

Note

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-
pyrans/ 3-methylene- β -lactams/

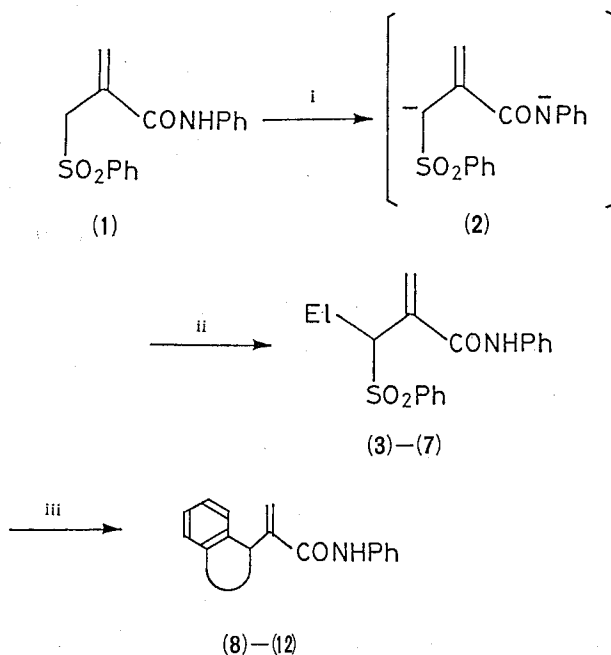
The α -methylene carbonyl system is a common structural feature of naturally occurring substances possessing cytotoxic, fungitoxic, and growth-inhibitory activity.¹⁾ Accordingly, various methods have been developed for the synthesis of α -methylene carbonyl derivatives.²⁾ However, there are relatively 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-[(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-pyrans, and 3-methylene- β -lactams.^{4,5)}

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 AlCl_3 ⁶⁾ in dichloromethane gives six- or seven-membered exocyclic α -methylene carboxamides (**8–11**). On the other hand, reaction of (**7**) with AlCl_3 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 methanolysis.⁸⁾

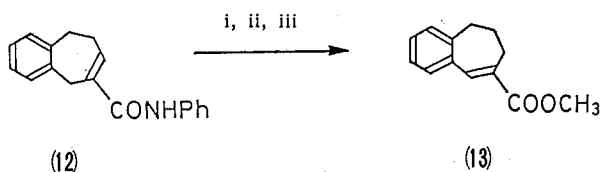
In these synthetic sequences, the amide (**1**) is synthetically equivalent to a 1,1-dipole or a 1,3-dipole (Scheme 3)⁶⁾ and perceived as a useful reagent for an efficient

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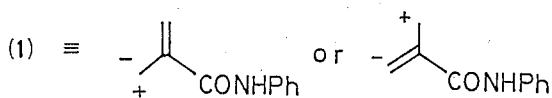
Synthetic Route to α -Methylenecarboxamides



Scheme 1. Reagents and conditions: i, 2 equiv. Bu^nLi , -78°C , Tetrahydrofuran-Hexamethylphosphoric triamide; ii, El-X , -78 to 0°C ; iii, AlCl_3 , dichloromethane.



Scheme 2. Reagent : i, Bu^tOK ; ii, $(\text{Bu}^t\text{OCO})_2\text{O}$; iii, CH_3ONa



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_4Cl (10 ml). The product was extracted with ethyl acetate (3×50 ml). The combined

Table 1. Alkylation of dianion (2) and cyclization of adduct.

Halide (El-X)	Adduct	% Yield	Product	% Yield
$\text{Ph}(\text{CH}_2)_3\text{Br}$		67%		63%
	(3)		(8) ^a	
$\text{PhO}(\text{CH}_2)_2\text{Br}$		46%		57%
	(4)		(9) ^b	
$\text{Ph}(\text{CH}_2)_4\text{Br}$		76%		47%
	(5)		(10) ^a	
		37%		67%
	(6)		(11) ^a	
$\text{Ph}(\text{CH}_2)_2\text{Br}$		54%		63%
	(7)		(12) ^a	

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_2SO_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): ^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 $\text{C}_{25}\text{H}_{25}\text{NO}_3\text{S}$ (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_2Cl_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_2Cl_2 (3×10 ml). The combined extracts were washed with water, dried over Na_2SO_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 $134\text{--}137^\circ\text{C}$; ^1H 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, 760, 700 cm^{-1} . Anal Calcd

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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REFERENCES

- (1) See, for instance, G. Schlewer, J.-L. Stamp, and C. Benezra, *J. Med. Chem.*, 1985, **24**, 94.
- (2) For a recent review see: H.M.R. Hoffmann and J. Rabe, *Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 94.
- (3) P. Beak and D.J. Kempf, *J. Am. Chem. Soc.*, 1980, **102**, 4550; K. Tanaka, Y. Nozaki, N. Tamura, R. Tanikaga, and A. Kaji, *Chem. Lett.*, 1980, 1567; J.J. Fitt and H.W. Gschwend, *J. Org. Chem.*, 1980, **45**, 4257.
- (4) K. Tanaka, H. Yoda, and A. Kaji, *Tetrahedron Lett.*, 1985, **26**, 4147.
- (5) K. Tanaka, H. Yoda, and A. Kaji, *Tetrahedron Lett.*, 1985, **26**, 4751.
- (6) B.M. Trost and M.R. Ghadiri, *J. Am. Chem. Soc.*, 1984, **106**, 7260.
- (7) J. Vebrel and R. Carrie, *Bull. Soc. Chim. Fr.*, 1982, II-116.
- (8) D.L. Flynn, R.E. Zelle, and P.A. Grieco, *J. Org. Chem.*, 1983, **48**, 2424.