A New Synthetic Route to α-Methylenecarboxamides Using Dianion of N-Phenyl-2-[ (phenylsulfonyl) methyl] propenamide

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A New Synthetic Route to α-Methylenecarboxamides Using Dianion of N-Phenyl-2-[(phenylsulfonyl)methyl]propenamide

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Regioselective reaction of the dianion of N-phenyl-2-[(phenylsulfonyl)methyl]propenamide with alkyl halides leads to β-substituted carboxamides, which upon Lewis acid mediated cyclization afford α-methylenecarboxamides in good yields.

KEY WORDS: α-Methylenecarboxamides/ (E)-trisubstituted carboxamides/ 3,4-dihydroxy-2-methylenecarboxamides/ 5,6-dihydro-2H-pyran/ 3-methylene-β-lactams/

The α-methylene carbonyl system is a common structural feature of naturally occuring substances possessing cytotoxic, fungitoxic, and growth-inhibitory activity.1) Accordingly, various methods have been developed for the synthesis of α-methylene carbonyl derivatives.2) However, there are relatively few methods available for the direct introduction of α-methylene carbonyl group using a carbanion derived from α-methylene carbonyl system because of the chemical instability of the carbanion.3) Recently we have found that the dianion of N-phenyl-2-[(phenylsulfonyl)methyl]propenamide (1) can be generated at −78°C and serve as a versatile reagent for the preparation of a variety of α,β-unsaturated carbonyl compounds like (E)-trisubstituted carboxamides, 3,4-dihydroxy-2-methylenecarboxamides, 5,6-dihydro-2H-pyran, and 3-methylene-β-lactams.4,6>

We now describe a convenient method for the preparation of α-methylene carbonyl derivatives having fused-ring system by regioselective alkylation and subsequent Lewis acid mediated cyclization procedure. The dilithiation of (1) proceeds readily with 2 equiv. of butyllithium to provide a yellow solution of (2) which can be converted to the β-substituted products (3-7) upon reaction with alkyl halides. Treatment of the adducts (3-6) with AlCl₃ in dichloromethane gives six- or seven-membered exocyclic α-methylene carboxamides (8-11). On the other hand, reaction of (7) with AlCl₃ under similar conditions afforded seven-membered endocyclic product (12). The endo structure was confirmed by conversion of (12) to the known methyl ester (13)⁷ via isomerization of the double bond of the amide, N-tert-butoxycarbonylation, and subsequent methanolation.⁸

In these synthetic sequences, the amide (1) is synthetically equivalent to a 1,1-dipole or a 1,3-dipole (Scheme 3)⁹ and perceived as a useful reagent for an efficient
Synthetic Route to α-Methylenecarboxamides

\[
\begin{align*}
\text{(1)} & \quad \text{CONHPh} \\
& \quad \text{SO}_2\text{Ph} \\
\quad \text{i} \quad \text{CONHPh} \\
\quad \text{SO}_2\text{Ph} \\
\text{(2)} \\
\text{ii} \quad \text{CONHPh} \\
\quad \text{SO}_2\text{Ph} \\
\text{(3)-(7)} \\
\text{iii} \quad \text{CONHPh} \\
\text{(8)-(12)}
\end{align*}
\]

Scheme 1. Reagents and conditions: i, 2 equiv. Bu\text{Li}, −78°C, Tetrahydrofuran-
Hexamethyphosphoric triamide; ii, E1-X, −78 to 0°C; iii, AlCl\text{3},
dichloromethane.

\[
\begin{align*}
\text{CONHPhCOOCH}_3 \\
\text{(12)} \\
\text{(13)}
\end{align*}
\]

Scheme 2. Beagent : i, Bu\text{t}OK ; ii, (Bu\text{t}OCO)\text{2}O ; iii, CH\text{3}ONa

\[
\begin{align*}
\text{(1)} & \equiv \text{CONHPh} \\
& \quad \text{or} \\
& \quad \text{CONHPh}
\end{align*}
\]

Scheme 3.

elaboration of α-methylene carbonyl derivatives that might otherwise prove difficult
to prepare.

**EXPERIMENTAL**

A typical procedure for the preparation of 3. To a solution of the dianion 2
(6.64 mmol) at −78°C under argon was added 1-bromo-3-phenylpropane (1.32 g,
6.64 mmol) in dry THF (3 ml). The reaction mixture was stirred at −78°C for 2
h and warmed to 0°C during 1 h, and quenched with saturated aqueous NH\text{4}Cl
(10 ml). The product was extracted with ethyl acetate (3×50 ml). The combined
Table 1. Alkylation of dianion (2) and cyclization of adduct.

<table>
<thead>
<tr>
<th>Halide (El-X)</th>
<th>Adduct</th>
<th>% Yield</th>
<th>Product</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph(CH₂)₃Br</td>
<td><img src="3" alt="Adduct" /></td>
<td>67%</td>
<td><img src="8" alt="Product" /></td>
<td>63%</td>
</tr>
<tr>
<td>PhO(CH₂)₂Br</td>
<td><img src="4" alt="Adduct" /></td>
<td>46%</td>
<td><img src="9" alt="Product" /></td>
<td>57%</td>
</tr>
<tr>
<td>Ph(CH₂)₄Br</td>
<td><img src="5" alt="Adduct" /></td>
<td>76%</td>
<td><img src="10" alt="Product" /></td>
<td>57%</td>
</tr>
<tr>
<td>Cl</td>
<td><img src="6" alt="Adduct" /></td>
<td>37%</td>
<td><img src="11" alt="Product" /></td>
<td>67%</td>
</tr>
<tr>
<td>Ph(CH₂)₂Br</td>
<td><img src="7" alt="Adduct" /></td>
<td>54%</td>
<td><img src="12" alt="Product" /></td>
<td>63%</td>
</tr>
</tbody>
</table>

a) 3 equiv. AlCl₃, dichloromethane, room temp., 1 h.
b) 5 equiv. AlCl₃, dichloromethane, reflux, 3 h.

extracts were washed with brine, dried over Na₂SO₄, filtered, and evaporated. The crude product was purified by chromatography (silica gel, hexane-ethyl acetate, 3:1) to give 1.87 g of 3 (67% yield): ¹H NMR δ 8.24 (s, 1H), 6.81–7.80 (m, 15H), 6.06 (s, 1H), 5.56 (s, 1H), 4.52 (dd, J=11.0, 4.0 Hz, 1H), 2.32–2.68 (m, 2H), 1.38–2.12 (m, 4H); IR (thin film) 3330, 1608, 1600, 1315, 770, 710 cm⁻¹; exact mass calcd for C₂₅H₂₅NO₃S (M⁺) 419.155, found 419.154.

A typical procedure for the conversion of 3 into 8. To a solution of 3 (0.48 g, 1.15 mmol) in dry CH₂Cl₂ (10 ml) at 0°C under argon was added powdered AlCl₃ (0.46 g, 3.45 mmol). After stirring at 0°C for 5 min and at room temperature for 1 h, the reaction mixture was poured into ice water and extracted with CH₂Cl₂ (3×10 ml). The combined extracts were washed with water, dried over Na₂SO₄, filtered and evaporated. The crude product was purified by chromatography (silica gel, hexane-ethyl acetate, 3:1) to give 0.20 g of 8 (85% yield): mp 134–137°C; ¹H NMR δ 7.40–6.80 (m, 10H), 5.87 (s, 1H), 5.05 (s, 1H), 4.20 (m, 2H), 2.78 (m, 2H), 1.40–2.20 (m, 4H); IR (nujol) 3250, 1650, 1600, 1315, 770, 710 cm⁻¹. Anal Calcd...
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for C_{19}H_{19}NO: C, 82.28; H, 6.90; N, 5.05. Found: C, 81.92; H, 7.07; N, 4.97.

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