



A mild and efficient method for the synthesis of 2,5-dihydro-5-imino-2-methylfuran-3,4-dicarboxylates via an isocyanide-based multicomponent reaction

Ahmad Shaabani*, Ali Hossein Rezayan, Sabrieh Ghasemi, Afshin Sarvary

Department of Chemistry, Shahid Beheshti University, PO Box 19396-4716, Tehran, Iran

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ABSTRACT

The zwitterion formed from an alkyl or aryl isocyanide and dialkyl acetylenedicarboxylate reacts with acetic anhydride or phthalic anhydride to form 2,5-dihydro-5-imino-2-methylfuran-3,4-dicarboxylates or benzo-fused spiro-lactones in relatively good yields at room temperature without using a catalyst.

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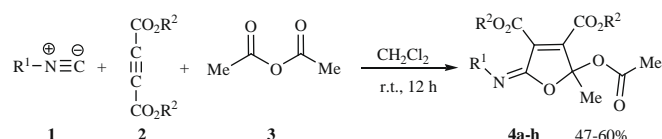
Furans and their derivatives play an important role in organic chemistry due to their presence as key structural units in many natural products and pharmaceuticals, and as essential building blocks for the total synthesis of complex naturally occurring metabolites. Furthermore, polyfunctionalized furans are versatile synthetic starting materials for the preparation of a variety of heterocyclic and acyclic compounds,^{1–9} and especially 2,5-disubstituted furan-3,4-dicarboxylates which are very important starting materials in the synthesis of natural products containing tetrahydrofuran rings.¹⁰ For these reasons, the development of new and efficient methods for the synthesis of furan derivatives remains an area of current interest.

Due to atom economy, simplicity, and amenability to automated synthesis, multicomponent condensation reactions (MCRs) have an advantageous position among other reactions. The development of new MCRs is an interesting research topic in applied sciences.^{11–13} Although isocyanide-based multicomponent reactions have been applied to the synthesis of various furan and furan derivatives,^{14–19} our literature survey revealed that the reactions of isocyanides and dialkyl acetylenedicarboxylates with acetic anhydride have not been investigated.

As part of our research on the development of new synthetic methods in heterocyclic chemistry and our interest in isocyanide-based multicomponent reactions,^{20–25} herein, we describe an efficient synthesis of 2,5-dihydro-5-imino-2-methylfuran-3,4-

dicarboxylates **4** via the reaction of an isocyanide **1** with a dialkyl acetylenedicarboxylate **2** and acetic anhydride **3** at room temperature without using any catalyst (Scheme 1).

As indicated in Table 1, the 1:1:1 addition reaction of isocyanides **1** with dialkyl acetylenedicarboxylates **2** and acetic anhydride **3** occurs smoothly in CH₂Cl₂ at room temperature to produce 2,5-dihydro-5-imino-2-methylfuran-3,4-dicarboxylates **4**. The structures of



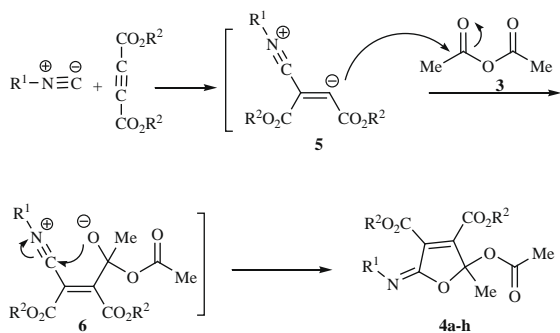
Scheme 1. Synthesis of 2,5-dihydro-5-imino-2-methylfuran-3,4-dicarboxylates.

Table 1
Synthesis of 2,5-dihydro-5-imino-2-methylfuran-3,4-dicarboxylates

Entry	R ¹	R ²	Product	Yield (%)
1	Cyclohexyl	Me	4a	60
2	Cyclohexyl	Et	4b	55
3	<i>tert</i> -Butyl	Me	4c	53
4	<i>tert</i> -Butyl	Et	4d	49
5	<i>tert</i> -Butyl	C(Me) ₃	4e	53
6	1,1,3,3-Tetramethylbutyl	Me	4f	47
7	1,1,3,3-Tetramethylbutyl	Et	4g	52
8	2,6-(Me) ₂ C ₆ H ₄	Et	4h	58

* Corresponding author. Tel.: +98 2129902800; fax: +98 2122431663.

E-mail address: a-shaabani@cc.sbu.ac.ir (A. Shaabani).



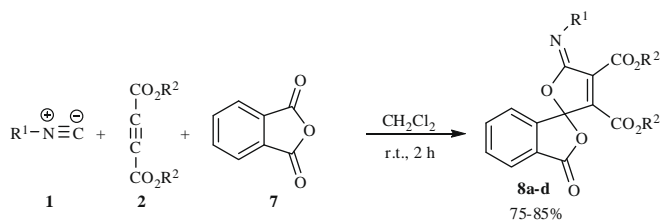
Scheme 2. Proposed mechanism.

the products were deduced from their IR, mass, ^1H NMR, and ^{13}C NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at the appropriate m/z values. The ^1H NMR spectrum of **4a** consisted of a multiplet for the cyclohexyl ring (δ 1.18–1.62), two singlets for the methyl groups (δ 1.76 and 1.96), a multiplet for the N–CH cyclohexyl proton (δ 3.51), two singlets for the methoxy groups (δ 3.74 and 3.80). The ^1H decoupled ^{13}C NMR spectrum of **4a** showed 17 distinct resonances, partial assignments of these resonances are given in the typical procedure.²⁶

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

Although the mechanism of this reaction has not been established, a plausible rationalization can be advanced to explain product formation, Scheme 2. On the basis of the well-established chemistry of isocyanides,^{11,27–29} it is reasonable to assume that zwitterionic intermediate **5** produced by reaction between the isocyanide and the dialkyl acetylenedicarboxylate adds to acetic anhydride resulting in the formation of **6**, which undergoes cyclization to deliver the 2,5-dihydro-5-imino-2-methylfuran-3,4-dicarboxylates **4a–h**.

The versatility of this multicomponent reaction with respect to the active carbonyl component was also studied (Scheme 3). As indicated in Table 2, reaction of phthalic anhydride **7** and dialkyl acetylenedicarboxylates with alkyl isocyanides in CH_2Cl_2 led to the formation of benzo-fused spiroactones¹⁸ **8a–d** in good yields at room temperature.³⁰



Scheme 3. Synthesis of benzo-fused spiroactones.

Table 2
Synthesis of various benzo-fused spiroactones

Entry	R ¹	R ²	Product	Yield (%)
1	Cyclohexyl	Me	8a	82
2	<i>tert</i> -Butyl	Me	8b	75
3	<i>tert</i> -Butyl	Et	8c	85
4	1,1,3,3-Tetramethylbutyl	Me	8d	80

In conclusion, a convenient, one-pot, three-component method for the synthesis of 2,5-dihydro-5-imino-2-methylfuran-3,4-dicarboxylates from readily accessible precursors has been developed. These compounds are important starting materials in the synthesis of natural products containing tetrahydrofuran rings.¹⁰ The present procedure has advantages such as good functional group tolerance and neutral reaction conditions.

Acknowledgments

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Supplementary data

Experimental procedures and mass, IR, ^1H NMR, and ^{13}C NMR spectral data for compounds **4a–h** and **8a–d** are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.01.069.

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- Typical procedure for the preparation of (5*Z*)-dimethyl 2-acetoxy-5-(cyclohexylimino)-2,5-dihydro-2-methylfuran-3,4-dicarboxylate (**4a**): To a magnetically stirred solution of acetic anhydride (0.11 g, 1.0 mmol) and dimethyl acetylenedicarboxylate (0.14 g, 1.0 mmol) in CH_2Cl_2 (10 mL) was added, dropwise, a solution of cyclohexyl isocyanide (0.11 g, 1 mmol) in CH_2Cl_2 (2 mL) at room temperature over 10 min. The mixture was stirred for 12 h. The solvent was removed under vacuum, and the residue was separated by column chromatography (silica gel, hexane/EtOAc, 4:1) to give the product as a yellow oil (0.21 g, yield 60%). IR (KBr) ($\nu_{\text{max}}/\text{cm}^{-1}$): 2933, 2855, 1754, 1734, 1692. MS, m/z (%): 333 ($\text{M}^+ - 20$, 2), 293 (2), 182 (20), 98 (30), 59 (30), 43 (100). ^1H NMR (300 MHz, CDCl_3): δ_{H} (ppm) 1.18–1.62 (10H, m, 5CH₂ of cyclohexyl), 1.76 (3H, s, CH₃), 1.96 (3H, s, CH₃), 3.51 (1H, m, CH–N), 3.74 (3H, s, O–CH₃), 3.80 (3H, s, O–CH₃). ^{13}C NMR (75 MHz, CDCl_3): δ_{C} (ppm) 21.48 (CH₃), 24.50 (CH₃), 24.22, 24.57, 25.56, 33.02, 33.18 (C-cyclohexyl), 52.71, 52.97 (2O–CH₃), 56.75 (CH–NH), 106.90 (O–C–O), 137.52, 139.90 (C-olefin), 152.00 (C-imine), 160.36, 161.93, 168.41 (3C=O). Anal. Calcd for C₁₇H₂₃NO₇: C, 57.78; H, 6.56; N, 3.96. Found: C, 57.81; H, 6.50; N, 3.89.
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30. *Typical procedure for the preparation of compound (8a)*: To a magnetically stirred solution of phthalic anhydride (0.15 g, 1.0 mmol) and dimethyl acetylenedicarboxylate (0.14 g, 1.0 mmol) in CH₂Cl₂ (10 mL) was added, dropwise, a solution of cyclohexyl isocyanide (0.11 g, 1 mmol) in CH₂Cl₂ (2 mL) at room temperature over 10 min. The mixture was stirred for 2 h. The solvent was removed under vacuum, and the residue was crystallized from *n*-hexane/dichloromethane (2:1) and washed with ether (3 × 5 mL). The product

8a was obtained as a white powder (0.33 g, yield 82%). IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 2930, 2852, 1785, 1722, 1700. MS, m/z (%): 399 (M^+ , 20), 367 (20), 302 (100), 243 (30), 163 (70), 97 (35). ¹H NMR (300 MHz, CDCl₃): δ_{H} (ppm) 1.14–1.85 (10H, m, 5CH₂ of cyclohexyl), 3.69 (1H, m, CH–N), 3.61 (3H, s, O–CH₃), 3.95 (3H, s, O–CH₃), 7.45–8.03 (4H, m, arom). ¹³C NMR (75 MHz, CDCl₃): δ_{C} (ppm) 24.43, 24.46, 25.49, 33.04, 33.14 (C-cyclohexyl), 52.96, 53.42 (2O–CH₃), 57.46 (CH–N), 109.08 (spiro carbon), 122.42, 125.70, 126.96, 131.25, 131.87, 134.64, 136.11, 143.48 (C-olefin and C-arom), 150.69 (C-imine), 159.36, 161.27, 166.41 (3C=O). Anal. Calcd for C₂₁H₂₁NO₇: C, 63.15; H, 5.30; N, 3.51. Found: C, 63.23; H, 5.20; N, 3.46.