH}$ 8.4 Hz). ^{13}C NMR ($CDCl_3$) δ: 29.87 (CMe_3), 51.20 and 52.70 (2OMe), 52.83 (*C*Me_3), 88.55 (C^3 furan), 113.70 (C^4 furan), 125.75 and 128.98 (4CH), 127.74 (C–Cl), 133.32 (C_{ipso}), 140.30 (C^5 furan), 161.57 (N–C–O), 164.91 and 165.87 (2C=O, ester). IR (KBr, ν/cm^{-1}): 3315 (NH), 1729 and 1675 (C=O). MS, *m*/*z* (%): 365 (M^+, 90), 309 (90), 277 (50), 245 (40), 139 (60), 57 (50). Found (%): C, 59.13; H, 5.48; N, 3.80. Calc. for $C_{18}H_{20}ClNO_5$ (%): C, 59.10; H, 5.51; N, 3.83.

3e: yield 0.27 g (70%), yellow oil. ^{1}H NMR ($CDCl_3$) δ: 1.43 (s, CMe_3), 3.65 and 3.81 (2s, 2OMe), 6.97 (s, NH), 7.43–8.10 (m, $C_{10}H_7$). ^{13}C NMR ($CDCl_3$) δ: 29.94 (CMe_3), 51.20 and 52.25 (2OMe), 52.78 (*C*Me_3), 87.56 (C^3 furan), 116.08 (C^4 furan), 125.17, 125.60, 126.15, 126.59, 128.48, and 129.71 (7CH), 126.70, 131.46, and 133.74 (3C), 142.97 (C^5 furan), 162.50 (N–C–O), 165.10 and 165.42 (2C=O, ester). IR (KBr, ν/cm^{-1}): 3385 (NH), 1717 and 1667 (C=O). MS, *m*/*z* (%): 381 (M^+, 90), 325 (75), 261 (90), 155 (90), 127 (60), 57 (50), 41 (50). Found (%): C, 69.30; H, 6.11; N, 3.64. Calc. for $C_{22}H_{23}NO_5$ (%): C, 69.28; H, 6.08; N, 3.67.



Scheme 2

addition product may tautomerise under the reaction conditions employed and produce compound **3**.

In summary, we have found an efficient synthetic method for the preparation of highly functionalised 2-aminofurans. This method carries the advantage that not only the reaction is performed under neutral conditions, but also the starting materials and reagents can be mixed without any activation or modification.

References

1 S. A. Looks, M. T. Burch, W. Fenical, Z. Qi-tai and J. Clardy, *J. Org. Chem.*, 1985, **50**, 5741.
2 W. Fenical, R. K. Okeeda, M. M. Basnadurraga, P. Culver and R. S. Jacobs, *Science*, 1983, **212**, 1512.
3 K. Nakanishi, *Natural Products Chemistry*, Kodansha Ltd, Tokyo, 1974.
4 T. L. Gilchrist, *J. Chem. Soc., Perkin Trans. 1*, 2001, 2491.
5 I. Yavari, M. Anary-Abbasinejad and A. Alizadeh, *Tetrahedron Lett.*, 2002, **43**, 4503.
6 V. Nair, A. R. Sreekanth and A. U. Vinod, *Org. Lett.*, 2001, **3**, 3495.
7 J. Sandstrom, *Top. Stereochem.*, 1983, **14**, 83.
8 J. Sandstrom, *Acc. Chem. Res.*, 1985, **18**, 48.
9 I. Ugi, *Isonitrile Chemistry*, Academic Press, London, 1971.
10 I. Ugi, *Angew. Chem., Int. Ed. Engl.*, 1982, **21**, 810.
11 A. Dömling and I. Ugi, *Angew. Chem., Int. Ed. Engl.*, 2000, **39**, 3168.
12 H. M. Walborsky and M. P. Periasamy, in *The Chemistry of Functional Groups, Supplement C*, eds. S. Patai and Z. Rappoport, Wiley, New York, 1983, ch. 20, p. 835.
13 S. Marcaccini and T. Torroba, *Org. Prep. Proced. Int.*, 1993, **25**, 141.

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3f: yield 0.37 g (90%), mp 122–124 °C. ^{1}H NMR ($CDCl_3$) δ: 3.66 and 3.83 (2s, 2OMe), 4.59 (d, CH_2, $^3J_{HH}$ 6.2 Hz), 7.13 (t, NH, $^3J_{HH}$ 6.2 Hz), 7.30–7.88 (m, $C_{10}H_7$ and Ph). ^{13}C NMR ($CDCl_3$) δ: 46.21 (CMe_3), 51.29 and 52.25 (2OMe), 87.44 (C^3 furan), 116.50 (C^4 furan), 125.07, 125.54, 126.10, 126.68, 127.29, 127.70, 128.40, 128.47, 128.84, and 129.82 (12CH), 126.40, 131.61, 133.68, and 137.94 (4C), 143.25 (C^5 furan), 162.16 (N–C–O), 164.81 and 165.10 (2C=O, ester). IR (KBr, ν/cm^{-1}): 3345 (NH), 1721 and 1667 (C=O). MS, *m*/*z* (%): 415 (M^+, 90), 324 (40), 264 (25), 155(80), 91 (90). Found (%): C, 72.30; H, 5.11; N, 3.40. Calc. for $C_{25}H_{21}NO_5$ (%): C, 72.28; H, 5.09; N, 3.37.

3g: yield 0.22 g (70%), red oil. ^{1}H NMR ($CDCl_3$) δ: 1.43 (s, CMe_3), 3.74 and 3.88 (2s, 2OMe), 6.82 (s, NH), 6.40 (m, CH), 6.54 (m, CH), 7.3 (m, CH). ^{13}C NMR ($CDCl_3$) δ: 29.67 (CMe_3), 51.12 and 52.36 (2OMe), 52.90 (CMe_3), 87.57 (C^3 furan), 107.20, 111.34, and 142.50 (3CH), 112.20 (C^4 furan), 135.02 (C^5 furan), 144.17 (C_{ipso}), 161.62 (N–C–O), 164.70 and 165.05 (2C=O, ester). IR (KBr, ν/cm^{-1}): 3305 (NH), 1727 and 1667 (C=O). MS, *m*/*z* (%): 321 (M^+, 50), 265 (90), 233 (90), 201 (60), 95 (75), 57 (60), 41 (75). Found (%): C, 59.85; H, 5.93; N, 4.32. Calc. for $C_{16}H_{19}NO_6$ (%): C, 59.81; H, 5.96; N, 4.36.