

# One-pot, four-component reaction of isocyanides, dimethyl acetylenedicarboxylate, and cyclobutene-1,2-diones: a synthesis of novel spiroheterocycles

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Dedicated with best wishes to Professor Douglas W. Young on the occasion of his 65th birthday

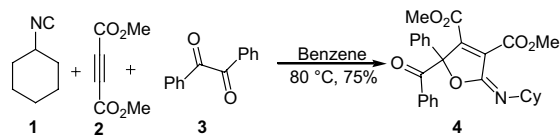
**Abstract**—Isocyanides, dimethyl acetylenedicarboxylate, and cyclobutene-1,2-diones react in one-pot to afford novel spirocyclic compounds with double insertion of the isocyanide.  
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Isocyanide-based multicomponent reactions (IMCR) now occupy a position of importance in synthetic organic chemistry, mainly due to the contributions of Ugi and co-workers.<sup>1</sup> In addition to many variations of the classical Ugi four-component condensation (U-4CC) other IMCRs have entered the arena in recent years.<sup>2</sup> One such class of diverse, yet conceptually different IMCRs involves the generation and interception of reactive zwitterionic intermediates by the nucleophilic addition of isocyanides to activated acetylenes.<sup>3</sup> This strategy has been successfully employed in the one-pot syntheses of various heterocyclic systems like 2-aminofurans, their pyrrole analogs, iminolactones, and aminopyrans.<sup>4</sup> The reaction of cyclohexyl isocyanide **1**, dimethyl acetylenedicarboxylate (DMAD) **2** and benzil **3** to afford iminolactone derivative **4** deserves special mention in the present context.<sup>4a</sup>

Cyclobutenediones constitute a special class of reactive 1,2-diones.<sup>5</sup> Their synthetic importance stems from the fact that they generate bisketene intermediates by the thermal, photochemical or metal-mediated opening of the strained four-membered ring.<sup>6</sup> A variety of transformations that exploit this feature of cyclobutenediones have been reported in the past, especially noteworthy

is Liebeskind's quinone synthesis.<sup>7</sup> In the context of our longstanding interest in the chemistry of 1,2-diones<sup>8</sup> and in the light of our recent success in the area of MCRs,<sup>3</sup> we envisaged the possibility of intercepting the zwitterion derived from isocyanides and DMAD with cyclobutene-1,2-diones with a view to constructing novel spirocyclic systems.

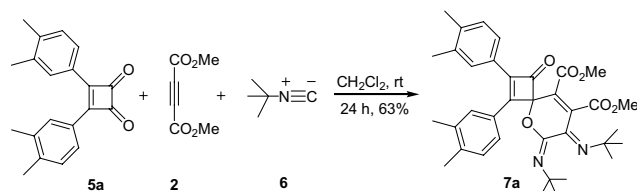
A number of substituted cyclobutenediones which are accessible by a reported protocol<sup>9</sup> starting from commercially available squaric acid were selected for the study. In a pilot experiment, a solution of equimolar quantities of bis-3,4-(3,4-dimethylphenyl)cyclobutene-1,2-dione **5a** and dimethyl acetylenedicarboxylate **2** in anhydrous dichloromethane was treated with *tert*-butyl isocyanide **6** at room temperature for 24 h. Processing of the reaction mixture followed by chromatographic separation afforded a flaky, yellow solid in 27% yield. <sup>1</sup>H NMR analysis of the product revealed that it contained two moles of isocyanide (two tertiary-butyl group resonances at δ 1.24 and 1.41 were seen) per mole of DMAD and the dione. Thus the reaction conditions were modified accordingly by using two equivalents of



Scheme 1.

**Keywords:** Multicomponent reactions; Isocyanides; Zwitterions; Dimethyl acetylenedicarboxylate.

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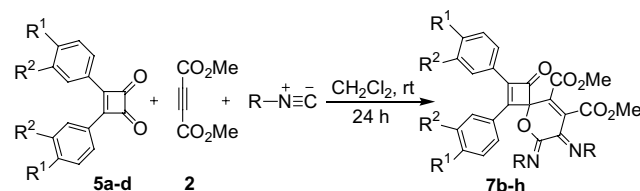
Scheme 2.

*tert*-butyl isocyanide (Scheme 2). The same yellow product **7a** was isolated and it was assigned to the spirocyclic structure by spectroscopic analysis.<sup>10</sup> The IR spectrum of **7a** showed absorptions at 1743 and 1692 cm<sup>-1</sup> indicating the presence of ester and ketone functionalities. In the <sup>13</sup>C NMR spectrum, the keto carbon resonated at  $\delta$  184.3 and the spiro carbon was visible at  $\delta$  92.1.

The reaction was found to be general with respect to a number of substituted cyclobutenediones affording the spirocyclic products in moderate yields. The results are summarized in Table 1. The zwitterion generated from cyclohexyl isocyanide and DMAD was also found to react with cyclobutenediones under similar conditions (Table 1, entries 4–7).

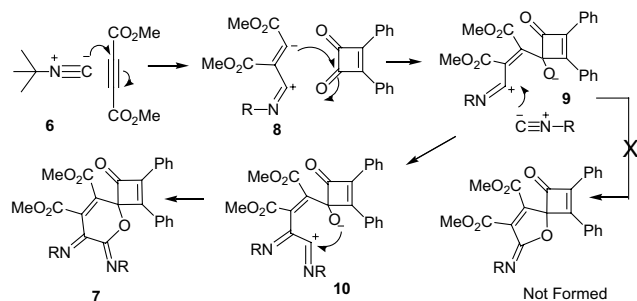
A tentative mechanism for the transformation is proposed in Scheme 3. It is conceivable that, the initial event is the formation of a 1,3-dipolar intermediate **8**

Table 1.



Entry	R	Cyclobutenedione	Product	Yield <sup>a</sup> (%)
1		<b>5b</b> R <sup>1</sup> = R <sup>2</sup> = H	<b>7b</b>	61
2	<i>tert</i> -butyl	<b>5c</b> R <sup>1</sup> = Me, R <sup>2</sup> = H	<b>7c</b>	58
3		<b>5d</b> R <sup>1</sup> = OMe, R <sup>2</sup> = H	<b>7d</b>	54
4		<b>5a</b> R <sup>1</sup> = R <sup>2</sup> = Me	<b>7e</b>	62
5	Cyclohexyl	<b>5b</b> R <sup>1</sup> = R <sup>2</sup> = H	<b>7f</b>	55
6		<b>5c</b> R <sup>1</sup> = Me, R <sup>2</sup> = H	<b>7g</b>	59
7		<b>5d</b> R <sup>1</sup> = OMe, R <sup>2</sup> = H	<b>7h</b>	58

<sup>a</sup> Isolated yield.



Scheme 3.

from isocyanide **6** and DMAD. Nucleophilic addition of **8** to the reactive carbonyl group of cyclobutenedione **5**, analogous to the reaction of the dipole toward 1,2-diones such as benzil,<sup>4a</sup> follows. The tetrahedral intermediate **9** thus formed can, in principle, cyclize to give a five-membered iminolactone (cf. Scheme 1) but the steric demands associated with the constrained four-membered ring presumably disfavor such a cyclization. The nitrilium ion **9** can receive electron density from another molecule of isocyanide and the resulting species **10** cyclizes to furnish the spirocyclic product **7**. The charge density localized at the alkoxide anion of **9** can potentially trigger a rupture of the four-membered ring but the isocyanide–DMAD dipole seems to be too weak a nucleophile to induce any such reaction, which is usually effected by very strong nucleophiles like phenyllithium or Grignard reagents.<sup>7</sup>

In conclusion, a novel one-pot, three-reagent pseudo-four-component reaction of isocyanides, DMAD, and cyclobutenediones leading to novel spirocyclic compounds in moderate yields has been described. The products are highly functionalized molecules potentially amenable to further manipulations.

### Acknowledgements

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- Representative experimental procedure and spectral data for **7a**: A solution of DMAD (40 mg, 0.28 mmol) and cyclobutenedione **5a** (73 mg, 0.25 mmol) in anhydrous

$\text{CH}_2\text{Cl}_2$  was stirred for 2 min. To this solution, *tert*-butyl isocyanide (42 mg, 0.5 mmol) was added via a syringe, and the reaction mixture was allowed to stand at rt for 24 h. On completion of the reaction, the solvent was removed on a rotavapor and the residue subjected to chromatography on a silica gel column using hexanes–ethyl acetate (90:10) to afford **7a** as a yellow, flaky solid (94 mg, 63%). Mp 54–57 °C **IR** (KBr)  $\nu_{\text{max}}$ : 3347, 2984, 2057, 1743, 1692, 1660, 1610, 1534, 1444, 1349, 1190, 1021  $\text{cm}^{-1}$ .  **$^1\text{H}$  NMR**

( $\text{CDCl}_3$ , 300 MHz):  $\delta$  1.24 (s, 9H), 1.41 (s, 9H), 2.15 (s, 3H), 2.21 (s, 3H), 2.22 (s, 3H), 2.25 (s, 3H), 3.68 (s, 3H), 3.89 (s, 3H), 6.83 (d,  $J = 7.65$  Hz, 1H), 6.91–7.24 (m, 5H).  **$^{13}\text{C}$  NMR** ( $\text{CDCl}_3$ , 75 MHz):  $\delta$  19.7, 19.8, 19.9, 29.4, 29.5, 52.5, 52.8, 54.8, 58.3, 92.1, 109.3, 126.6, 127.2, 129.5, 129.6, 129.7, 129.9, 130.5, 136.4, 136.8, 137.4, 138.7, 139.7, 147.5, 156.0, 156.1, 160.5, 162.1, 184.3. Elemental analysis calculated for  $\text{C}_{36}\text{H}_{42}\text{N}_2\text{O}_6$ : C, 72.22; H, 7.07; N, 4.68%. Found: C, 72.41; H, 6.92; N, 5.07%.