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<th>A New Synthetic Route to α-Methylenecarboxamides Using Dianion of N-Phenyl-2-[(phenylsulfonyl) (Commemoration Issue Dedicated to Professor Shinzaburo OKA On the Occasion of His Retirement) methyl] propenamide</th>
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<td>Author(s)</td>
<td>Tanaka, Kazuhiko; Ushio, Hideki; Horiuchi, Hiroshi</td>
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Kyoto University
A New Synthetic Route to α-Methylene carboxamides Using Dianion of N-Phenyl-2-[(phenylsulfonfyl)methyl]propenamide

Kazuhiko Tanaka,* Hideki UsHi, and Hiroshi HORIUCHI

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

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

The α-methylene carbonyl system is a common structural feature of naturally occurring 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-[(phenylsulfonfyl)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-methylene carboxamides, 5,6-dihydro-2H-pyrans, 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) via isomerization of the double bond of the amide, N-tert-butoxycarbonylation, and subsequent methanolysis.8

In these synthetic sequences, the amide (1) is synthetically equivalent to a 1,1-dipole or a 1,3-dipole (Scheme 3)⁶ and perceived as a useful reagent for an efficient
Synthetic Route to α-Methylenecarboxamides

(1) → CONHPh

(2) → CONHPh

(3) → CONHPh

(4) → CONHPh

(5) → CONHPh

(6) → CONHPh

(7) → CONHPh

(8) → CONHPh

Scheme 1. Reagents and conditions: i, 2 equiv. Bu^Li, -78°C, Tetrahydrofuran-Hexamethyolphosphoric triamide; ii, E1-X, -78 to 0°C; iii, AlCl₃, dichloromethane.

(1) → (13)

Scheme 2. Beagent: i, Bu^OK; ii, (Bu^OOCO)₂O; iii, CH₃ONa

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 NH₄Cl (10 ml). The product was extracted with ethyl acetate (3 × 50 ml). The combined

(129)
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(CH$_2$)$_3$Br</td>
<td>[insert structure]</td>
<td>67%</td>
<td>[insert structure]</td>
<td>63%</td>
</tr>
<tr>
<td>PhO(CH$_2$)$_2$Br</td>
<td>[insert structure]</td>
<td>46%</td>
<td>[insert structure]</td>
<td>57%</td>
</tr>
<tr>
<td>Ph(CH$_2$)$_4$Br</td>
<td>[insert structure]</td>
<td>76%</td>
<td>[insert structure]</td>
<td>47%</td>
</tr>
<tr>
<td>Ph(CH$_2$)$_2$Br</td>
<td>[insert structure]</td>
<td>37%</td>
<td>[insert structure]</td>
<td>67%</td>
</tr>
</tbody>
</table>

a) 3 equiv. AlCl$_3$, dichloromethane, room temp., 1 h.

b) 5 equiv. AlCl$_3$, dichloromethane, reflux, 3 h.

extracts were washed with brine, dried over Na$_2$SO$_4$, 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): $^1$H 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 C$_{25}$H$_{25}$NO$_3$S (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 CH$_2$Cl$_2$ (10 ml) at 0°C under argon was added powdered AlCl$_3$ (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 CH$_2$Cl$_2$ (3 × 10 ml). The combined extracts were washed with water, dried over Na$_2$SO$_4$, 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; $^1$H NMR δ 7.40–6.80 (m, 10H), 5.87 (s, 1H), 5.05 (s, 1H), 4.20 (m, 1H), 2.78 (m, 2H), 1.40–2.20 (m, 4H); IR (nujol) 3250, 1650, 1600, 1315, 770, 710 cm$^{-1}$. Anal Calcd
Synthetic Route to $\alpha$-Methylenecarboxamides

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.

ACKNOWLEDGMENT

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REFERENCES