Iranian Journal of Organic Chemistry Vol. 5, No. 1 (2013) 953-957

Synthesis of functionalized 2-aminofuran derivatives using mild, three-component reactions

Khatereh Khandan-Barani[a*], Malek Taher Maghsoodlou[b] and Seyed Sajad Sajadikhah[b]

[a] *Department of Chemistry, Zahedan Branch, Islamic Azad University, Zahedan, Iran.*
[b] *Department of Chemistry, Faculty of Science, The University of Sistan & Baluchestan, P. O. Box 98135-674 Zahedan, Iran.*

Received: December 2012; Revised: January 2013; Accepted: January 2013

Abstract: The reactive 1:1 intermediate is trapped from reaction between alkyl isocyanides and activated acetylenic esters by 3,5-dinitrobenzoylchloride or 2-fluorobenzaldehyde. An effective and one-pot route is presented to synthesize 2-aminofurans in good yields.

Keywords: Isocyanide, Three-component reaction, Aminofuran, Acetylenic esters, One-pot.

Introduction

The rapid assembly of molecular diversity utilizing multicomponent reactions (MCRs) has received a great deal of attention, most notably for the construction of heterocyclic 'drug-like' libraries [1-3]. Heterocycles, are of immense importance not only biologically and industrially but also because of their use of any developed human society [4]. Polysubstituted furans play an important role in organic chemistry, because of their presence as key structural units in many natural products [5] and in important pharmaceuticals [6] and also because of their use in synthetic chemistry as building blocks.

The atom economical and convergent character, the simplicity of a one-pot procedure, the possible structural variations, and accessible compounds are among the described advantages of MCRs [7]. Thus, they are perfectly amenable to automation for combinatorial synthesis [8]. Isocyanide-based multicomponent reactions (IMCRs) now occupy a position of importance in synthetic organic chemistry, mainly due to the contributions of Ugi and co-workers [9].

*Corresponding author. Tel: (+98) 5412443600, Fax: (+98) 5412441099, E-mail: kh_khandan_barani@yahoo.com

Multi-component processes are at a premium for the achievement of high levels of diversity and brevity, as they allow three or more simple and flexible building blocks to be combined in practical, one-pot operations [10-12]. A few years ago it was reported [13], that the reaction between alkyl isocyanides and 3-benzylidene-2,4-pentanedione was a convenient route to prepare densely functionalized furans. Indeed, 2-aminofurans are quite rare and, according to the previous literature, rather difficult to prepare [14, 15].

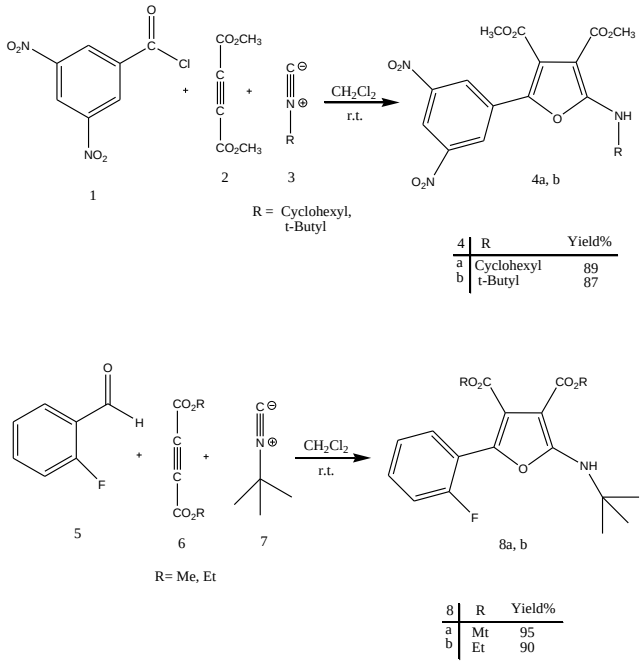
In continuation of our interest in the application of isocyanides in heterocyclic synthesis [16-22] we now report the reaction between alkyl isocyanides **3** or **7** and dialkyl acetylenedicarboxylate **2** or **6** in the presence of 3,5-dinitrobenzoylchloride **1** or 2-fluorobenzaldehyde **5** (Scheme **1**). These reactions have been the subject of detailed investigation by a number of research groups [23-25].

Results and discussion

The reaction of alkyl isocyanide **3** or **7** with dialkyl acetylenedicarboxylate **2** or **6** in the presence of carbonyl compounds **1** or **5** leads to the stable products **4a**, **b** or **8a**, **b** in excellent yields.

A mechanistic rationale could be proposed for the formation of 2-aminofurans is shown (Scheme **2**).The

1:1 zwitterionic intermediate **9** which adds to the 3,5-dinitrobenzoylchloride **1** or 2-fluorobenzaldehyde **5** leading to a dipolar species **10** or **14**, cyclization of the latter leads to the furan derivatives **11** or **15**. The intermediate **15**, undergoes a [1,5]- hydrogen shift to yield the aminofuran derivatives **4a**, **b** and the intermediate **11** eliminates Cl^+ ion to produce**.** Nucleophilic attack of H_2O on this intermediate leads to **8a**, **b**. It is conceivable that these multicomponent reactions will be applicable to the synthesis of heterocyclic rings with high hindrance.



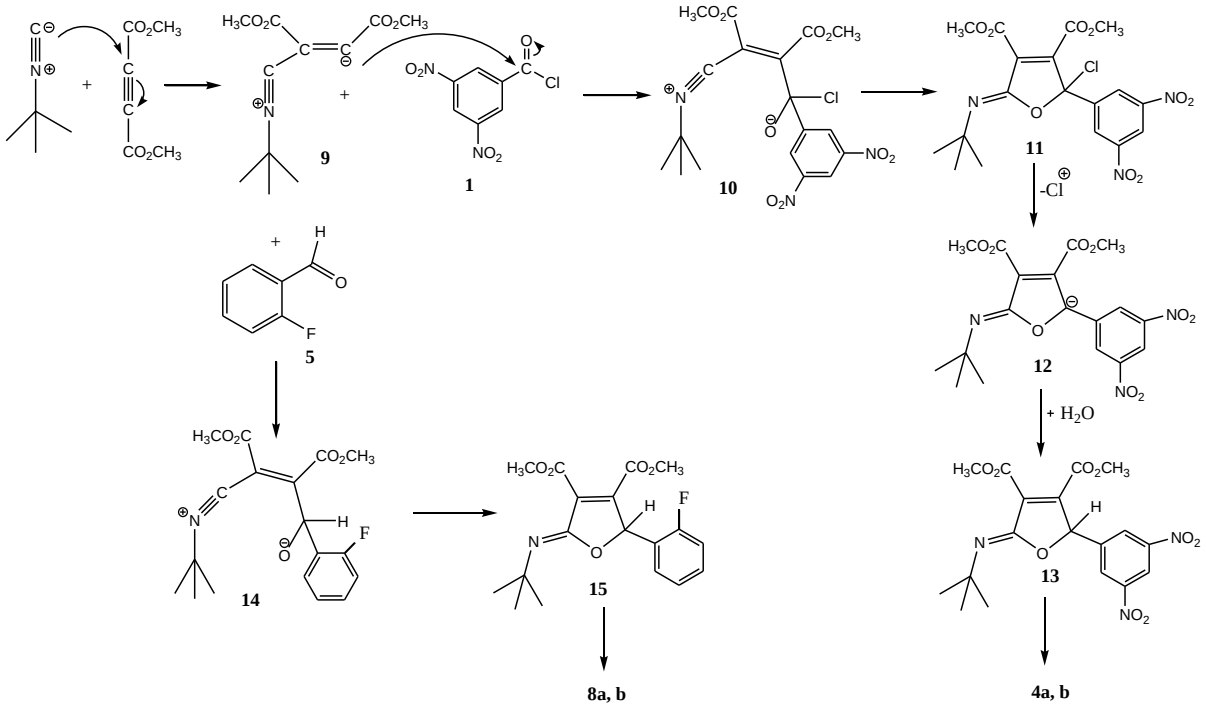
Scheme 1: Synthesis of dimethyl 2-(alkylamino)-5-(3,5-dinitrophenyl)furan-3,4-dicarboxylate and dialkyl 2-(*tert*-butylamino)-5-(2-fluororophenyl)furan-3,4-dicarboxylate derivatives.

Products **4a**, **b** and **8a**, **b** are stable solids which structures deduced from their IR, ^{1}H NMR, ^{13}CNMR, ^{19}FNMR, Mass spectral data and elemental analysis.

The ^{1}H NMR spectrum of compound **4b** exhibited three single sharp lines, readily recognizable as arising from *tert*-butyl (δ 1.56) and two carbomethoxy groups (δ 3.83 and 4.04) ppm. NH proton resonated at (δ 7.08) ppm supporting the IR absorption at 3166 cm^{-1}. The aromatic hydrogens gave rise to characteristic multiplet signal in the aromatic region of the spectrum (δ 8.21-9.22 ppm).

The ^{13}C NMR spectrum of **4b** showed sixteen distinct resonances in an agreement with proposed structure. Signals resulting from two ester carbonyl were discernible at (δ 164.4 and 164.6) ppm in the ^{13}C NMR spectrum.

The ^{1}H NMR spectrum of compound **8a** exhibited three single sharp lines, recognizable as arising from *tert*-butyl (δ 1.09) and two carbomethoxy groups (δ 3.79 and 3.92) ppm. NH proton resonated at (δ 6.21) ppm supporting the IR absorption at 3315 cm^{-1}. The aromatic hydrogens gave rise to characteristic multiplet signal in the aromatic region of the spectrum (δ 7.20-7.99 ppm). The ^{13}C NMR spectrum of **8a** showed sixteen distinct resonances in an agreement with proposed structure. The ^{19}F NMR spectrum of **8a** exhibited a single sharp line at δ = 107.32 ppm. Partial assignments of these resonances are given in the experimental data. The mass spectra of these compounds **8a** and **8b** displayed molecular ion peaks at appropriate *m/z* values.



Scheme 2: Proposed mechanisms for the formation of compounds **4a, b** and **8a, b**.

Conclusion

In conclusion, we have found the reaction of alkyl isocyanides with activated acetylenes in the presence of carbonyl compounds that leads to the one-pot and important synthesis of functionalized 2-aminofuran derivatives at room temperature. The present procedure has the advantage that not only is the reaction performed under neutral conditions but also the reactants can be mixed without any activation or modification.

Experimental

Cyclohexyl isocyanide, *tert*-butyl isocyanide, dialkyl acetylenedicarboxylate, 3,5-dinitrobenzoyl chloride and 2-fluorobenzaldehyde were purchased from Fluka and Aldrich and used without further purification. Melting points and IR spectra were measured on an Electrothermal 9100 apparatus and a JASCO FT-IR spectrometer, respectively. The ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded on a BRUKER DRX–250 and 400 AVANCE instrument with $CDCl_3$ as solvent at 250.1, 400.1 and 62.9, 100.6 and 282.4 MHz, respectively. Mass spectra were recorded on a Shimadzu GC/MS QP 1100 EX mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyser.

General procedure:

The process for the preparation of **4b** is described as an example. The solution of *tert*-butyl isocyanide (1 mmol) in 3 mL of CH_2Cl_2 solvent was slowly added dropwise, to the mixture of 3,5-dinitrobenzoyl chloride (1 mmol) and dimethyl acetylenedicarboxylate (1 mmol) in 20 mL of CH_2Cl_2 solvent at room temperature for 3 minutes. After the addition, we began stirring the solution for 24 h. Then, the solvent was removed under reduced pressure, and the residue was washed with cold diethyl ether (2×3 mL) to afford the pure product.

Dimethyl 2-(cyclohexylamino)-5-(3,5-dinitrophenyl) furan-3,4-dicarboxylate (**4a**):

Orange powder (0.39 g, 89%); m.p. 151-153 ˚C; IR (KBr) (ν_{max}, cm^{-1}): 3154 (NH), 1720 and 1665 (2C=O); ^{1}H NMR (400.1 MHz, $CDCl_3$): δ_H 1.22-1.86 (10H, m, $5CH_2$), 3.83 and 4.04 (6H, 2s, $2OCH_3$), 3.88 (1H, m, N-CH), 6.85 (1H, d, ^{3}J = 8.4 Hz, NH), 8.63-9.26 (3H, m, Ar-H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C 24.2 25.3, 33.4, 51.4, 51.6, 53.0, 88.8, 117.8, 122.9, 124.3, 127.8, 129.6, 135.0, 137.9, 145.9, 161. 6, 164.6, 165.5; Anal. Calcd for $C_{20}H_{21}N_3O_9$ (447.40): C, 53.69; H, 4.73; N, 9.39; Found: C, 53.81; H, 4.78; N, 9.46 %.

Dimethyl 2-(tert-butyl amino)-5-(3,5-dinitrophenyl)furan-3,4-dicarboxylate (**4b**):

Orange powder (0.37 g, 87%); m.p. 158-160 ˚C; IR (KBr) (ν_{max}, cm^{-1}): 3166 (NH), 1730 and 1660 (2C=O);

^{1}H NMR (400.1 MHz, $CDCl_3$): δ_H 1.56 (9H, s, $C(CH_3)_3$), 3.83 and 4.04 (6H, 2s, $2OCH_3$), 7.08 (1H, br, NH), 8.21-9.22 (3H, m, Ar-H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C 29.8, 51.5, 53.1, 53.3, 89.6, 115.7, 118.6, 123.0, 128.1, 129.8, 132.4, 136.4, 149.1, 162.0, 164.4, 164.6; Anal. Calcd for $C_{18}H_{19}N_3O_9$ (421.36): C, 51.31; H, 4.55; N, 9.97; Found: C, 51.42; H, 4.58; N, 9.99%.

General procedure:

The process for the preparation of dimethyl 2-(*tert*-butylamino)-5-(2-fluorophenyl)furan-3,4-dicarboxylate ***8a*** is described as an example. The solution of *tert*-butyl isocyanide (1 mmol) in 3 mL of CH_2Cl_2 solvent was slowly added dropwise to a mixture of 2-fluorobenzaldehyde (1mmol) and dimethyl acetylenedicarboxylate (1 mmol) in 20 mL of CH_2Cl_2 solvent at room temperature for 3 min. After the addition, we began stirring the solution for 24 h. Then, the solvent was removed under reduced pressure, and the residue was washed with mixture of cold diethyl ether and n-hexane with 1: 3 ratio (2×3 mL) to afford the pure product.

Dimethyl 2-(tert-butylamino)-5-(2-fluorophenyl)furan-3,4-dicarboxylate (**8a**):

Yellow oil (0.33 g, 95%); IR (KBr) (ν_{max}, cm^{-1}): 3315 (NH), 1766 and 1698 (2C=O); ^{1}H NMR (250.1 MHz, $CDCl_3$): δ_H 1.09 (9H, s, $C(CH_3)_3$), 3.79 and 3.92 (6H, 2s, $2OCH_3$), 6.21 (1H, br, NH), 7.20-7.99 (4H, m, Ar-H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ_C 27.9, 52.1, 53.5, 53.9, 91.4, 116.7, 117.1, 124.7, 130.7, 136.8, 159.0, 160.4, 163.8, 164.0, 164.5; ^{19}F NMR (282.4 MHz, $CDCl_3$): δ_F 107.32; MS (*m/z*, %): 350 (M^++1, 31), 349 (M^+, 42), 333 (5), 293 (54), 278 (5), 253(32), 230 (9), 123 (100), 95 (35), 57 (77). Anal. Calcd for $C_{18}H_{20}FNO_5$ (349.35): C, 61.88; H, 5.77; N, 4.01; Found: C, 61.96; H, 5.81; N, 4.07 %.

Diethyl 2-(tert-butylamino)-5-(2-fluorophenyl)furan-3,4-dicarboxylate (**8b**):

Yellow oil (0.34 g, 90%); IR (KBr) (ν_{max}, cm^{-1}): 3334 (NH), 1762 and 1687 (2C=O); ^{1}H NMR (250.1 MHz, $CDCl_3$): δ_H 1.08 (9H, s, $C(CH_3)_3$), 1.16 and 1.28 (6H, 2t, ^3J = 7.0 Hz, $2CH_3$), 4.21 and 4.32 (4H, 2q, ^3J = 7.0 Hz, $2OCH_2$), 6.19 (1H, br, NH), 7.14-7.26 (4H, m, Ar-H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ_C 13.7, 14.3, 27.9, 51.9, 62.8, 63.4, 88.4, 116.3, 117.4, 124.3, 124.7, 130.7, 136.6, 159.2, 161.9, 163.2, 164.7, 164.8; ^{19}F NMR (282.4 MHz, $CDCl_3$): δ_F 107.17; MS (*m/z*, %): 378 (M^++1, 45), 377 (M^+, 87), 332 (12), 321 (45), 2828 (13), 151(10), 123 (100), 95 (20), 57 (50). Anal. Calcd for $C_{20}H_{24}FNO_5$ (377.41): C, 63.65; H, 6.41; N, 3.71; Found: C, 63.72; H, 6.44; N, 3.76%.

Acknowledgement

We are much obliged to the financial support received from the Research Council of University of Sistan and Baluchestan.

References

[1] Gerencser, J.; Dormon, G.; Darvas, F. *QSAR Comb. Sci.* **2006**, *25*, 439.
[2] Ramon, D. J.; Yus, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 1602.
[3] Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51.
[4] Martins, M. A. P.; Frizzo, C. P.; Moreira, D. N.; Buriol, L.; Machado, O. *Chem. Rev.* **2009**, *109*, 4140.
[5] Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795.
[6] Nakanish, K. *Natural Products Chemistry*, Kodansha, Tokyo, **1974**.
[7] Trost, B. M. *Angew. Chem. Int .Ed.*, **1995**, *34*, 259.
[8] Bienayme, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321.
[9] Domling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168.
[10] Dömling, A.; Herdtweck, E.; Heck, S. *Tetrahedron Lett.* **2006**, *47*, 1745.
[11] Nair, V.; Sreekanth, A. R.; Abhilash, N. P.; Nair-Biju, A. T.; Varma, L.; Viji, S.; Mathew, S. *Arkivoc* **2005**, (xi), 178.
[12] Sapi, J.; Laronze, J. Y. *Arkivoc* **2004**, (vii), 208.
[13] Yavari, I.; Shaabani, A.; Maghsoodlou, M. T. *Monatsh. Chem.* **1997**, *128*, 697.
[14] (a) John, I. G.; Radom, L. *J. Am. Chem. Soc.* **1978**, *100*, 3981. (b) Lythgoe, D. J.; McClenaghan, I.; Ramsden, C. A. *J. Heterocycl. Chem.* **1993**, *30*, 113.
[15] Quai, M.; Frattini, S.; Vendrame, U.; Mondoni, M.; Dossena, S.; Cereda, E. *Tetrahedron Lett.* **2004**, *45*, 1413.
[16] Maghsoodlou, M. T.; Hazeri, N.; Habibi-Khorassani, S. M.; Solimani, V.; Marandi, G.; Razmjoo, Z. *J. Chem. Res.* **2008**, 198.
[17] Hazeri, N.; Maghsoodlou, M. T.; Habibi-Korassani, S. M.; Marandi, G.; Khandan-Barani, K.; Ziyadini, M.; Aminkhani, A. *Arkivoc* **2007**, *(i)*, 173.
[18] Hazeri, N.; Maghsoodlou, M. T.; Habibi-Korassani, S. M.; Ziyadini, M.; Marandi, G.; Khandan-Barani, K.; Bijanzadeh, H. R. *Arkivoc* **2007**, *(xiii)*, 34.
[19] Hazeri, N.; Maghsoodlou, M.T.; Habibi-Khorasani, S. M.; Ebrahimi, A.; Khandan-Barani, K.; Marandi, G.; Ziyadini, M.; Bijanzadeh, H. R.; Kazemian, M. A. *Iran. J. Org. Chem.* **2009**, *1*, 33.
[20] Maghsoodlou, M. T.; Hazeri, N.; Habibi-Khorassani, S. M.; Ziyadini, M.; Marandi, G.; Khandan-Barani, K.; Ebrahimi, P.; Rostami Charati, F.; Sobolev, A.; Makha, M. *J. Heterocyclic. Chem.* **2009**, *46*, 843.
[21] Khandan-Barani, K.; Maghsoodlou, M. T.; Habibi-Khorassani, S. M.; Hazeri, N.**;** Sajadikhah, S. S. *J. Chem. Res.* **2011**, 231.

[22] Khandan-Barani, K.; Maghsoodlou, M. T.; Habibi-Khorassani, S. M.; Hazeri, N.; Sajadikhah, S. S. *Arkivoc* **2011**, (xi), 22.
[23] Nair, V.; Vinod, A. U.; Somarajan Nair, J.; Sreekanth, A. R.; Rath, N. P. *Tetrahedron Lett.* **2000**, *41*, 6675.
[24] Yavari, I.; Mokhtarporyani-Sanandaj, A.; Moradi, L.; Mirzaei, A. *Tetrahedron* **2008**, *64*, 5221.
[25] Maghsoodlou, M. T.; Hazeri, N.; Habibi-Khorassani, S. M.; Marandi, G.; Nassiri, M. *Synth. Commun*. **2005**, *35*, 2771.