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A novel reaction of vicinal tricarbonyl compounds with the isocyanide–DMAD zwitterion: formation of highly substituted furan derivatives

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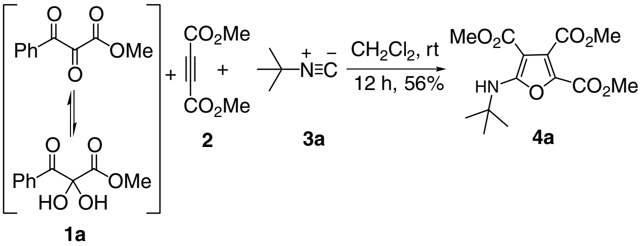
Abstract—The vicinal tricarbonyl system participates in a novel reaction with the zwitterion derived from isocyanide and dimethyl acetylenedicarboxylate to form fully substituted furan derivatives.

Apart from their well known and much exploited reactivity in Passerini and Ugi reactions,[1] isocyanides are known to form zwitterions with activated acetylene compounds such as dimethyl acetylenedicarboxylate (DMAD).[2] In recent years, work in our laboratory has shown that these type of zwitterions can be trapped by a variety of electrophiles such as aldehydes, tosylimines, 1,2- and 1,4-quinones and activated styrenes thus constituting a novel protocol for the synthesis of heterocycles and carbocycles.[3] A similar approach subsequently developed by Yoshida, which involves trapping of the zwitterion generated by the reaction of isocyanides and benzynes is also noteworthy.[4] Against this background, it was of interest to investigate the reactivity of the isocyanide–DMAD zwitterion towards vicinal tricarbonyl compounds. The latter have been known to engage in a variety of interesting transformations often leading to heterocycles, largely due to the efforts of Wasserman and co-workers,[5,6] but their reaction with zwitterions has not been investigated. In this paper, we report the results of our studies involving the reactions of zwitterions, derived from isocyanides and DMAD, and some vicinal tricarbonyl compounds which constitute a novel synthesis of highly substituted furans.

In a pilot experiment, a solution of diketoester **1a** and DMAD **2** in dry dichloromethane was treated with *tert*-butyl isocyanide **3a** at room temperature. After completion of the reaction as indicated by TLC, the solvent was removed and the residue was subjected to column chromatography to yield **4a** as a colourless liquid in 56% yield (Scheme 1).[7]

The IR spectrum of **4a** displayed characteristic ester carbonyl and N–H vibrations at 1743, 1722 and 3345 cm^{-1}, respectively. In the ^{1}H NMR spectrum, the protons of the *tert*-butyl group resonated as a sharp singlet at δ 1.47 while the methoxy protons of the ester moieties resonated at δ 3.92, δ 3.82 and δ 3.76. The ^{13}C NMR spectrum showed the characteristic signals for the ester carbonyl carbons at δ 164.2, δ 163.8 and δ 162.1. The compound gave satisfactory mass analysis also. Regarding the variability of the three-component reaction, a number of diketoesters were found to react with both *tert*-butyl and cyclohexyl isocyanides to yield a variety of substituted furans (Table 1). The diketoesters used in our studies were prepared from the corresponding β-ketoesters by a literature procedure.[8]



Scheme 1.

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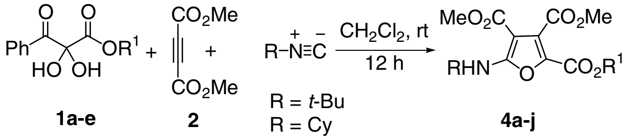
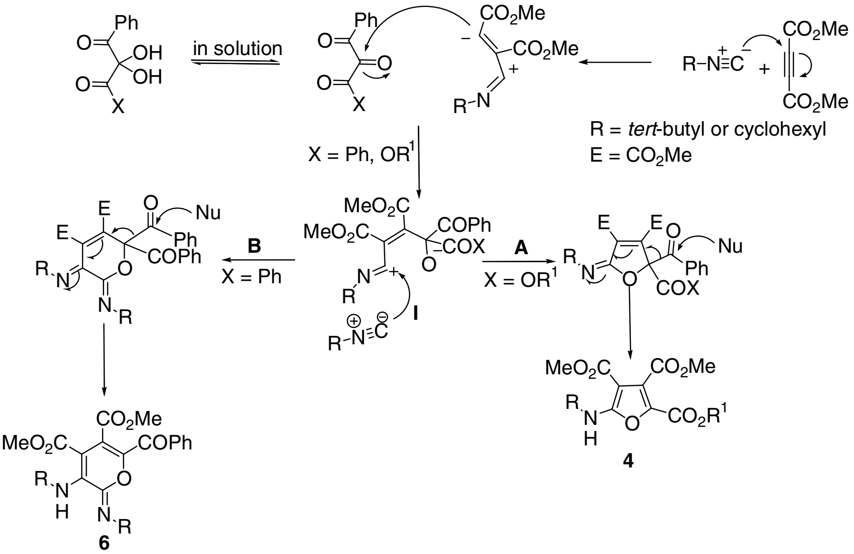
Table 1.



Entry	R	Diketoester	Product	Yield (%)[a]
1		**1a** $R^1 = Me$	**4a**	56
2		**1b** $R^1 = Et$	**4b**	52
3	*tert*-Butyl	**1c** $R^1 = Bu$	**4c**	59
4		**1d** $R^1 = CH_2Ph$	**4d**	49
5		**1e** $R^1 = CH_2CH{=}CHPh$	**4e**	50
6		**1a** $R^1 = Me$	**4f**	51
7		**1b** $R^1 = Et$	**4g**	58
8	Cyclohexyl	**1c** $R^1 = Bu$	**4h**	60
9		**1d** $R^1 = CH_2Ph$	**4i**	37
10		**1e** $R^1 = CH_2CH{=}CHPh$	**4j**	45

[a] Isolated yields after silica gel column chromatography.



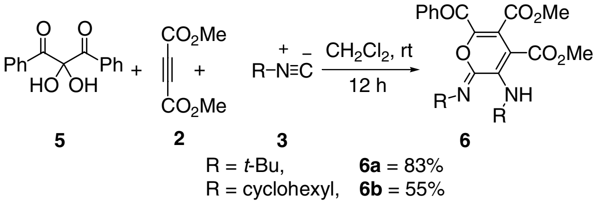
Scheme 2.

A mechanistic postulate as shown in Scheme 2 may be invoked to rationalize the formation of aminofuran **4**.

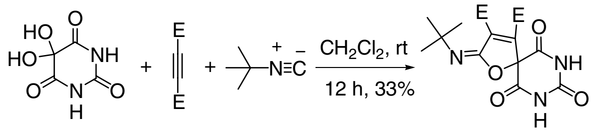
Vicinal tricarbonyl compounds in solution are known to be in equilibrium with their hydrates. Nucleophilic addition of the isocyanide–DMAD zwitterion to the central carbonyl of the tricarbonyl compound leads to the formation of the tetrahedral intermediate **I**, which in turn can cyclize according to path A to form the iminofuran. This is followed by debenzoylation of the iminofuran conceivably by attack of excess isocyanide present in the system to yield aminofuran **4**.

Manifestation of another reaction was observed on treating a solution of diphenyl triketone **5** and DMAD **2** in dry dichloromethane with *tert*-butyl isocyanide **3a** at room temperature. After completion of the reaction as indicated by TLC, the reaction mixture was processed as before to yield **6a** as a viscous liquid in 83% yield (Scheme 3).

The IR spectrum of **6a** displayed characteristic ester and benzoyl carbonyl vibrations at 1741 and 1681 cm^{-1}, respectively. In the ^1H NMR spectrum, the two *tert*-butyl group protons appeared as sharp singlets at δ 1.51 and δ 1.38 and the protons of the carbomethoxy



Scheme 3.



7 **2** **3a** E = CO_2Me **8**

Scheme 4.

groups resonated at δ 3.87 and δ 3.66. The ^{13}C NMR spectrum showed resonance signals at δ 185.6, δ 163.8 and δ 162.3 corresponding to the benzoyl and ester carbonyl carbons, respectively. Mass spectral data also agreed with the proposed structure. Formation of the iminopyrone may be rationalized as occurring via path B. Presumably path A leading to the furan derivative is not operative in this case due to the steric demands imposed by the two benzoyl groups, thus allowing the participation of another molecule of the isocyanide.

The cyclic tricarbonyl compound, alloxan hydrate **7**, on reaction with the zwitterion afforded the spiroadduct **8** albeit in low yield (Scheme 4). Unfortunately, reaction of isocyanide–DMAD zwitterion with other cyclic triones led to intractable mixtures.

In summary, we have uncovered a novel one-pot synthesis of highly substituted furan derivatives. Substituted furans are useful intermediates in synthetic organic chemistry[9] and there have been numerous approaches towards their synthesis.[10] The mild reaction conditions used in the present reaction are particularly noteworthy.

Acknowledgements

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7. Typical experimental procedure: To a solution of the diketoester **1a** (70 mg, 0.33 mmol) and dimethyl acetylenedicarboxylate (71 mg, 0.50 mmol) in anhydrous dichloromethane, was added after two minutes, *tert*-butyl isocyanide (0.04 mL, 0.40 mmol) via a syringe and the mixture was stirred at room temperature for 12 h. On completion of the reaction, solvent was removed and the residue was subjected to chromatography on silica gel (100–200 mesh) using 15% ethyl acetate–hexane mixture as eluent to afford **4a** as a colourless liquid (58 mg, 56%). Spectral data for **4a**. IR (thin film) υ_{max}: 3345, 2957, 1743, 1722, 1605, 1490, 1370, 1340, 1265, 1225, 1154, 1001. ^1H NMR (300 MHz, $CDCl_3$): δ 7.01 (s, 1H), 3.92 (s, 3H), 3.82 (s, 3H), 3.76 (s, 3H), 1.47 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.2, 163.8, 162.1, 157.7, 133.3, 130.1, 128.7, 128.4, 89.0, 53.3, 52.8, 51.8, 51.4, 29.7. HRMS (EI): *m/z* calcd for $C_{14}H_{19}NO_7$: 313.1162, found: 313.1139.
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