

Improved Titanium Tetrachloride Procedure for Enamine Synthesis. II.* Scope of the Reaction

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The scope of enamine formation by a procedure where the carbonyl compound is added to a preformed titanium tetrachloride-amine complex was investigated with a series of different types of carbonyl compounds and two secondary amines (morpholine and pyrrolidine). The carbonyl compounds include aldehydes, cyclic ketones and some substituted aryl alkyl ketones.

Yields of isolated products were in the range 67–100 % with the exception of the pyrrolidine enamine from camphor which gave 53 % of the isolated product.

Recently we reported an improved titanium tetrachloride procedure for enamine formation where the ketone was added to a preformed complex between amine and titanium tetrachloride.¹ The method permits synthesis of enamines from sterically congested ketones. Optimum conditions for enamine formation were reported for acyclic ketones with different steric hindrance reacting with three different amines. In the present paper we report a study on the scope of the reaction applied to different types of carbonyl compounds *viz.* aldehydes, cyclic ketones and some substituted aryl alkyl ketones. Two different secondary amines (morpholine, pyrrolidine) were studied.

RESULTS

Eight different carbonyl compounds were selected to evaluate the scope of the reaction. The model compounds were chosen to allow a






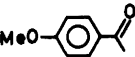
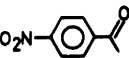

variation in steric and electronic effects that might influence the reaction. The results are summarized in Tables 1 and 2. Unless otherwise stated the yields given refer to isolated yields of purified products. The reactions were monitored by GLC and the time for complete conversion of starting material was recorded. These reaction times are given in Tables 1 and 2.

DISCUSSION

Several methods for enamine synthesis have been described over the years.² The most common method is condensation of amines with carbonyl compounds, where different methods for removal of water have been used, *e.g.* azeotropic distillation with benzene or toluene as solvent or the use of drying agents such as potassium carbonate or molecular sieves. The use of titanium tetrachloride for removal of water was introduced in 1967 by White and Weingarten,³ and opened up a route for enamine formation from acyclic ketones such as methyl ketones, which previously had been difficult to prepare. We have recently described a modified titanium tetrachloride procedure for acyclic ketones.¹ Tables 1 and 2 show that this procedure can be applied to a variety of carbonyl compounds, generally in excellent yields. Tables 1 and 2 also show that a sterically hindered carbonyl compound like camphor requires a larger amount of titanium tetrachloride-amine complex and prolonged reaction time compared to less hindered carbonyl compounds (see also Ref. 1). However, even in these cases the

* Part 1, see Ref. 1.

Table 1. Conditions for morpholine enamine synthesis. ^a Yields of isolated products.

Substrate	Yield %	TiCl ₄ eq.	Amine eq.	Temp. °C	Reaction time
	86	0.9	6.0	70	15 min
	93	0.9	6.0	70	15 min
	86	0.9	6.0	70	5 min
	80	1.3	9.2	70	44 h
	88	0.7	4.6	70	10 min
	77	0.7	4.6	70	30 min
	96	0.9	6.0	70	3 min
	88	1.0	6.9	70	1 h

reaction times are conveniently short compared with other methods. A direct comparison is possible with the original titanium tetrachloride procedure with isobutyrophenone which by our procedure afforded 87 % isolated yield after 15 min compared to 62 % yield after several hours by the White and Weingarten procedure.³ To compare with the methods employing azeotropic removal of water, some examples can be taken from *Org. Synth.* Cyclohexanone pyrrolidine enamine gave by the present procedure 89 % isolated yield (instantaneous reaction) compared to 98 % yield after 4–5 h in refluxing benzene.⁴ 2-Methylpropanal pyrrolidine enamine gave 67 % yield (GLC yield >90 %) after 3 min compared to 94–95 % yield after 3.5 h of reflux in excess aldehyde.⁵ Acetophenone morpholine enamine gave 88 % isolated yield after 10 min by our method compared to 57–64 % yield after






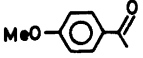
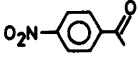

180 h in refluxing benzene.⁶ Another advantage of our method is that benzene, in most cases, can be avoided (see note under Experimental).

Conclusion. The modified titanium tetrachloride procedure for enamine synthesis described in this paper is of general scope and can be applied to aldehydes, cyclic and acyclic aliphatic ketones as well as aryl alkyl ketones. The procedure is the most rapid synthetic method for enamines hitherto described. With regard to the excellent yields obtained it is likely to be a preferred method for enamine synthesis.

Physical properties of the enamines. The ¹H NMR of known enamines are all in accordance with published spectra. Spectra of new enamines and/or previously described enamines for which spectroscopic data have not been given in the literature are given below.

Morpholine enamines from, 2-Methylpropanal,

Table 2. Conditions for pyrrolidine enamine synthesis. ^a Unless otherwise stated, yields of isolated products. ^b GLC (internal standard) showed yields 90%. ^c r.t.=room temperature. ^d Instantaneous reaction. ^e Decomposes on distillation. Yields calculated on crude product after evaporation of solvent and unreacted amine.

Substrate	Yield ^a %	TiCl ₄ eq.	Amine eq.	Temp. °C	Reaction time
	67 ^b	0.9	6.0	70	3 min
	71	0.9	6.0	0	15 min
	89	0.9	6.0	r.t. ^e	- ^d
	53	1.33	8.5	70	9 h
	91	0.7	4.5	r.t. ^e	2 min
	91 ^e	0.7	4.5	70	3 min
	100 ^e	0.9	6.1	r.t. ^e	5 min
	87	0.7	9.2	70	15 min

b.p. 52–53 °C/10 mmHg (lit.⁷ 89–93 °C/20 mmHg).

3-Methylbutanal, b.p. 118–120 °C/27 mmHg, ¹H NMR (250 MHz, CDCl₃): δ 0.91 (6H, d, *J* 6.6 Hz, *Z*-isomer), 0.98 (6H, d, *J* 6.7 Hz, *E*-isomer), 2.23 (1H, m), 2.73–2.89 (4H, m), 3.66–3.70 (4H, m), 4.43 (1H, dd, *J* 14.0 and 6.8 Hz), 5.78 (1H, d, *J* 14.0 Hz). The *E/Z* ratio=72/28.

Cyclohexanone, b.p. 112–113 °C/13 mmHg (lit.⁸ 118–120 °C/20 mmHg).

Camphor, b.p. 72–73 °C/0.01 mmHg (lit.⁹ 140 °C/0.3 mmHg).

Acetophenone, b.p. 96–97 °C/1 mmHg (lit.⁶ 85–90 °C/0.03 mmHg).

p-Methoxyacetophenone, b.p. 128–129 °C/0.5 mmHg, ¹H NMR (60 MHz, CDCl₃): δ 2.75–2.93 (4H, m), 3.70–3.86 (4H, m), 3.82 (3H, s), 4.18

(1H, s), 4.32 (1H, s), 6.82–7.05 (2H, m), 7.37–7.55 (2H, m).

p-Nitroacetophenone, m.p. 111.5–112.2 °C (acetone–hexane), ¹H NMR (250 MHz, CDCl₃): δ 2.86–2.84 (4H, m), 3.77–3.80 (4H, m), 4.38 (1H, s), 4.49 (1H, s), 7.62–7.65 (2H, m), 8.10–8.23 (2H, m), (lit.¹⁰ m.p. 115 °C).

Isobutyrophenone, b.p. 98–100 °C/0.4 mmHg (lit.¹¹ 103–106 °C/1 mmHg).

Pyrrolidine enamines from, 2-Methylpropanal, b.p. 55–56 °C/17 mmHg (lit.⁵ 92–106 °C/115–118 mmHg).

3-Methylbutanal, b.p. 80–83 °C/20 mmHg, ¹H NMR (250 MHz, CDCl₃): δ 0.90 (6H, d, *J* 6.5 Hz, *Z*-isomer), 0.98 (6H, d, *J* 6.6 Hz, *E*-isomer), 1.80–1.85 (4H, m), 2.25 (1H, spt), 2.92–2.97 (4H, m), 4.12 (1H, dd, *J* 13.8 and 6.7 Hz), 6.14

(1H, d, *J* 13.8 Hz). The *E/Z* ratio=97/3.

Cyclohexanone, b.p. 100–100.5 °C/9 mmHg (lit.⁴ 105–106 °C/13 mmHg).

Camphor, b.p. 75–76 °C/0.01 mmHg (lit.¹² 80–82 °C/0.5 mmHg).

Acetophenone, b.p. 72–74 °C/0.005 mmHg (lit.¹³ 82–90 °C/0.001 mmHg).

p-Methoxyacetophenone, b.p. 106–108 °C/0.005 mmHg (decomposes on distillation), ¹H NMR (60 MHz, CDCl₃): δ 1.72–1.97 (4H, m), 2.88–3.13 (4H, m), 3.83 (3H, s), 3.87 (1H, s), 3.93 (1H, s), 6.80–7.03 (2H, m), 7.28–7.53 (2H, m).

p-Nitroacetophenone, Orange-yellow oil, decomposes on distillation, ¹H NMR (60 MHz, CDCl₃): δ 1.60–2.03 (4H, m), 2.87–3.13 (4H, m), 4.05 (2H, s), 7.37–7.73 (2H, m), 8.10–8.37 (2H, m).

Isobutyrophenone, b.p. 91–92 °C/0.05 mmHg (lit.³ 86 °C/1 mmHg).

EXPERIMENTAL

GLC analyses. PYE M 64 Gas Chromatograph with FID were used with 5 % PEG 20M+0.5 % KOH (1.5m, 4mm ID) and 6 % QF 1 (2.1m, 2mm ID) on Chromosorb W AW DMCS (100–120 mesh) glass columns.

¹H NMR. Spectra were recorded on a Bruker WM-250 or a JEOL C-60HL. Chemical shifts were measured at 26 °C using TMS as internal reference.

Chemicals. Carbonyl compounds and amines were commercial *puriss.* or *p.a.* products, titanium tetrachloride was of technical grade and was used without purification. Isobutyrophenone was prepared by Friedel-Crafts acylation of benzene.¹⁴

Solvent. Hexane (b.p. 70 °C) of technical grade was dried over sodium wire prior to use.

General procedure for enamine synthesis. A 250 ml three-necked flask equipped with a dropping funnel, reflux condenser and a stirrer (Hershberg) was purged with dry nitrogen prior to use and protected from moisture. The reaction flask was charged with the amount of amine given in Tables 1 and 2 and 100 ml of hexane. The given amount of titanium tetrachloride was dissolved in about 40 ml of hexane and added dropwise to the cold (0 °C) amine solution. After the addition was complete 0.1 mol of the carbonyl compound was added in one portion (see Notes, a). The reaction was allowed to proceed at the tempera-

ture and for the time according to Tables 1 and 2. After cooling, the reaction mixture was filtered through a sintered glass filter (pore size 3) and the solvent was removed under reduced pressure. If the residue was not clear the crude enamine was filtered a second time using a sintered glass filter of pore size 4. (The turbidity usually originates from TiO₂ which might pass the less tight filter. By using the filter of pore size 4 in the first filtration the time of filtration becomes inconveniently long). The crude product was fractionated on a 20 cm Vigreux column under reduced pressure (Notes, b and c).

Notes. ^a Camphor was dissolved in hexane. *p*-Methoxyacetophenone and *p*-nitroacetophenone are only slightly soluble in hexane and were dissolved in benzene prior to addition to the titanium tetrachloride-amine complex.

^b Two enamines could not be distilled without decomposition. These crude products were freed from solvent and unreacted amine by prolonged evaporation at 0.5 mmHg (Tables 1 and 2). The purity of products (¹H NMR, GLC) was >95 %.

^c The pyrrolidine enamines are sensitive to oxygen and moisture and must be handled under nitrogen.

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