Reaction between Isocyanides, Dialkyl Acetylenedicarboxylates and 2-Hydroxy-1-aryl-2-(arylamino)ethanones: One-Pot Synthesis of Highly Functionalized 2-Aminofurans

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Received 26 May 2009

Abstract: A facile synthesis of highly functionalized 2-aminofuran derivatives by the multicomponent reaction of alkyl isocyanides, dialkyl acetylenedicarboxylates and 2-hydroxy-1-aryl-2-(arylamino)ethanone is described. The reaction is characterized by mild conditions, high selectivity, and tolerance to various functional groups.

Key words: alkyl isocyanide, dialkyl acetylenedicarboxylate, multicomponent reaction, 2-aminofuran

Substituted furans play an important role in organic chemistry, not only as key structural units in many natural products and important pharmaceuticals[1] but also as useful building blocks in synthetic chemistry.[2]

Multicomponent reactions (MCRs) have been attracting much interest from synthetic chemists because they provide simple one-pot routes for the synthesis of complex molecules from simple and easily available starting materials. These processes do not require separation and purification of intermediates and so save time, energy and raw materials. Due to the unique reactivity of the isocyanide functional group, isocyanide-based MCRs (I-MCRs) are among the most versatile, in terms of the number and variety of compounds that can be generated.[3–6] A recently developed class of I-MCRs is the reaction of isocyanides with electron-deficient acetylenes in the presence of an electrophile. Addition of isocyanides to acetylene diesters is well known to produce a reactive zwitterionic intermediate, which further reacts with electrophiles to afford a wide variety of carbo- and heterocycles. A wide variety of electrophiles has been applied to trap isocyanide–dimethyl acetylenedicarboxylate (DMAD) intermediate; among them are carbon electrophiles such as aldehydes,[7,8] quinones,[7] 1,2-diketones,[9] 1,2,3-tricarbonyl compounds,[10] imines,[11] isocyanates,[12] and hydrogen electrophiles such as pyrrole,[13] amides,[14] 4-hydroxycoumarine,[15] phenols,[16] phthalic anhydride,[17] and isatoic anhydride.[18] This class of reactions has also been used for the synthesis of 2-aminofuran derivatives.[7,19] In the course of our studies on the reaction of acetylene diesters with isocyanides in the presence of acidic organic compounds,[13–15,20–22] we decided to investigate the reaction of isocyanides with acetylene diesters in the presence of 2-hydroxy-1-aryl-2-(arylamino)ethanone derivatives, already prepared by the reaction of the requisite aniline with arylglyoxal monohydrate derivatives,[23] in order to trap the active zwitterionic intermediate. Thus, we reacted cyclohexyl isocyanide with dimethyl acetylenedicarboxylate (DMAD) and 2-hydroxy-1-(4-nitrophenyl)-2-(4-nitrophenylamino)ethanone (**3a**) in dichloromethane at room temperature. We anticipated the isocyanide–DMAD intermediate to be protonated by one of the NH or OH protons followed by the addition of the conjugate base of **3a** to the nitrilium cation **6** and finally afford oxazine derivatives **9**,[15,16] but after separation of the product and elucidation of its structure by elemental and spectral data we found that 2-aminofuran derivative **4a** had been produced (Scheme 1).[24]

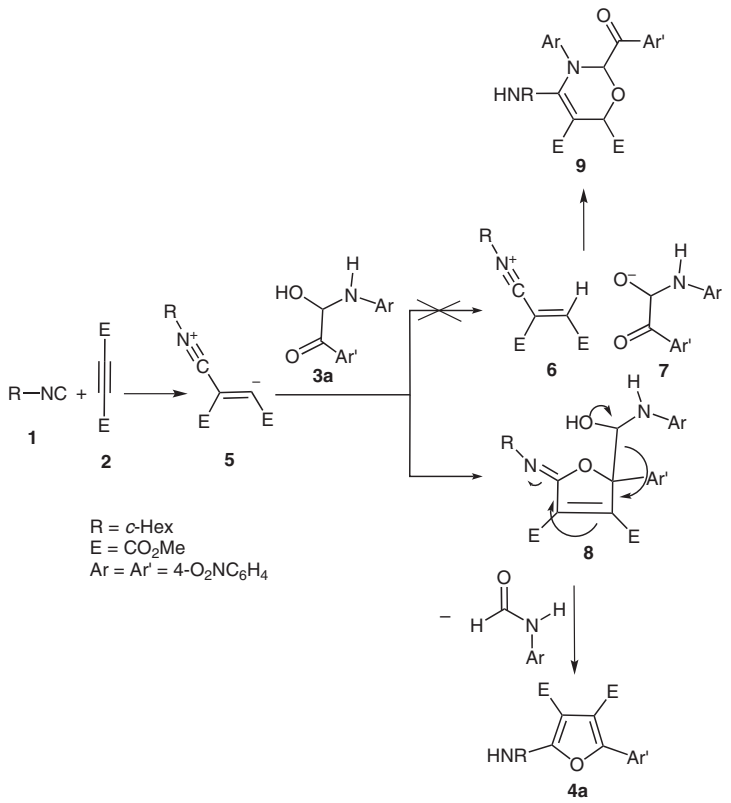
The ^{1}H NMR spectrum of **4a** consisted of a multiplet for the cyclohexyl ring (δ = 1.28–2.15 ppm), a multiplet for CH of cyclohexyl (δ = 3.62 ppm) and two singlets for methoxy groups (δ = 3.94 ppm and 3.78 ppm) supported by the absorptions at 1729 and 1677 cm^{-1} in the IR spectrum. A fairly broad doublet (δ = 8.89 ppm, $^3J_{HH}$ = 8.0 Hz) was observed for the NH proton and the phenyl protons exhibited characteristic signals in the aromatic region of the spectrum. The ^{1}H decoupled ^{13}C NMR spectrum of **4a** showed 16 distinct resonances, consistent with the proposed structure.

Although the mechanism of this reaction has not been established, a plausible rationalization can be advanced to explain product formation (Scheme 1). It is reasonable to assume that zwitterionic intermediate **5** produced by reaction between cyclohexyl isocyanide and DMAD adds to carbonyl group of **3a** resulting in the formation of 2,5-dihydrofuran derivative **8**, which undergoes aromatization to furan ring by losing of a molecule of *N*-(4-nitrophenyl)formamide.

To explore the scope and limitations of this reaction further, we extended our studies to the reaction of various dialkyl acetylenedicarboxylates and alkyl isocyanides with 2-hydroxy-1-aryl-2-(arylamino)ethanones. As indicated in Table 1, the reactions proceeded very efficiently in relatively good yields.

In conclusion, we have developed a simple and efficient method for the preparation of functionalized 2-aminofurans of potential synthetic and pharmacological interest. This method has the advantage that, not only is the reac-

SYNLETT 2009, No. 16, pp 2676–2678
Advanced online publication: 04.09.2009
DOI: 10.1055/s-0029-1217951; Art ID: D13409ST



Scheme 1 Reaction between cyclohexyl isocyanide, DMAD and 2-hydroxy-1-(4-nitrophenyl)-2-(4-nitrophenylamino)ethanone

Table 1 Reaction of Alkyl Isocyanides, Dialkyl Acetylenedicarboxylates and 2-Hydroxy-1-aryl-2-(arylamino)ethanone

4	R	E	Ar′	Ar	Yield (%)[a]
a	Cy	CO_2Me	$4\text{-}O_2NC_6H_4$	$4\text{-}O_2NC_6H_4$	89
b	*t*-Bu	CO_2Me	$4\text{-}O_2NC_6H_4$	$4\text{-}O_2NC_6H_4$	90
c	Cy	CO_2Et	Ph	$3\text{-}O_2NC_6H_4$	91
d	*t*-Bu	CO_2Me	$4\text{-}ClC_6H_4$	$3\text{-}O_2NC_6H_4$	89
e	Cy	CO_2Et	$4\text{-}O_2NC_6H_4$	$4\text{-}ClC_6H_4$	91
f	*t*-Bu	CO_2Me	$4\text{-}BrC_6H_4$	$4\text{-}ClC_6H_4$	88
g	*t*-Bu	CO_2Me	Ph	$4\text{-}BrC_6H_4$	85

[a] Isolated yields.

tion performed under neutral conditions, but also the substances can be mixed without any further manipulation. The simplicity of this procedure makes it an interesting alternative to other approaches.

References and Notes

(1) Dean, F. A. *Naturally Occurring Oxygen Ring Compounds*; Butterworth: London, **1963**.
(2) Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795.
(3) Ugi, I.; Werner, B.; Dömling, A. *Molecules* **2003**, *8*, 53.
(4) Dömling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168.
(5) Nair, V.; Menon, R. S.; Sreekumar, V. *Pure Appl. Chem.* **2005**, *77*, 1191.
(6) Dömling, A. *Chem. Rev.* **2006**, *106*, 17.
(7) Nair, V.; Unni Vinod, A.; Abhilash, N.; Rajeev Menon, S.; Santhi, V.; Luxmi Varma, R.; Viji, S.; Mathew, S.; Srinivas, R. *Tetrahedron* **2003**, *59*, 10279.
(8) Yadav, J. S.; Subba Reddy, B. V.; Shubashree, S.; Sadashiv, K.; Krishna Rao, D. *J. Mol. Catal. A.: Chem.* **2007**, *272*, 128.
(9) Nair, V.; Menon, R. S.; Deepthi, A.; Devi, B. R.; Biju, A. T. *Tetrahedron Lett.* **2005**, *46*, 1337.
(10) Nair, V.; Deepthi, A. *Tetrahedron Lett.* **2006**, *47*, 2037.
(11) Nair, V.; Vinod, A. U. *J. Org. Chem.* **2001**, *66*, 4427.
(12) Alizadeh, A.; Rostamnia, S.; Zohreh, N.; Bijanzadeh, H. R. *Chem. Month.* **2008**, *139*, 49.
(13) Anary-Abbasinejad, M.; Mosslemin, M. H.; Anaraki-Ardakani, H.; Tahan, S. *J. Chem. Res.* **2006**, 306.
(14) Anary-Abbasinejad, M.; Mosslemin, M. H.; Tahan, S.; Anaraki-Ardakani, H. *J. Chem. Res.* **2006**, 170.
(15) Anary-Abbasinejad, M.; Anaraki-Ardakani, H.; Rastegari, F.; Hassanabadi, A. *J. Chem. Res.* **2007**, 602.
(16) Yavari, I.; Djahaniani, H.; Nasiri, F. *Tetrahedron* **2003**, *59*, 9409.
(17) Shaabani, A.; Teimouri, M. B.; Bijanzadeh, H. R. *J. Chem. Res.* **2002**, 381.
(18) Shaabani, A.; Teimouri, M. B.; Mirzaei, P.; Bijanzadeh, H. R. *J. Chem. Res.* **2003**, 82.
(19) Alizadeh, A.; Rostamnia, S.; Zhu, L. Z. *Synthesis* **2008**, 1788.
(20) Anary-Abbasinejad, M.; Ghanea, F.; Anaraki-Ardakani, H. *Synth. Commun.* **2009**, *39*, 544.
(21) Anary-Abbasinejad, M.; Anaraki-Ardakani, H.; Ghanea, F. *Monatsh. Chem.* **2009**, *140*, 397.
(22) Anary-Abbasinejad, M.; Moslemine, M. H.; Anaraki-Ardakani, H. *J. Fluorine Chem.* **2009**, *130*, 368.
(23) **Synthesis of 3a as a Typical Route for the Preparation of 2-Hydroxy-1-aryl-2-(arylamino)ethanone Derivatives**: A solution of 4-nitroaniline (10 mmol) and 4-nitrophenylglyoxal monohydrate (10 mmol) in EtOH (20 mL) was

refluxed for 3 h. The solution was cooled in ice-water bath. The precipitate was filtered of to afford pure **3a** as yellow crystals; mp 150–151 °C. IR (KBr): 3645 (OH), 3390 (NH), 1690 (C=O) cm^{-1}. MS (%): *m*/*z* = 317 (7) [M^+]. Anal. Calcd for $C_{14}H_{11}N_3O_6$ (317): C, 53.00; H, 3.49; N, 13.24. Found: C, 53.12; H, 3.52; N, 13.08. ^1H NMR (500.1 MHz, $CDCl_3$): δ = 5.96 (d, $^3J_{HH}$ = 6.5 Hz, 1 H, CH), 6.64 (d, $^3J_{HH}$ = 6.5 Hz, 1 H, NH), 6.84 (d, $^3J_{HH}$ = 9.0 Hz, 2 H, 2 × CH of Ar), 7.96 (d, $^3J_{HH}$ = 9.0 Hz, 2 H, 2 × CH of Ar), 8.18 (d, $^3J_{HH}$ = 8.7 Hz, 2 H, 2 × CH of Ar), 8.23 (d, $^3J_{HH}$ = 8.7 Hz, 2 H, 2 × CH of Ar). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 81.92 (CHN), 113.56, 124.20, 126.33, 131.12, 138.47, 140.14, 151.08, 151.13 (C_{Ar}), 192.67 (C=O).

(24) To a magnetically stirred solution of dialkyl acetylenedicarboxylate (2 mmol) and 2-hydroxy-1-aryl-2-(arylamino)ethanone (2 mmol) in CH_2Cl_2 (10 mL) was added a solution of alkyl isocyanide (2 mmol) in CH_2Cl_2 (5 mL) dropwise at r.t. over 10 min. The mixture was then allowed to stir for 24 h. The solvent was removed under reduced pressure, and the residue was separated by column chromatography (silica gel; hexane–EtOAc, 5:1) to afford the pure title compounds. **4a**: yellow crystals (yield: 0.35 g, 89%); mp 172–173 °C. IR (KBr): 3385 (NH), 1729, 1677 (C=O) cm^{-1}. MS (%): *m*/*z* = 402 (7) [M^+]. Anal. Calcd for $C_{20}H_{22}N_2O_7$ (402): C, 59.70; H, 5.51; N, 6.96. Found: C, 59.82; H, 5.60; N, 6.82. ^1H NMR (500.1 MHz, $CDCl_3$): δ = 1.25–2.06 (m, 10 H, 5 × CH_2 of Cy), 3.74 (m, 1 H, CHN), 3.78 (s, 3 H, OMe), 3.94 (s, 3 H, OMe), 6.73 (d, $^3J_{HH}$ = 7.9 Hz, 1 H, NH), 7.61 (d, $^3J_{HH}$ = 9.0 Hz, 2 H, 2 × CH of Ar), 8.21 (d, $^3J_{HH}$ = 9.0 Hz, 2 H, 2 × CH of Ar). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 24.91, 25.77, 33.80 (5 × CH_2 of Cy), 52.13 (CHN), 51.80 (OMe), 53.41 (OMe), 89.23, 118.26, 124.40, 124.71, 135.41, 138.35, 146.39, 162.01 (C_{Ar}), 164.85 (CO_2Me), 165.81 (CO_2Me). **4b**: yellow crystals (yield: 0.33 g, 90%); mp 173–174 °C. IR (KBr): 3420 (NH), 1730, 1675 (C=O) cm^{-1}. MS (%): *m*/*z* = 376 (5) [M^+]. Anal. Calcd for $C_{18}H_{20}N_2O_7$ (376): C, 57.44; H, 5.36; N, 7.44. Found: C, 57.55; H, 5.29; N, 7.49. ^1H NMR (500.1 MHz, $CDCl_3$): δ = 1.51 (s, 9 H, CMe_3), 3.78 (s, 3 H, OMe), 3.96 (s, 3 H, OMe), 6.96 (s, 1 H, NH), 7.61 (d, $^3J_{HH}$ = 8.8 Hz, 2 H, 2 × CH of Ar), 8.22 (d, $^3J_{HH}$ = 8.8 Hz, 2 H, 2 × CH of Ar). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 29.75 (CMe_3), 51.43 (CMe_3), 53.05 (OMe), 53.10 (OMe), 89.56, 117.46, 123.87, 124.38, 134.93, 138.26, 145.89, 161.87 (C_{Ar}), 164.53 (CO_2Me), 165.50 (CO_2Me). **4c**: yellow oil (yield: 0.31 g, 91%). IR (KBr): 3345 (NH), 1732, 1672 (C=O) cm^{-1}. MS (%): *m*/*z* = 385 (2) [M^+]. Anal. Calcd for $C_{22}H_{27}NO_5$ (385): C, 68.55; H, 7.06; N, 3.63. Found: C, 68.63; H, 7.12; N, 3.60. ^1H NMR (500.1 MHz, $CDCl_3$): δ = 1.27–2.12 (m, 10 H, 5 × CH_2 of Cy), 1.23 (t, $^3J_{HH}$ = 7.1 Hz, 3 H, OCH$_2$CH_3), 1.32 (t, $^3J_{HH}$ = 7.1 Hz, 3 H, OCH$_2$CH_3), 3.74 (m, 1 H, CHN), 4.13 (q, $^3J_{HH}$ = 7.1 Hz, 2 H, OCH_2CH$_3$), 4.26 (q, $^3J_{HH}$ = 7.1 Hz, 2 H, OCH_2CH$_3$), 6.73 (d, $^3J_{HH}$ = 7.9 Hz, 1 H, NH), 7.39–7.58 (5 H, m, Ar). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 14.47, 14.81 (2 × OCH$_2$CH$_3$), 24.90, 25.78, 33.82 (5 × CH_2 of Cy), 52.07 (CHN), 60.42, 60.55 (2 × OCH$_2$CH$_3$), 89.43, 118.26, 124.40, 124.71, 135.41, 138.35, 146.39, 162.41 (C_{Ar}), 164.75 (CO_2Et), 165.81 (CO_2Et). **4d**: yellow crystals (yield: 0.32 g, 89%); mp 95–97 °C. IR (KBr): 3335 (NH), 1735, 1679 (C=O) cm^{-1}. MS (%): *m*/*z* = 365 (5) [M^+]. Anal. Calcd for $C_{18}H_{20}ClNO_5$ (365): C, 59.10; H, 5.51; N, 3.83. Found: C, 59.22; H, 5.41; N, 3.72. ^1H NMR (500.1 MHz, $CDCl_3$): δ = 1.45 (s, 9 H, CMe_3), 3.73 (s, 3 H, OMe), 3.87 (s, 3 H, OMe), 6.81 (s, 1 H, NH), 7.37 (d, $^3J_{HH}$ = 8.6 Hz, 2 H, 2 × CH of Ar), 7.46 (d, $^3J_{HH}$ = 8.6 Hz, 2 H, 2 × CH of Ar). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 30.12 (CMe_3), 51.63 (CMe_3), 53.12 (OMe), 53.25 (OMe), 89.03, 114.27, 121.85, 126.39, 128.59, 132.33, 140.70, 162.00 (C_{Ar}), 165.30 (CO_2Me), 166.26 (CO_2Me). **4e**: yellow crystals (yield: 0.39 g, 91%); mp 101–103 °C. IR (KBr): 3410 (NH), 1722, 1675 (C=O) cm^{-1}. MS (%): *m*/*z* = 430 (7) [M^+]. Anal. Calcd for $C_{22}H_{26}N_2O_7$ (385): C, 61.39; H, 6.09; N, 6.51. Found: C, 61.46; H, 6.14; N, 6.43. ^1H NMR (500.1 MHz, $CDCl_3$): δ = 1.36–2.05 (m, 10 H, 5 × CH_2 of Cy), 1.30 (t, $^3J_{HH}$ = 7.1 Hz, 3 H, OCH$_2$CH_3), 1.39 (t, $^3J_{HH}$ = 7.1 Hz, 3 H, OCH$_2$CH_3), 3.72 (m, 1 H, CHN), 4.24 (q, $^3J_{HH}$ = 7.2 Hz, 2 H, OCH_2CH$_3$), 4.42 (q, $^3J_{HH}$ = 7.2 Hz, 2 H, OCH_2CH$_3$), 6.76 (d, $^3J_{HH}$ = 7.9 Hz, 1 H, NH), 7.60 (d, $^3J_{HH}$ = 8.9 Hz, 2 H, 2 × CH of Ar), 8.20 (d, $^3J_{HH}$ = 8.9 Hz, 2 H, 2 × CH of Ar). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 14.42, 14.82 (2 × OCH$_2$CH_3), 24.87, 25.78, 33.80 (5 × CH_2 of Cy), 52.06 (CHN), 60.42, 62.55 (2 × OCH$_2$CH$_3$), 89.52, 118.26, 124.71, 124.22, 135.55, 138.35, 146.39, 162.06 (C_{Ar}), 164.58 (CO_2Et), 165.38 (CO_2Et). **4f**: yellow crystals (yield: 0.35 g, 88%); mp 99–101 °C. IR (KBr): 3335 (NH), 1735, 1679 (C=O) cm^{-1}. MS (%): *m*/*z* = 409 (5) [M^+]. Anal. Calcd for $C_{18}H_{20}BrNO_5$(409): C, 52.70; H, 4.91; N, 3.41. Found: C, 52.62; H, 4.80; N, 3.62. ^1H NMR (500.1 MHz, $CDCl_3$): δ = 1.46 (s, 9 H, CMe_3), 3.75 (s, 3 H, OMe), 3.88 (s, 3 H, OMe), 6.81 (s, 1 H, NH), 7.32 (d, $^3J_{HH}$ = 8.6 Hz, 2 H, 2 × CH of Ar), 7.44 (d, $^3J_{HH}$ = 8.6 Hz, 2 H, 2 × CH of Ar). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 30.34 (CMe_3), 51.66 (CMe_3), 53.15 (OMe), 53.29 (OMe), 87.04, 112.18, 124.23, 126.22, 127.44, 131.79, 138.78, 162.05 (C_{Ar}), 163.38 (CO_2Me), 164.32 (CO_2Me). **4g**: yellow crystals (yield: 0.28 g, 85%); mp 78–80 °C. IR (KBr): 3345 (NH), 1740, 1679 (C=O) cm^{-1}. MS (%): *m*/*z* = 332 (5) [M^+ + 1]. Anal. Calcd for $C_{18}H_{21}NO_5$ (331): C, 65.24; H, 6.39; N, 4.23. Found: C, 65.44; H, 6.35; N, 4.36. ^1H NMR (500.1 MHz, $CDCl_3$): δ = 1.48 (s, 9 H, CMe_3), 3.77 (s, 3 H, OMe), 3.91 (s, 3 H, OMe), 6.82 (s, 1 H, NH), 7.24–7.66 (m, 5 H, Ar). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 30.14 (CMe_3), 51.46 (CMe_3), 52.95 (OMe), 53.69 (OMe), 88.52, 113.18, 124.23, 126.22, 127.44, 129.79, 140.23, 162.05 (C_{Ar}), 163.30 (CO_2Me), 166.12 (CO_2Me).