Reaction of Electrophilic Allyl Halides with Amines: A Reinvestigation

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Abstract: The Michael-induced ring closure (MIRC) of amines with 2-bromoalkylidenemalonates has been reinvestigated and the reaction products with primary amines have been identified as (2-iminoethyl)malonates and not 2-aminoalkylidenemalonates as previously reported. The (2-iminoethyl)malonates are formed by ring opening of the intermediate unstable 2-aminocyclopropane-1,1-dicarboxylates (β-ACCs) and were characterized spectroscopically and via chemical transformation.

Key words: Michael additions, ring closure, cyclopropanes, ring opening, imines

Recently, we described the synthesis of 2-(diphenylmethylidenediamino)- and 2-azidocyclopropane-1,1-dicarboxylates via Michael-induced ring closure (MIRC) of diphenylmethylideneamine and azide, respectively, to 2-bromoalkylidenemalonates. The former cyclopropanes are protected derivatives of 2-aminocyclopropane-1,1-dicarboxylates (β-ACCs) 1, which are one of the most conformationally constrained classes of β-amino acid derivatives and find applications in the field of β-peptide chemistry and synthetic organic chemistry. However, an appropriate N-protecting group has to be introduced during the synthesis of β-ACCs to inhibit their ring opening to γ-oxocarboxylates, due to the 1,2-push–pull substitution on the cyclopropane ring (Scheme 1). From earlier research, it has been reported that treatment of dimethyl 2-bromo-2-methylpropylidenemalonate 3a with primary and secondary amines gave rise to the formation of the formal substitution products, i.e. 2-aminoalkylidenemalonates 4, while the reaction of diethyl 2-bromoethylidenemalonate with benzhydrylamine, some signals were present in the 1H NMR spectrum of the reaction mixture corresponding to the presence of about 19% of aziridine 8c [δ = 1.17, 1.26 (2 × s, 2 × 3 H), 2.17 (d, J = 9.63 Hz, 1 H), 3.10 (s, 3 H), 3.17 (d, J = 9.63 Hz, 1 H), 3.71 (s, 3 H), 4.22 (s, 1 H)]. A rapid chromatography over a plug of silica gel was performed to obtain the pure aldimine 5c, while avoiding hydrolysis to the corresponding aldehyde 10. The unsaturated γ-lactam 6e was also isolated in 11% yield, resulting from the acid-catalyzed ring opening of aziridine 8c to the corresponding allyl amine 4 [R1 = (Ph)2CH, R2 = H] and further lactamization.

Spectral analysis allows the discrimination between substitution products 4 and aldimines 5. Obviously, the aldimines 5a–e have a malonate methine function, not present in the corresponding substitution products 4. This malonate CH-function resonates at δ = 3.67–3.88 ppm in the 1H NMR spectrum (CDCl3), close to the signal of the two methoxy groups (δ = 3.57–3.70 ppm). This CH-proton of 5a and 5b was not detected during the first investigation since it did not give a resolved resonance signal in the 1H NMR spectra obtained with a 60 MHz apparatus. This, together with the unavailability of 13C NMR explains the incorrect characterization. However, a clear difference exists in the chemical shift of the aldimine proton of 5 (δ = 7.51–7.86 ppm) and the olefinic proton of 4 (δ = 6.88–6.97 ppm). In the latter compounds the two methoxy
groups give two separate signals in $^1$H NMR. Also in the IR spectra, a distinction can be made between the aldimine function ($1660–1666$ cm$^{-1}$) and the C=C bond ($1641–1645$ cm$^{-1}$).

Besides spectroscopic evidence for the characterization of the aldimines, chemical transformation also allowed to confirm their structure (Scheme 3). From our experience in the reduction of 2-(diphenylmethylamino)cyclopropane-1,1-dicarboxylates to 3-(alkoxycarbonyl)pyrrolidin-2-ones via the intermediate $\gamma$-iminodicarboxylates, it was expected that treatment of the aldimines with sodium cyanoborohydride would give the corresponding $\gamma$-lactams. Indeed, 3-(methoxycarbonyl)pyrrolidin-2-ones $9a$ and $9c$ were formed in good to excellent yields from reduction of aldimines $5a$ and $5c$ with sodium cyanoborohydride in methanol at room temperature. The aldimine structure of compounds $5$ was further proven by the hydrolysis of $5a$ to the known aldehyde $10$.8

The formation of the aldimines and 2-aminoalkylidene-malonates can be explained via a single mechanistic scheme (Scheme 4). Both primary and secondary amines give 1,4-addition to the 2-bromoalkylidenemalonates to afford the adducts $11$. With primary amines, a further ring closure via C-alkylation occurs to the corresponding 2-aminocyclopropane-1,1-dicarboxylates $12$. The latter $\beta$-ACC derivatives are however not stable and undergo ring opening spontaneously to the iminium enolates $13$, which suffer proton transfer to form the stable aldimines $5$. With secondary amines, the addition products $11$ probably undergo further N-alkylation to the aziridinium compounds $8$.

### Table 1 Reaction of 2-Bromoalkylidenemalonates 3 with Two Equivalents of Amine in Diethyl Ether at Reflux Temperature

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Amine</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>Ratio of reaction products (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$3a$</td>
<td>$i$-PrNH$_2$</td>
<td>3</td>
<td>94</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>$i$-BuNH$_2$</td>
<td>12</td>
<td>96</td>
<td>–</td>
</tr>
<tr>
<td>$3a$</td>
<td>(Ph)$_2$CHNH$_2$</td>
<td>5</td>
<td>100</td>
<td>2</td>
</tr>
<tr>
<td>$3b$</td>
<td>$i$-PrNH$_2$</td>
<td>10</td>
<td>95</td>
<td>–</td>
</tr>
<tr>
<td>$3c$</td>
<td>$i$-PrNH$_2$</td>
<td>16</td>
<td>81</td>
<td>–</td>
</tr>
<tr>
<td>$3a$</td>
<td>(CH$_3$)$_2$NH</td>
<td>5</td>
<td>82</td>
<td>–</td>
</tr>
<tr>
<td>$3a$</td>
<td>(CH$_3$)$_3$NH</td>
<td>6</td>
<td>100</td>
<td>9</td>
</tr>
<tr>
<td>$3a$</td>
<td>(O(CH$_2$)$_4$)NH</td>
<td>4</td>
<td>100</td>
<td>13</td>
</tr>
</tbody>
</table>

$^a$ Crude yield of aldimine 5 or allyl amine 4.

$^b$ Based on integration of $^1$H NMR of reaction crude.

$^c$ Parentheses indicate isolated yields.

$^d$ $\gamma$-Lactam 6c was formed from aziridine 8c during purification via chromatography (silica gel).

$^e$ Traces of aldehyde 10 and other unidentified side-products were observed in the reaction crude.

$^f$ Acid–base extraction afforded the analytically pure amines, but the yield dropped due to losses in the aqueous phase.

![Scheme 2](image-url)
which are prone to ring opening to the stable allyl amines 4. It is clear that with the primary amines minor pathways are present, either via compounds 14 or through ring opening of β-ACCs 12, which lead to the formation of aziridine 8c and γ-lactams 6 and 7. With the secondary amines, it is also reasonable that cyclopropanes 12, in equilibrium with the ring-opened compounds 13, are minor intermediates leading to allyl amines 4 via aziridinium enolates 15.

In conclusion, while secondary amines afforded, as already described, 2-aminoalkylidenemalonates upon reaction with 2-bromoalkylidenemalonates, primary amines efficiently yielded 2-(iminoethyl)malonates. The latter compounds are suitably functionalized for further transformations to γ-amino acid derivatives and N-heterocyclic compounds.

Dimethyl [(2E)-2-(N-Isopropylimino)-1,1-dimethylethyl]-malonate (5a)
Bp 76–82 °C/0.8 mmHg.
IR (NaCl): 1757, 1736, 1666 cm⁻¹.
1H NMR (300 MHz, CDCl 3): δ = 1.09 (d, J = 6.33 Hz, 6 H), 1.25 (s, 6 H), 3.28 (sept, J = 6.33 Hz, 1 H), 3.70 (s, 6 H), 3.75 (s, 1 H), 7.65 (s, 1 H).
13C NMR (75 MHz, CDCl 3): δ = 23.8 (4 × CH₃), 40.5, 52.0, 58.6, 60.7, 165.8, 168.8.
MS (ES, +ve mode): m/z (%): 244 (100) [M + H⁺].

Dimethyl [(2E)-2-(N-tert-Butylimino)-1,1-dimethylethyl]-malonate (5b)
IR (NaCl): 1758, 1736, 1666 cm⁻¹.
1H NMR (300 MHz, CDCl 3): δ = 1.10 (s, 9 H), 1.23 (s, 6 H), 3.70...
(s, 6 H), 3.80 (s, 1 H), 7.51 (s, 1 H).

\[^{13}\text{C} \text{NMR} (75 \text{ MHz, CDCl}_3): \delta = 23.8, 29.4, 40.8, 51.9, 56.2, 58.4, 162.1, 169.1.\]

MS (ES, +ve mode): \( m/z (%) = 258 \) (100) [M + H\(^+\)].

Anal. Calcld for \( \text{C}_9\text{H}_8\text{NO}_3 \): C, 60.68; H, 9.01; N, 5.44. Found: C, 60.80; H, 9.12; N, 5.22.

Dimethyl [(2E)-2-(N-[Diphenylmethyl]imino)-1,1-dimethyl-ethyl]malonate (5c)

\( R'_c = 0.71 \) [PE–EtOAc (3:7)].

IR (NaCl): 1753, 1726, 1699 cm\(^{-1}\).

\[^{13}\text{C} \text{NMR} (75 \text{ MHz, CDCl}_3): \delta = 23.8, 41.3, 52.0, 58.4, 77.1, 126.8, 127.5, 128.3, 143.7, 168.7, 168.9.\]

MS (ES, +ve mode): \( m/z \) (%) = 368 (100) [M + H\(^+\)].

Anal. Calcld for \( \text{C}_9\text{H}_8\text{NO}_3 \): C, 71.91; H, 6.86; N, 3.81. Found: C, 71.78; H, 6.98; N, 3.52.

Methyl 1-[Diphenylmethyl]-5,5-dimethyl-2-oxo-2,5-dihydro-I/H-pyrrole-3-carboxylate (6c)

Bp 65–70 \(^\circ\)C/0.4 mmHg.

IR (NaCl): 1735, 1644 cm\(^{-1}\).

\[^{13}\text{C} \text{NMR} (75 \text{ MHz, CDCl}_3): \delta = 14.1, 23.8, 40.4, 59.0, 60.8, 61.0, 166.1, 166.4.\]

MS (ES, +ve mode): \( m/z \) (%) = 270 (100) [M + H\(^+\)].

Anal. Calcld for \( \text{C}_9\text{H}_8\text{NO}_3 \): C, 57.39; H, 7.83; N, 5.10.

Kugelrohr distillation: \( T_{\text{vap}} = 80–95 \) \(^\circ\)C/0.01 mbar.

IR (NaCl): 1754, 1737, 1660 cm\(^{-1}\).

\[^{13}\text{C} \text{NMR} (75 \text{ MHz, CDCl}_3): \delta = 23.8, 41.3, 52.0, 58.4, 77.1, 126.8, 127.5, 128.3, 143.7, 168.7, 168.9.\]

MS (ES, +ve mode): \( m/z \) (%) = 258 (100) [M + H\(^+\)].

Anal. Calcld for \( \text{C}_9\text{H}_8\text{NO}_3 \): C, 61.16; H, 8.29; N, 5.49. Found: C, 60.90; H, 8.41; N, 5.42.

Methyl 1-Isopropyl-4,4-dimethyl-2-oxopyrrolidine-3-carboxylate (9c)

\[^{13}\text{C} \text{NMR} (75 \text{ MHz, CDCl}_3): \delta = 23.2, 23.4, 46.1, 51.9, 52.4, 56.0, 126.3, 154.5, 164.9, 167.0.\]

MS (ES, +ve mode): \( m/z \) (%) = 256 (100) [M + H\(^+\)].

Anal. Calcld for \( \text{C}_9\text{H}_8\text{NO}_3 \): C, 60.5, 61.6, 165.4, 168.3.

Anal. Calcld for \( \text{C}_9\text{H}_8\text{NO}_3 \): C, 63.58; H, 8.89; N, 4.94. Found: C, 63.80; H, 8.78; N, 5.12.

Dimethyl (2-Methyl-2-pyrrolidin-1-ylpylidinedimaleonate (4a)

IR (NaCl): 1735, 1644 cm\(^{-1}\).

\[^{13}\text{C} \text{NMR} (75 \text{ MHz, CDCl}_3): \delta = 1.24\) (s, 6 H), 1.67 (m, 4 H), 2.54 (m, 4 H), 3.76 (s, 3 H), 3.77 (s, 3 H), 6.97 (s, 1 H).\]

MS (ES, +ve mode): \( m/z \) (%) = 368 (100) [M + H\(^+\)].

Anal. Calcld for \( \text{C}_9\text{H}_8\text{NO}_3 \): C, 57.39; H, 7.83; N, 5.10.
Dimethyl (1,1-Dimethyl-2-oxoethyl)malonate (10)

To a mixture of aldimine $5a$ (122 mg, 0.5 mmol) and H$_2$O (1 mL) and CH$_2$Cl$_2$ (1 mL) was added aq HCl (2 N, 0.4 mL). The reaction mixture was stirred at r.t. overnight and extracted with CH$_2$Cl$_2$ (3 x 3 mL). After drying of the organic layer (MgSO$_4$), filtration and evaporation, the aldehyde 10 (91 mg, 90%) was obtained. $^1$H NMR data were in good agreement with reported data.$^8$

$^1$H NMR (300 MHz, CDCl$_3$): $\delta = 1.24$ (s, 6 H), 3.75 (s, 6 H), 3.78 (s, 1 H), 9.62 (s, 1 H).

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References