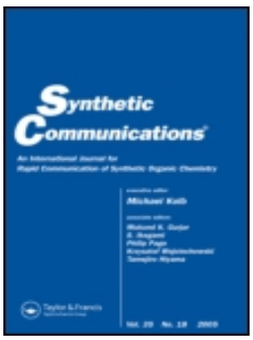

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THE CONVENIENT SYNTHESIS OF 3-ALKYLOXYCARBONYLPYRROLIDINE DERIVATIVES

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ABSTRACT

A series of 3-alkyloxycarbonylpyrrolidine derivatives are readily achieved via 1,3-dipolar cycloaddition of α,β-unsaturated esters with nonstabilized azomethine ylides in the presence of samarium diiodide.

Owing to ubiquitous distribution of pyrrolidine moieties in several biologically important alkaloids (such as epibatidine,[1] atropine[2] etc.), their synthesis has always attracted the attention of synthetic organic chemists. Among the variety strategies for the construction of pyrrolidine units, one of the most important methods is 1,3-dipolar cycloaddition of nonstabilized azomethine ylides with dipolarophiles.[3]

In the 1,3-dipolar cycloaddition, the desilylation approach is most frequently applied to generate the nonstabilized azomethine ylides. Among a variety of desilylation reagents, fluoride reagent is often been used. However, most of all fluoride reagents are highly hygroscopic and

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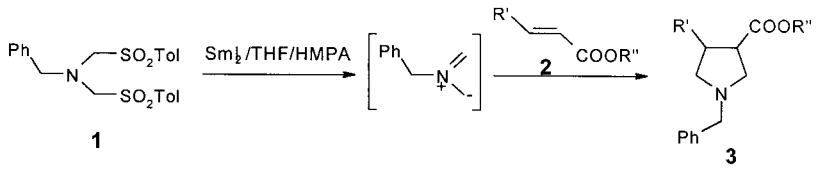
not much soluble in organic solvents. Moreover, many nonstabilized azomethine ylides generated by the desilylation procedure only react with activated dipolarphiles[3l,m] and the preparation of these 1,3-dipole precursors is commonly not easy.[3n]

Recently, Katritzky A. R. et al.[4] found that *N*,*N*-*bis*(sulfonylmethyl)-alkylamines[5] could be used as precursors of nonstabilized azomethine ylides to synthesize some substituted pyrrolidines via 1,3-dipolar cycloaddition with some activated or unactivated dipolarophiles in the presence of SmI_2 in THF-HMPA. In this method, the 1,3-dipoles precursors could be easily prepared than that of desilylation procedure. The reaction condition is mild and easily controllable. However, this method was unsuitable for electron deficient dipolarophiles, such as methyl acrylate.

In the course of our research for the synthesis of epibatidine derivatives, we need some pyrrolidines possessing alkyloxy carbonyl group as intermediates. Analyzing the operation of Katritzky's method and the potent reactivity of samarium(II) reagent with α,β-unsaturated esters,[6] we considered that the Katritzky's method should be suitable for electron deficient dipolarophiles, as long as the reaction of samarium(II) reagent with α,β-unsaturated esters was avoided.



Scheme.

Table. Synthesis of Substituted Pyrrolidines by 1,3-Dipolar Cycloaddition

Entry	Esters	R′	R″	Time (h)	Product	Yield (%)*
1	**2a**	Ph	Me	6	**3a**	55(78)[3f]
2	**2b**	4-Cl-C_6H_4	Me	12	**3b**	63
3	**2c**	2-Cl-C_6H_4	Me	12	**3c**	57
4	**2d**	2,4-Cl-C_6H_3	Me	12	**3d**	69
5	**2e**	2-MeO-C_6H_4	Me	4	**3e**	30[7]
6	**2f**	4-MeO-C_6H_4	Me	4	**3f**	22[7]
7	**2g**	H	Et	4	**3g**	37(58)[3f]
8	**2h**	4-NO_2-C_6H_4	Me	0.2–12		no

*Isolated yields. Mole ratios (SmI_2 : 2 : 1) is 5 : 1.1 : 1.

Based on the above conception, we altered Katritzky's operation and reaction conditions. The result showed that when solution of SmI_2 in THF and α,β-unsaturated ester (**2**) were added dropwise separately into the solution of *N*,*N*-*bis*(sulfonylmethyl)benzylamine in THF at same time at −30°C and the mole ratios (SmI_2 : 2 : 1) was 5 : 1.1 : 1, the corresponding pyrrolidine (**3**) was obtained smoothly.

The different α,β-unsaturated esters (**2**) were chosen to react with *N*,*N*-*bis*(sulfonylmethyl)benzylamines (**1**) under our reaction conditions (see table). It can be found from table that this improved method is suitable for most of α,β-unsaturated esters. However, the electron withdrawing group bearing on the benzene ring of cinnamate is not favorable to this reaction (Entry 8).

In conclusion, our improved method is very useful for the synthesis of 3-alkyloxycarbonylpyrrolidine derivatives. The application of this method in synthesis of alkaloids containing pyrrolidine unit is in progress.

EXPERIMENTAL

^{1}H NMR and ^{13}C NMR spectra were recorded on a VXR 300 spectrometer (300 MHz) with TMS as internal standard in $CDCl_3$, acetone-d_6 or DMSO-d_6. *J* values are given in hertz. Elemental analyses were performed on PE-2400 instrument. High-resolution MS were recorded on Bruker APEX II. Tetrahydrofuran was freshly distilled from sodium-benzophenone and HMPA was distilled from calcium hydride under nitrogen atmosphere. *N*,*N*-*bis*(sulfonylmethyl)benzylamine was prepared according to literature.[5]

General experimental procedure: A solution of **2** (1.07 mmol) in 2 ml THF and solution of SmI_2/THF, which was freshly prepared from samarium (0.78 g, 5.20 mmol) and iodine (1.50 g, 5.90 mmol) in THF (20 ml) under nitrogen, were added dropwise separately into the solution of compound **1** (0.44 g, 1.00 mmol) in THF (5 ml) and HMPA (1 ml) at −30°C over a period of 15 min. The resulting mixture was stirred for additional 2 h under same condition and the deep purple color was gradually disappeared. The mixture was allowed to stir at room temperature for further 10 h and the reaction was completed (monitored by TLC, petroleum ether : acetone 9 : 1). The reaction mixture was quenched by adding H_2O (5 ml) and extracted with ethyl acetate (3 × 10 ml) and dried (Na_2SO_4). After evaporation, the pure oil products could be obtained through silica gel column chromatography using petroleum ether : acetone mixture (30 : 1) as elution.

1-Benzyl-3-methyloxycarbonyl-4-phenylpyrrolidine (3a) Thick oil, ^{1}H NMR (acetone-d_6) δ ppm 2.66–2.71 (1H, dd, $J = 6.3$ Hz, 9.3 Hz), 2.87 (2H, s), 2.94–3.06 (2H, m), 3.08–3.12 (1H, dd, $J = 6.3$ Hz, 8.4 Hz), 3.60

(3H, s), 3.63–3.72 (2H, m), 7.16–7.39 (10H, m). Anal. calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.32; H, 7.15; N, 4.79.

1-Benzyl-3-methyloxycarbonyl-4-(4-chlorophenyl)pyrrolidine (3b) Oil, ^{1}H NMR ($CDCl_3$) δ ppm 2.78–2.84 (2H, m), 2.96–3.01 (1H, t, $J = 8.7$ Hz), 3.07–3.20 (2H, m), 3.66 (3H, s), 3.68–3.74 (2H, m), 4.12–4.20 (1H, m), 7.10–7.15 (1H, dd, $J = 6.0$ Hz, 7.5 Hz), 7.24–7.37 (6H, m), 7.51–7.54 (1H, dd, $J = 1.5$ Hz, 7.8 Hz), HRMS (FAB, MH^+), Calcd for $C_{19}H_{20}ClNO_2$ 329.1255; Found: 329.1253.

1-Benzyl-3-methyloxycarbonyl-4-(2-chlorophenyl)pyrrolidine (3c) Oil, ^{1}H NMR (DMSO-d_6) δ ppm 2.50–2.55 (1H, m), 2.81–2.86 (1H, dd, $J = 6.6$ Hz, 9.0 Hz), 2.91–2.96 (2H, t, $J = 8.7$ Hz), 3.04–3.12 (1H, dd, $J = 6.6$ Hz, 15.0 Hz), 3.50–3.68 (7H, m), 7.22–7.39 (9H, m); ^{13}C NMR (300 MHz, DMSO-d_6), δ ppm 45.94, 50.25, 51.85, 56.45, 58.91, 61.41, 126.95, 128.25, 128.37, 128.49, 129.28, 131.04, 138.70, 142.71, 173.87. HRMS (FAB, MH^+), Calcd for $C_{19}H_{20}ClNO_2$ 329.1255; Found: 329.1257.

1-Benzyl-3-methyloxycarbonyl-4-(2,4-dichlorophenyl)pyrrolidine (3d) Oil, ^{1}H NMR ($CDCl_3$) δ ppm 2.71–2.80 (2H, m), 2.88–2.94 (1H, t, $J = 8.7$ Hz), 2.97–3.05 (1H, q, $J = 7.2$ Hz), 3.09–3.15 (1H, t, $J = 8.7$ Hz), 3.55–3.60 (3H, m), 3.66 (3H, s), 7.14–7.17 (1H, dd, $J = 2.1$ Hz, 8.1 Hz), 7.24–7.35 (6H, m), 7.43–7.44 (1H, d, $J = 2.1$ Hz), HRMS (FAB, MH^+), Calcd for $C_{19}H_{19}Cl_2NO_2$ 363.0866; Found: 363.0870.

1-Benzyl-3-methyloxycarbonyl-4-(2-methyloxyphenyl)pyrrolidine (3e) Oil, ^{1}H NMR ($CDCl_3$) δ ppm 2.58–2.63 (2H, m), 2.73–2.79 (2H, m), 2.87–2.90 (1H, m), 3.44–3.50 (1H, m), 3.64 (2H, s), 3.67 (3H, s), 3.75 (3H, s), 6.85–6.89 (1H, dd, $J = 2.4$ Hz, 7.8 Hz), 6.95–6.97 (1H, m), 7.17–7.35 (7H, m). Anal. calcd. for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.77; H, 7.14; N, 4.39.

1-Benzyl-3-methyloxycarbonyl-4-(4-methyloxyphenyl)pyrrolidine (3f) Oil, ^{1}H NMR ($CDCl_3$) δ ppm 2.57–2.63 (2H, m), 2.74–2.78 (2H, m), 2.90–2.93 (1H, m), 3.48–3.52 (1H, m), 3.62 (2H, s), 3.66 (3H, s), 3.77 (3H, s), 6.80–6.85 (2H, dd, $J = 2.1$ Hz, 7.2 Hz), 6.93–6.99 (2H, dd, $J = 2.4$ Hz, 7.2 Hz), 7.20–7.39 (5H, m). Anal. calcd. for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.72; H, 7.09; N, 4.32.

1-Benzyl-3-ethyloxycarbonylpyrrolidine (3g) Oil, ^{1}H NMR (acetone-d_6) δ ppm 1.17–1.22 (3H, t, $J = 7.2$ Hz), 1.61–1.63 (2H, m), 2.29 (2H, m), 2.78–2.84 (3H, m), 3.66 (2H, s), 4.03–4.10 (2H, q, $J = 7.2$ Hz), 7.15–7.32 (5H, m).

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