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PYRROLIDINE RING FORMATION BY A NEW BASE-PROMOTED 1,3-DIPOLAR CYCLOADDITION OF N-(PHENYLTHIOMETHYL)AMINO ACID ESTERS

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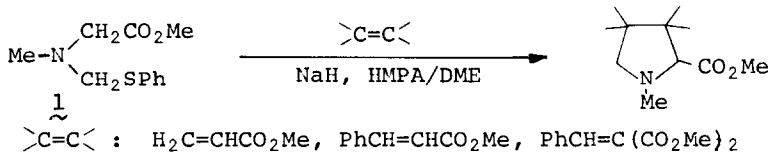
Summary: N-Phenylthiomethyl derivatives of α-amino acid esters are attacked by α,β-unsaturated carboxylates in the presence of sodium hydride, undergoing 1,3-dipolar cycloaddition to give pyrrolidines.

The 1,3-dipolar cycloaddition leading to alicyclic amines has received continuous synthetic interest in recent years in connection with the syntheses of naturally occurring and physiologically active alicyclic amines.[1] Esters of N-(phenylthiomethyl)amino acids, representatively N-(phenylthiomethyl)sarcosine methyl ester (1), have been found to undergo a new base-promoted 1,3-dipolar cycloaddition with olefinic dipolarophiles to give pyrrolidines.



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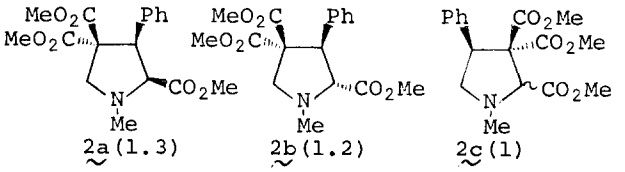
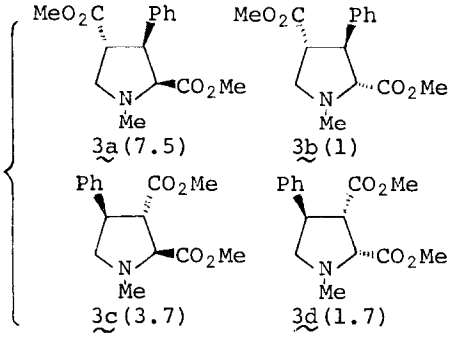
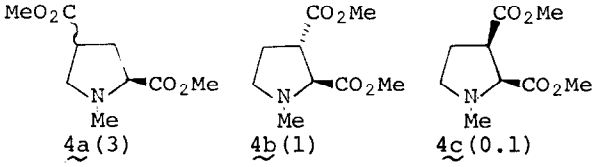
>C=C< : $H_2C{=}CHCO_2Me$, $PhCH{=}CHCO_2Me$, $PhCH{=}C(CO_2Me)_2$

Compound 1[2] was first prepared by the condensation reaction among methyl ester of sarcosine, formaldehyde and thiophenol in methanol. The cycloaddition reaction was carried out with several dipolarophiles under the conditions using sodium hydride in hexamethylphosphoramide (HMPA)-dimethoxyethane (DME). The results are summarized in Table 1 and a typical experiment (entry 1) is described below.

To HMPA-DME (0.9 ml + 10 ml) suspended with sodium hydride (10 mmol) N-(phenylthiomethyl)sarcosine methyl ester (5 mmol) and dimethyl benzylidenemalonate (6 mmol) were added. The mixture was refluxed with stirring for 9 hr.

Table 1 Synthesis of Pyrrolidines

Entry No.	Olefin	Reaction[a] conditions	Product[b]	Total yield(%)
1	$PhCH=C(CO_2Me)_2$	reflux 9 hr	 2a(1.3) 2b(1.2) 2c(1)	71
2	$PhCH=CHCO_2Me$	r.t. 1.5 hr	 3a(7.5) 3b(1) 3c(3.7) 3d(1.7)	84
3	$CH_2=CHCO_2Me$	r.t. 24 hr	 4a(3) 4b(1) 4c(0.1)	47

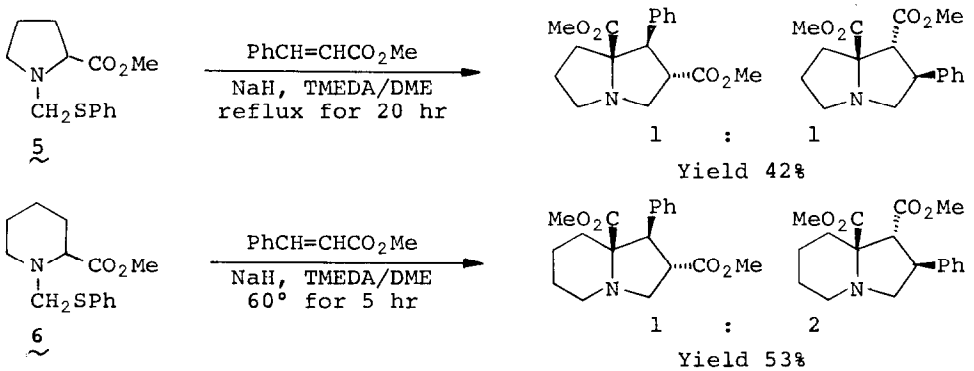
a) Base : NaH, Solvent : HMPA/DME. b) Ratio of the products, which was estimated on the basis of GLC and ^{1}H-NMR spectrum, is described in parentheses.

An insoluble material was filtered off and the filtrate was concentrated under reduced pressure. The resulting residue was triturated with benzene. The benzene solution was washed with 30% aq. K_2CO_3 and dried over $MgSO_4$. After removal of benzene, three regioisomers, 2a, 2b, and 2c, were isolated by silica gel column chromatography using diisopropylether-hexane (1 : 2) as an eluent and their structures were determined on the basis of the following spectral data. 2a: mp 108-110°, IR(KBr); 1746 cm^{-1}(CO), ^{1}H-NMR δ ($CDCl_3$); 2.42(3H, s, NCH_3), 2.62 (1H, d, J=10.7 Hz, 5-CH_A), 3.10(3H, s, OCH_3), 3.29(3H, s, OCH_3), 3.63(1H, d, J= 7.2 Hz, 2-CH), 3.79(3H, s, OCH_3), 4.29(1H, d, J=10.7 Hz, 5-CH_B), 4.43(1H, d, J= 7.2 Hz, 3-CH), 7.12-7.41(5H, m, C_6H_5), ^{13}C-NMR δ ($CDCl_3$); 41.4(q), 51.1(q),51.9 (q), 53.0(q), 54.1(d), 61.2(t), 63.7(s), 72.7(d), 127.4(d), 127.8(d), 129.7(d),

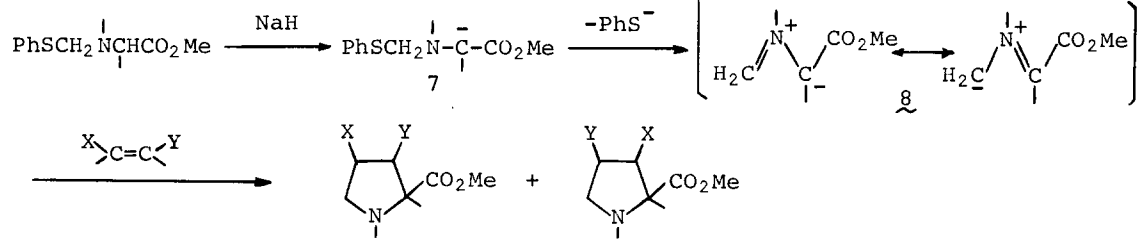
137.3(s), 168.4(s), 170.2(s), 171.7(s). 2b: oil, IR(neat); 1746 cm^{-1}(CO), ^{1}H-NMR δ ($CDCl_3$); 2.49(3H, s, NCH_3), 3.10(3H, s, OCH_3), 3.39(1H, d, J=12.9 Hz, 5-CH_A), 3.50(1H, d, J=8.6 Hz, 2-CH), 3.66(3H, s, OCH_3), 3.70(1H, d, J=12.9 Hz, 5-CH_B), 3.77(3H, s, OCH_3), 4.54(1H, d, J=8.6 Hz, 3-CH), 7.27(5H, s, C_6H_5), ^{13}C-NMR δ ($CDCl_3$); 40.6(q), 52.2(q), 53.3(q, 2C), 54.3(d), 62.3(t), 64.9(s), 73.6(d), 127.8(d), 128.4(d), 129.3(d), 137.8(s), 169.0(s), 171.1(s), 172.1(s). 2c: oil, IR(neat); 1732 cm^{-1}(CO), ^{1}H-NMR δ ($CDCl_3$); 2.50(3H, s, NCH_3), 2.93(1H, dd, J=9.1, 10.5 Hz, 5-CH_A), 3.13(3H, s, OCH_3), 3.39(1H, dd, J=7.1, 9.1 Hz, 4-CH), 3.68(3H, s, OCH_3), 3.74(3H, s, OCH_3), 4.14(1H, s, 2-CH), 4.52(1H, dd, J=7.1, 10.5 Hz, 5-CH_B), 7.28(5H, s, C_6H_5), ^{13}C-NMR δ ($CDCl_3$); 40.3(q), 49.9(d), 52.4(q), 53.0(q, 2C), 60.1(t), 69.0(s), 74.0(d), 127.7(d), 128.3(d), 129.3(d), 137.6(s), 169.2(s), 169.4(s), 171.4(s).

Stereochemistry of the three carbomethoxy groups of 2a and 2b was established on the basis of the chemical shifts of the ester methyls in their ^{1}H-NMR spectra. The signal of the ester methyl oriented cis to phenyl group on five membered ring has been known to appear in a higher field due to shielding effect of phenyl group.[1b,3] The structures of the products obtained in entries 2 and 3 were well determined by the analogy of that for 2a-c.

The reaction was extended to the use of N-phenylthiomethyl derivatives of proline (5)[4] and pipecolinic acid esters (6),[5] where bicyclic pyrrolizidine and indolizidine derivatives were obtained, respectively. The reaction proceeded similarly to that with 1, but tetramethylethylenediamine (TMEDA) was preferable to HMPA in these cases.



The mechanistic rationale for the present reaction can be illustrated as follows. The 1,3-dipole (8) formed from the carbanion (7) with the release of phenylthiolate anion may be attacted by olefinic dipolarophile to form pyrrolidine ring. The two probable extremes in the resonance hybrid of 8 may give the two regioisomers.



Further basic and applied investigation of this new 1,3-dipolar cycloaddition which is convenient for synthesis of functionalized alicyclic amines is under way.

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2) bp 110-111°(0.1 mmHg). IR(neat); 1772 cm^{-1}(CO), ^{1}H-NMR δ ($CDCl_3$); 2.46(3H, s, NCH_3) 3.37(2H, s, NCH_2C), 3.62(3H, s, OCH_3), 4.56(2H, s, NCH_2S), 7.14-7.61 (5H, m, C_6H_5), ^{13}C-NMR δ ($CDCl_3$); 41.3(q), 51.5(q), 55.5(t), 66.3(t), 126.6 (d), 129.0(d), 131.8(d), 137.2(s), 170.6(s).

3) M. Joucla, D. Dree, and J. Hamelin, Tetrahedron, 29, 2315(1973).

4) bp 119-120°(0.05 mmHg). IR(neat); 1762 cm^{-1}(CO), ^{1}H-NMR δ ($CDCl_3$); 1.63-2.08 (4H, m, CH_2CH_2), 2.73-3.02(2H, m, NCH_2C), 3.48-3.78(1H, m, NCH), 3.57(3H, s, OCH_3), 4.66(2H, s, NCH_2S), 7.03-7.48(5H, m, C_6H_5), ^{13}C-NMR δ ($CDCl_3$); 23.5(t), 29.7(t), 51.3(t), 51.6(q), 61.1(d), 61.1(t), 126.3(d), 128.8(d), 131.2(d), 137.5(s), 173.5(s).

5) bp 142-143°(0.05 mmHg). IR(neat); 1742 cm^{-1}(CO), ^{1}H-NMR δ ($CDCl_3$); 1.20-1.87 (6H, m, $CH_2CH_2CH_2$), 2.53-2.82(2H, m, NCH_2C), 3.24-3.50(1H, m, NCH), 3.39(3H, s, OCH_3), 4.30(1H, d, J=13.8 Hz, NCH_AS), 4.60(1H, d, J=13.8 Hz, NCH_BS), 6.96-7.38(5H, m, C_6H_5), ^{13}C-NMR δ ($CDCl_3$); 22.8(t), 25.1(t), 29.6(t), 50.3(t), 51.4(q), 61.3(d), 65.1(t), 126.5(d), 128.8(d), 132.0(d), 137.5(s), 172.9(s).

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