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A New Synthesis of Enaminoketones

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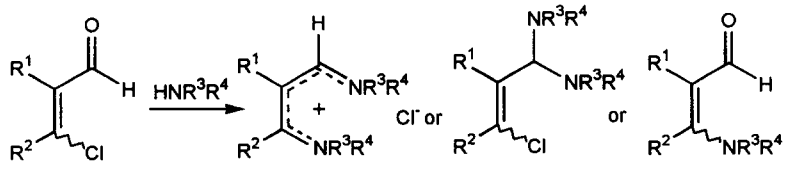
Abstract :A new and efficient synthesis of enaminoketones is described. E,Z β-chloroacroleine derivatives react with secondary amines to produce enaminoketones. The reaction was essentially studied with β-trifluoromethylacroleines. Copyright © 1996 Elsevier Science Ltd

In the context of our going interest in the synthetic potential of trifluoromethyl compounds, we set out to study the synthesis of trifluoromethyl-enaminoketones[1], using these compounds as key intermediates[2]. Generally, condensation of ketone with dimethylformamide dimethylacetal gives N,N-dimethyl-enaminoketone. An unusual amine exchange reaction provides the amino desirable compound[3,4,5,6,7,8].

We want to describe here another synthesis of enaminoketones which avoids the amino exchange step and uses β-chloroacroleines. Indeed, it has been reported (scheme 1) that β-chloroacroleines **1** react with secondary amines to form iminohydrochlorides[9,10] or aminals or enaminoaldehydes[11], but the enaminoketones formation was never reported by this way.

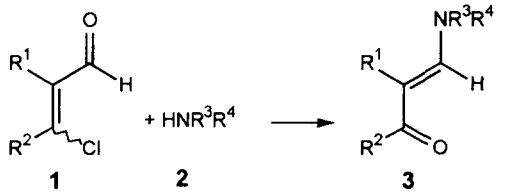


1

Scheme 1

Results

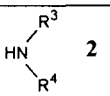
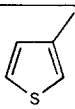
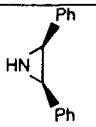
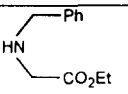
The reaction of β-chloroacroleine **1** (scheme 2) and secondary amine **2** led to enaminoketone **3** (table 1). Only one diastereoisomer was formed ; its configuration was proved by homo or hetero NOE experiments. Chloroacroleines **1** are easily obtained by a Vilsmeier reaction.



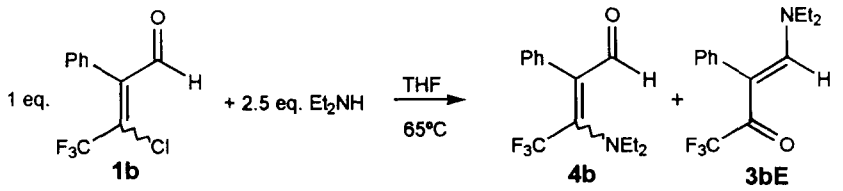
1 **2** **3**

Scheme 2

Table 1 : Enaminoketones 3

	R^1	R^2	 **2**	**3** yield %
1a	C_6H_5	CH_3	$HNEt_2$	**3aE** 45
1b	C_6H_5	CF_3	$HNEt_2$	**3bE** 70
1c	$pClC_6H_4$	CF_3	$HNEt_2$	**3cE** 51
1d		CF_3	$HNEt_2$	**3dE** 44
1b	C_6H_5	CF_3		**3eE** 69
1b	C_6H_5	CF_3		**3fE** 84
1g	CO_2Et	CF_3	$HN(iPr)_2$	**3gZ** 57

To try to understand the formation of **3**, we studied the reaction of **1b** (1 eq.) with diethylamine (2.5 eq.) in THF at 67°C with different reaction time (scheme 3, table 2).



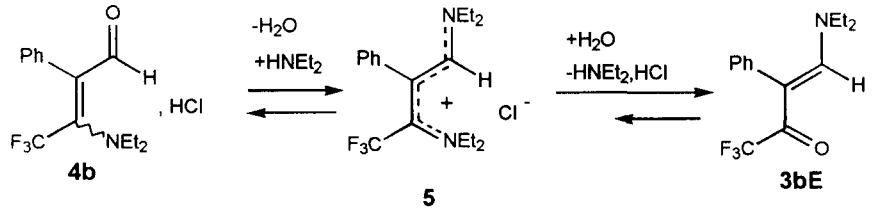
Scheme 3

Table 2 : Formation of 3bE from 4b

Entry	Time (h)	1b %	4b %	3bE %	Identified* Compounds %
1	3.5	23	42	35	89
2	14		33	67	93
3	62		12	88	89

* identified compounds (**1b**+**4b**+**3b**)

After 3.5 h (entry 1), the enaminoaldehyde **4b** was the major compound. But the ratio between **4b** and **3bE** decreased (entries 2 and 3) during the reaction. It is clear that the first reaction is a Michael substitution to give **4b**. A second molecule of amine must react on the aldehyde function to form the salt **5** and a molecule of water (scheme 4). The next step must be the addition of the water to the salt to form a tetrahedral intermediate which gives **3bE**.



Scheme 4

Typical procedures -

3a. To a stirred solution of **1a** (1 mmol) in THF (5 mL), diethylamine (2.5 mmol) was added. The mixture was stirred and heated at 67°C for 69 h. The reaction mixture was cooled, precipitate (Et_2NH,HCl) filtred off, solvent evaporated and crude product separated on silica gel by flash chromatography (ethyl ether, petroleum ether).

3b,c,d. 1b,c,d (1.5 mmol) was added to a solution of diethylamine (1.5 mmol) and Et_3N (2.5 mmol) in ether (9mL) and stirring was continued during 90 h. An additional portion of Et_2NH (1.5 mmol) was added and the mixture was stirred for 24 h. The precipitate filtered off and solution evaporated. The crude was purified by flash chromatography (ethyl ether, petroleum ether).

3e,f. A solution of *cis* diphenylaziridine (3 mmol) or benzylglycinate (3 mmol), triethylamine (0.5 mL) and **1b** (3 mmol) in dry ether (10 mL) was stirred at room temperature for 24 h. The precipitate filtered off. Classical work up. The residue chromatographied on aluminium oxide using petroleum ether/CH_2Cl_2 as eluent.

3g. A solution of **1g** (5.2 mmol) in ethyl ether (7 mL) was added to a solution of diisopropylamine (26.2 mmol) in ethyl ether (60 mL). The mixture was stirred at RT during 6 h. Work up. Flash chromatography.

Representative spectral data : ^1H NMR (200 MHz, $CDCl_3$, TMS) ; ^{19}F NMR (188.3 MHz, $CFCl_3$) ; ^{13}C NMR (50.32 MHz, $CDCl_3$, TMS) ; MS (70 eV).

3aE. Yellow oil. ^1H NMR : 7.7 (s, 1H), 7.4-7.2 (m, 5H), 3.0 (m, 4H), 1.9 (s, 3H), 1.0 (m, 6H). ^{13}C NMR : 12.9, 27.8, 41.9, 110,6, 126.9, 128.2, 131.9, 139.0, 147.5, 196.3. MS m/z : 217 ($M^{+\cdot}$) 202, 200, 56, 43 (100 %) $C_{14}H_{19}NO$.

3bE. Mp : 44-45°C. ^{19}F NMR : -68.6. ^1H NMR : 7.8 (s, 1H), 7.2-7.4 (m, 5H), 3.3 (m, 2H), 2.8 (m, 2H), 1.26 (m, 3H), 0.78 (m, 3H). ^{13}C NMR : 12.59, 14.37, 42.74, 51.95, 105.44, 118.28 ($^1J_{CF}$=292.2), 127.41, 127.77, 131.90, 134.31, 176.61 ($^2J_{CF}$=30.4).

3eE. ^{19}F NMR : -69.7. ^1H NMR : 8.02 (s, 1H), 6.81-7.4 (m, 15 H), 3.50 (s, 2H). ^{13}C NMR :50.8, 117.3 (q, $^1J_{CF}$=292.1), 123.3, 127.3, 127.4, 127.6, 127.8, 128.0, 128.8, 129.4, 129.5, 130.6, 131.2, 133.0, 157.9, 179.1 ($^2J_{CF}$=33.4). MS m/z : 393 (M^+ 100 %) 304, 206, 178, 115, 91, 77.

3fE. Mp : 67-68°C. ^{19}F NMR : -69.0. ^1H NMR : 7.94 (s, 1H), 7.19-7.35 (m, 10H), 4.41 (m, 2H), 4.02 (m, 2H), 3.44 (m, 2H), 1.15 (t, 3H, ^3J=6.8). ^{13}C NMR : 13.95, 49.54, 61.58, 62.59, 107.53, 118.09 (q, $^1J_{CF}$=292.2), 128.04, 128.26, 128.72, 129.12, 132.21, 133.39, 134.49, 153.36, 167.59, 178.12 (q, $^2J_{CF}$=31.1). MS m/z : 391 ($M^{+\cdot}$) 322, 318, 294, 91. Anal. Calc. for $C_{21}H_{20}NO_3F_3$: C, 64.45 ; H, 5.12 ; N, 3.58. Found : C,64.50 ; H, 5.24 ; N, 3.74.

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