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Key words: Huisgen zwitterion, Morita–Baylis–Hillman acetate, β-amino acid

Although Huisgen zwitterion1 was known for nearly four decades, its synthetic potential remained largely unexploited except in some notable reactions like Mitsunobu Reaction.2 In view of our longstanding interest in zwitterion chemistry,3 recently we have explored the reactivity of Huisgen zwitterion towards various substrates like aldehydes, ketones, chalcones, diaryl 1,2-diones, quinones, isatins, and allenes.4–6 In this context it was of interest to examine the reactivity of Huisgen zwitterion towards Morita–Baylis–Hillman (MBH) adducts,7,8 which are unique substrates of great synthetic potential incorporating three manipulatable groups, namely, a hydroxy group, a double bond, and an electron-withdrawing group. In this paper, we describe the results of our investigations on the reaction of Huisgen zwitterion with MBH acetates.

The present studies were initiated by treating methyl 2-[(4-chlorophenyl)acetyloxymethyl]acrylate (1a) with diisopropyl azodicarboxylate and triphenylphosphine in THF at room temperature for 2 hours. The reaction afforded two products, namely, diisopropyl N-acetyl-N'-[3-(4-chlorophenyl)-2-(methoxycarbonyl)allyl]hydrazine-1,2-dicarboxylate (3a) and diisopropyl N-[3-(4-chlorophenyl)-2-(methoxycarbonyl)allyl]hydrazine-1,2-dicarboxylate (4a) in 46% and 51% yield, respectively (Scheme 1).

The structure elucidation of 3a and 4a was accomplished by usual spectroscopic analysis. The 1H NMR spectrum of the compound 3a showed singlet resonance signals at δ = 2.35 and 3.81 due to CH3CO group and CH3OCO groups. The NCH2 group was discernable at δ = 4.14–4.73 as a multiplet. In the 13C NMR spectrum the three ester carbonyl groups were present at δ = 169.4, 167.4 and 154.7 and that of the keto carbonyl group appeared at δ = 152.7, supporting the IR absorption observed in the region 1750–1700 and 1631 cm–1. All other signals were also in good agreement with the proposed structure. The structure and stereochemistry of the compound was unambiguously established by single crystal X-ray analysis (Figure 1) of a representative compound, 3g.

Figure 1 Single crystal X-ray structure of di-tert-butyl N-acetyl-N'-[3-(3,4-dichlorophenyl)-2-(methoxycarbonyl)allyl]hydrazine-1,2-dicarboxylate (3g)

Scheme 1 Reaction of Huisgen zwitterion with MBH acetate
The IR spectrum of the compound 4a showed strong absorptions at 3308 and 1703–1722 cm⁻¹ due to NH group and the ester carbonyl groups, respectively. The 1H NMR showed singlets at δ = 4.5 and 6.71 due to NCH₂ and NH groups. In the 13C NMR spectrum signals due to the ester carbonyl groups were discernable at δ = 155.5, 156.3, and 167.7. Other signals were also in good agreement with the proposed structure.

The mechanism of the reaction may be rationalized by invoking an SN₂⁺ process, involving the Huisgen zwitterion and the Morita–Baylis–Hillman acetate (Scheme 2). Evidently, the first step of the reaction is the formation of Huisgen zwitterion by the addition of triphenylphosphine to diisopropyl azodicarboxylate. The SN₂⁺ displacement of the acetate from 1a induced by Huisgen zwitterion would lead to the formation of the cationic intermediate 5. The attack of the acetate on 5 followed by rearrangement and the elimination of Ph₃PO, would result in the formation of disopropyl N-acetyl-N'-[3-(4-chlorophenyl)-2-(methoxycarbonyl)allyl]hydrazine-1,2-dicarboxylate (3a).

Similarly by the addition of hydroxy anion to 5, an intermediate 7 is formed, and the latter on elimination of triphenylphosphine oxide would deliver disopropyl N-[3-(4-chlorophenyl)-2-(methoxycarbonyl)allyl]hydrazine-1,2-dicarboxylate (4a).

As disclosed in Table 1, the reaction was found to be general with various Morita–Baylis–Hillman acetates and Huisgen zwitterions.

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>X</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>4-ClC₆H₄</td>
<td>i-Pr CO₂Me</td>
<td>46 51</td>
</tr>
<tr>
<td>b</td>
<td>4-CF₃C₆H₄</td>
<td>Et CO₂Me</td>
<td>57 41</td>
</tr>
<tr>
<td>c</td>
<td>3-ClC₆H₄</td>
<td>Et CO₂Me</td>
<td>38 49</td>
</tr>
<tr>
<td>d</td>
<td>Ph</td>
<td>i-Pr CO₂Me</td>
<td>35 56</td>
</tr>
<tr>
<td>e</td>
<td>Ph</td>
<td>i-Pr CN</td>
<td>57 37</td>
</tr>
<tr>
<td>f</td>
<td>4-FC₆H₄</td>
<td>t-Bu CO₂Me</td>
<td>37 46</td>
</tr>
<tr>
<td>g</td>
<td>3,4-Cl₂C₆H₃</td>
<td>t-Bu CO₂Me</td>
<td>58 30</td>
</tr>
<tr>
<td>h</td>
<td>Ph</td>
<td>Et CO₂Me</td>
<td>35 49</td>
</tr>
<tr>
<td>i</td>
<td>4-MeC₆H₄</td>
<td>i-Pr CO₂Me</td>
<td>40 36</td>
</tr>
<tr>
<td>j</td>
<td>4-BrC₆H₄</td>
<td>i-Pr CO₂Me</td>
<td>54 40</td>
</tr>
</tbody>
</table>

In conclusion, herein we have reported a facile C–N bond-forming reaction, which incidentally constitutes the first example of the participation of Huisgen zwitterions in an SN₂⁺ reaction.

Melting points were recorded on a Büchi melting point apparatus and are uncorrected. NMR spectra were recorded at 300 MHz (1H) and 75 MHz (13C) respectively on a Bruker Avance DPX-300 MHz NMR spectrometer. Chemical shifts are reported (δ) relative to TMS (1H) and CDCl₃ (13C) as the internal standards. Coupling constants (J) are reported in Hertz (Hz). High-resolution mass spectra were recorded under EI/HRMS (at 5000 resolution) or FAB+ HRMS using Jeol JMS 600H mass spectrometer. IR spectra were recorded on Nicolet Impact 400D FT-IR spectrophotometer. Commercial grade solvents were distilled prior to use.

Reactions of Morita–Baylis–Hillman Acetates with Huisgen Zwitterions; General Procedure

The Morita–Baylis–Hillman acetate 1 (1 equiv) dissolved in THF (5 mL) was treated with the respective azodicarboxylate 2 (1.2 equiv) and Ph₃P (1.2 equiv) at r.t. for 2 h under N₂. The solvent was removed under reduced pressure and the crude reaction mixture was purified by column chromatography using silica gel (60–120 mesh) and hexane–EtOAc.
**Diisopropyl N-Acetyl-N’-[3-(4-chlorophenyl)-2(methoxycarbonyl)allyl]hydrazine-1,2-dicarboxylate (3a)**

Yield: 51%.

IR (KBr): 3421, 2988, 2216–1703 (br), 1752–1715 (br), 1481, 1381 cm⁻¹.


**Diisopropyl N-Acetyl-N’-[3-(3-Chlorophenyl)-2(methoxycarbonyl)allyl]hydrazine-1,2-dicarboxylate (3b)**

Yield: 37%.

IR (KBr): 1715, 1240 cm⁻¹.

HRMS (EI): m/z calcd for C₁₇H₂₁ClN₂O₆: 379.18; found: 379.20.

**Diethyl N-Acetyl-N’-[3-(4-trifluoromethylphenyl)-2(methoxycarbonyl)allyl]hydrazine-1,2-dicarboxylate (3c)**

Yield: 57%.

IR (KBr): 3309, 2983, 1722–1703 cm⁻¹.

HRMS (EI): m/z calcd for C₁₉H₂₃ClN₂O₇: 426.1217; found: 426.1219.

**Diethyl N-Acetyl-N’-[3-(3-Phenyl-2-cyano)allyl]hydrazine-1,2-dicarboxylate (3d)**

Yield: 56%.

IR (KBr): 1712, 1249 cm⁻¹.


**Diethyl N-Acetyl-N’-[3-(3-Phenyl-2-(methoxycarbonyl)allyl)hydrazine-1,2-dicarboxylate (3e)**

Yield: 37%.

IR (KBr): 3413, 2988, 2216, 1752–1715 (br), 1481, 1381 cm⁻¹.

HRMS (+FAB): m/z calcd for C₁₉H₂₁ClN₂O₆: 388.18; found: 388.21.

**Diisopropyl N-Acetyl-N’-[3-(3-Phenyl-2-cyano)allyl]hydrazine-1,2-dicarboxylate (4e)**

Yield: 49%.

IR (KBr): 3424, 2983, 1759–1699 (br), 1487 cm⁻¹.

HRMS (EI): m/z calcd for C₁₇H₂₁N₂O₆: 246.1217; found: 246.1219.

**Diethyl N-[3-(3-Chlorophenyl)-2-(methoxycarbonyl)allyl]hydrazine-1,2-dicarboxylate (4a)**

Yield: 51%.

IR (KBr): 3211, 2991, 1753–1703 (br), 1481, 1381 cm⁻¹.

HRMS (EI): m/z calcd for C₁₉H₂₅ClN₂O₆ (M + H)+: 379.18; found: 379.20.

**Diethyl N-[3-(3-Chlorophenyl)-2-(methoxycarbonyl)allyl]hydrazine-1,2-dicarboxylate (4b)**

Yield: 41%.

IR (KBr): 3421, 2999, 1755–1697 (br), 1723 cm⁻¹.

1H NMR (300 MHz, CDCl3): δ = 1.25–1.33 (m, 12 H), 4.43–4.53 (m, 2 H), 4.89–5.05 (m, 2 H), 6.89 (s, 1 H), 7.41–7.75 (m, 5 H), 7.76 (s, 1 H).

13C NMR (75.47 MHz, CDCl3): δ = 21.6, 21.9, 52.5, 52.5, 69.5, 69.9, 106.5, 128.8, 128.9, 130.5, 132.9, 154.8, 156.4.

LRMS-FAB: m/z: calecd for C18H17N2O6 (M + H)+: 425.21; found: 425.21.

Di-tert-butyl N-Acetyl-N-3-(3,4-dichlorophenyl)-2-(methoxycarbonyl)allyl]hydrazine-1,2-dicarboxylate (3g)

Yield: 58%.

IR (KBr): 3037, 2985, 1762, 1745, 1703, 1382, 1286, 1240 cm⁻¹.

1H NMR (300 MHz, CDCl3): δ = 1.43–1.51 (m, 18 H), 2.36 (s, 3 H), 3.82 (s, 3 H), 4.45–4.63 (m, 2 H), 7.29 (d, J = 9 Hz, 1 H), 7.45 (d, J = 9 Hz, 1 H), 7.60 (s, 1 H), 7.75 (s, 1 H).

13C NMR (75.47 MHz, CDCl3): δ = 22.7, 25.3, 26.9, 27.7, 27.8, 42.2, 52.3, 81.5, 83.8, 128.0, 129.0, 130.5, 131.6, 138.7, 142.2, 151.7, 152.3, 167.2, 169.9.

LRMS-FAB: m/z: calecd for C31H32Cl2N2O8 (M + H)+: 517.14; found: 517.15.

Di-tert-butyl N-Acetyl-N-3-(3,4-dichlorophenyl)-2-(methoxycarbonyl)allyl]hydrazine-1,2-dicarboxylate (3g)

Yield: 36%.

IR (KBr): 3304, 2983, 1788–1711, 1634, 1587 cm⁻¹.

1H NMR (300 MHz, CDCl3): δ = 1.14–1.33 (m, 12 H), 2.36 (s, 3 H), 3.81 (s, 3 H), 4.52–4.62 (m, 2 H), 4.90–4.96 (m, 2 H), 7.15–7.55 (m, 5 H), 7.81 (s, 1 H).

13C NMR (75.47 MHz, CDCl3): δ = 21.3, 21.6, 21.8, 22.0, 25.3, 29.7, 42.8, 51.7, 70.8, 71.7, 123.8, 126.8, 130.2, 133.4, 140.5, 143.7, 152.7, 154.2, 167.7, 169.5.

HRMS (EI): m/z: calecd for C2H25ClNO: 499.1002; found: 499.1010.

Diisopropyl N-Acetyl-N-3-(4-bromophenyl)-2-(methoxycarbonyl)allyl]hydrazine-1,2-dicarboxylate (3k)

Yield: 40%.

IR (KBr): 3314, 2982, 1739–1723, 1634, 1109 cm⁻¹.

1H NMR (300 MHz, CDCl3): δ = 1.12–1.44 (m, 12 H), 2.30 (s, 3 H), 2.37 (s, 3 H), 3.80 (s, 3 H), 4.52–4.80 (m, 2 H), 4.75–4.99 (m, 2 H), 7.15–7.32 (m, 4 H), 7.87 (s, 1 H).

13C NMR (75.47 MHz, CDCl3): δ = 21.2, 21.4, 21.6, 21.9, 46.3, 51.9, 69.3, 69.7, 69.9, 126.1, 128.3, 128.8, 129.2, 129.5, 131.5, 139.2, 143.8, 155.6, 156.3, 168.1.

LRMS-FAB: m/z: calecd for C34H32BrN2O2 (M + H)+: 457.0986; found: 457.0912.

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References