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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

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ABSTRACT

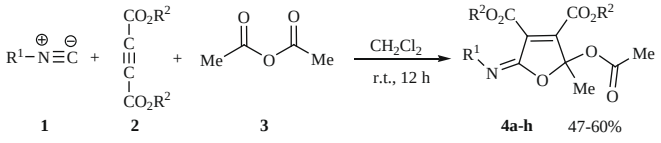
The zwitterion formed from an alkyl or aryl isocyanide and dialkyl acetylenedicarboxylate reacts with acetic anhydride or phthalic anhydride to form 2,5-dihydro-5-imino-2-methylfuran-3,4-dicarboxylates or benzo-fused spirolactones in relatively good yields at room temperature without using a catalyst.

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 CH_2Cl_2 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	*tert*-Butyl	Me	**4c**	53
4	*tert*-Butyl	Et	**4d**	49
5	*tert*-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-$(Me)_2C_6H_4$	Et	**4h**	58

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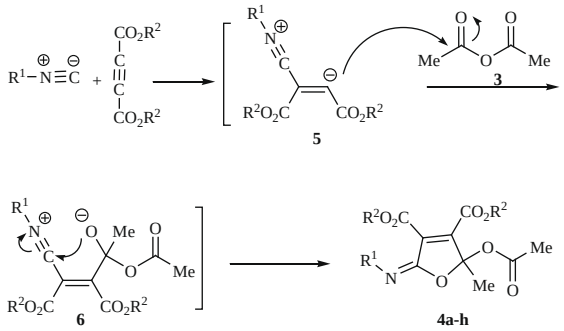


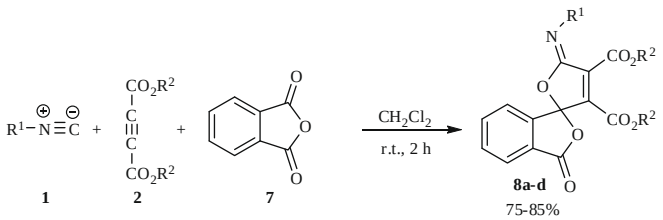
Scheme 2. Proposed mechanism.

the products were deduced from their IR, mass, ^{1}H NMR, and ^{13}C NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at the appropriate *m/z* values. The ^{1}H 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–C*H* cyclohexyl proton (δ 3.51), two singlets for the methoxy groups (δ 3.74 and 3.80). The ^{1}H 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 **3** 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 spirolactones[18] **8a–d** in good yields at room temperature.[30]



Scheme 3. Synthesis of benzo-fused spirolactones.

Table 2
Synthesis of various benzo-fused spirolactones

Entry	R^1	R^2	Product	Yield (%)
1	Cyclohexyl	Me	**8a**	82
2	*tert*-Butyl	Me	**8b**	75
3	*tert*-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, ^{1}H 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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26. *Typical procedure for the preparation of (5Z)-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) (ν_{max}/cm^{-1}): 2933, 2855, 1754, 1734, 1692. MS, *m/z* (%): 333 (M^+–20, 2), 293 (2), 182 (20), 98 (30), 59 (30), 43 (100). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) 1.18–1.62 (10H, m, 5CH_2 of cyclohexyl), 1.76 (3H, s, CH_3), 1.96 (3H, s, CH_3), 3.51 (1H, m, C*H*–N), 3.74 (3H, s, O–CH_3), 3.80 (3H, s, O–CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 21.48 (CH_3), 24.50 (CH_3), 24.22, 24.57, 25.56, 33.02, 33.18 (C-cyclohexyl), 52.71, 52.97 (2O–CH_3), 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 $C_{17}H_{23}NO_7$: 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 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 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) (ν_{max}/cm^{-1}): 2930, 2852, 1785, 1722, 1700. MS, *m*/*z* (%): 399 (M^+, 20), 367 (20), 302 (100), 243 (30), 163 (70), 97 (35). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) 1.14–1.85 (10H, m, $5CH_2$ of cyclohexyl), 3.69 (1H, m, *CH*–N), 3.61 (3H, s, O–CH_3), 3.95 (3H, s, O–CH_3), 7.45–8.03 (4H, m, arom). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 24.43, 24.46, 25.49, 33.04, 33.14 (C-cyclohexyl), 52.96, 53.42 (2O–CH_3), 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 $C_{21}H_{21}NO_7$: C, 63.15; H, 5.30; N, 3.51. Found: C, 63.23; H, 5.20; N, 3.46.