Reactions of Trifluoroacetonitrile Oxide or -nitrilimines with β-Diketones and β-Keto Esters

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Synopsis. *N*-Phenyl-*C*-(trifluoromethyl)nitrilimine cyclized with β-diketones or β-keto esters under alkaline conditions to give the corresponding 3-trifluoromethylpyrazoles with acyl or alkoxycarbonyl group at the 4-position of the ring, respectively. While trifluoroacetonitrile oxide with β-diketones provided the corresponding trifluoromethylisoxazoles, its reactions with β-keto esters gave 4-acyl-5-hydroxy-3-trifluoromethylisoxazoles as well as the expected isoxazoles without the regioselectivity.

The reaction of nitrile oxides or nitrilimines with the doubly activated methylene compounds provides a regiospecific synthesis of isoxazoles or pyrazoles with a wide variety of substituents.[1] For example, acyl group attached to methylene group is regarded as a functional group for an introduction of alkyl group into the 5-position of the azole ring. In the course of our program researching on the reactivity of the fluorinated 1,3-dipolar compounds, we now wish to describe the synthesis of 3-trifluoromethylpyrazoles or -isoxazoles having carbonyl functions through the reactions of *N*-phenyl-*C*-(trifluoromethyl)nitrilimine (**2**) or trifluoroacetonitrile oxide (**6**) with various β-diketones or β-keto esters and also to report the regioselectivity of the cycloaddition.[2]

The nitrilimine **2**, derived in situ from *N*-phenyltrifluoroacetohydrazonoyl bromide (**1**), reacted with methyl acetoacetate under alkaline conditions in methanol to give 4-methoxycarbonyl-5-methyl-1-phenyl-3-trifluoromethylpyrazole (**3a**) in fairly good yield. The pyrazole **3a** was easily transformed into 5-methyl-1-phenyl-3-trifluoromethylpyrazole (**4**) by hydrolysis followed by decarboxylation. This transformation confirmed the structure of **3a** having methoxycarbonyl group at the 4-position of the ring, indicating that cycloaddition proceeds with high regioselectivity. Similarly, **2** reacted with 2,4-pentanedione, giving rise to the corresponding acetylpyrazole **3b**. The reactions of **6**, generated in situ from trifluoroacetohydroximoyl bromide etherate (**5**), are also related to the synthesis of the acylisoxazoles **7a, b, c** from 2,4-pentanedione, dibenzoylmethane, and 1,3-cyclohexanedione,[3] respectively (Table 1). However, methyl acetoacetate produced 4-acetyl-5-hydroxy-3-trifluoromethylisoxazole (**9**), disturbing the high regioselectivity, in substantial quantity together with the expected isoxazole **8a** which was also converted into 5-methyl-3-trifluoromethylisoxazole (**10**). Although ethyl acetoacetate also produced **9** in as low as 7% yield besides **8b**, methyl benzoylacetate afforded only **8c**, accompanied by no corresponding hydroxyisoxazole.

The formation of **9** can be reasonably explained by the stepwise path involving electrophilic substitution of **6** toward the anion **11** of β-keto ester followed by intramolecular cyclization of thus formed anion **12** with the ester moiety. These ionic or hard properties are characteristic of **6** and seem to be caused by the strong electron-withdrawing effects of trifluoromethyl group.[4] On the other hand, intramolecular cyclization of the anion **12** with the acetyl group may produce the expected isoxazole **8**[5] and , however, the alternative direct formation of **8** by a concerted cycloaddition of **6** with **11** can not be still ruled out.

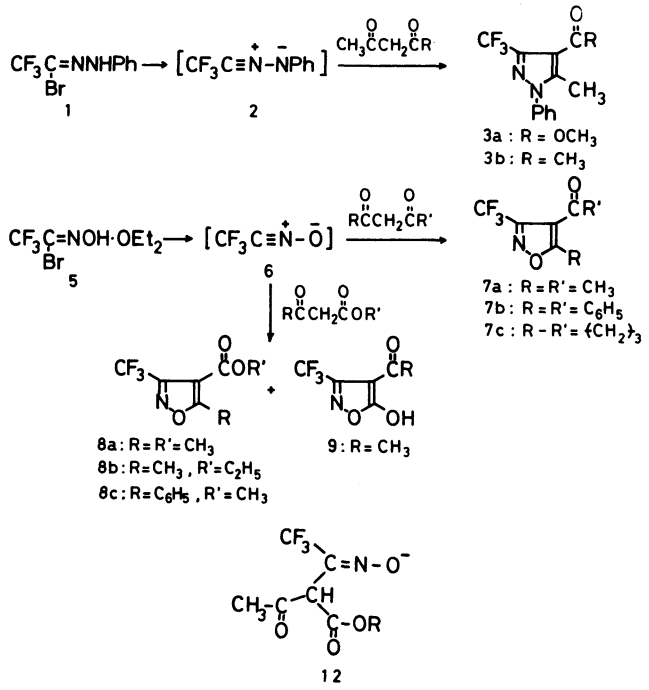
Experimental

All melting and boiling points are uncorrected. The IR spectra were recorded on a JASCO A-100 spectrometer. The

Table 1. Preparation of Trifluoromethylpyrazoles (**3**) and -isoxazoles (**7** and **8**)

Compound	Yield %	Mp(θ_m/°C) [Bp(θ_b/°C/mmHg)]	Formula	Calcd(Found)/% C	H	N	IRν/cm^{-1} C=O	^{1}H NMR δ[a]
3a	92	73—75[b]	$C_{13}H_{11}F_3N_2O_2$	54.93 (55.12)	3.90 (3.89)	9.86 (9.87)	1727	2.55(s, 3H), 3.89(s, 3H) 7.2—7.7(m, 5H)
3b	88	91—93[b]	$C_{13}H_{11}F_3N_2O$	58.21 (58.35)	4.13 (4.12)	10.44 (10.48)	1668	2.51(s, 3H), 2.58(s, 3H) 7.3—7.7(m, 5H)
7a	54	[60—62/10]	$C_7H_6F_3NO_2$	43.54 (43.35)	3.13 (2.80)	7.25 (7.35)	1700	2.50(s, 3H), 2.76(s, 3H)
7b	25	66—67[b]	$C_{17}H_{10}F_3NO_2$	64.36 (64.21)	3.18 (3.01)	4.41 (4.37)	1655	7.1—8.0(m)
7c	29	44—45[c]	$C_8H_6F_3NO_2$	46.84 (46.61)	2.95 (2.83)	6.83 (6.87)	1702	2.1—2.8(m, 4H), 3.10(t, 2H)
8a	24[d]	Oil	$C_7H_6F_3NO_3$	40.20 (40.12)	2.89 (2.90)	6.70 (6.83)	1740	2.75(s, 3H), 3.90(s, 3H)
8b	61[e]	Oil	$C_8H_8F_3NO_3$	43.06 (43.21)	3.61 (3.75)	6.28 (6.16)	1740	1.36(t, 3H), 2.76(s, 3H) 4.33(q, 2H)
8c	23	69—70[f]	$C_{12}H_8F_3NO_3$	53.15 (52.87)	2.97 (2.82)	5.16 (5.21)	1740	3.90(s, 3H), 7.4—8.0(m, 5H)

a) Measured in $CDCl_3$. b) Recrystallized from hexane. c) Recrystallized from hexane–diethyl ether. d) Other than **8a**, **9** was isolated in 16% yield. e) Other than **8b**, **9** was isolated in 7% yield. f) Recrystallized from chloroform.



^{1}H NMR spectra were measured with JEOL JNM-PMX 60 spectrometer, using tetramethylsilane as an internal standard, the chemical shifts being given in δ ppm downfield. The MS spectra were obtained on a Finnigan 4023 GC-MS DS spectrometer. The bromides **1** and **5** were prepared by the methods reported in our previous papers.[6]

Preparations of 3 and 7. General Procedure. A solution of **1** (4.5 mmol) in 10 cm^3 of methanol was added dropwise to a solution of sodium methoxide (9.0 mmol) and 13.5 mmol of methyl acetoacetate or 2,4-pentanedione in 20 cm^3 of methanol. After stirring at room temperature for 2 h, 100 cm^3 of diethyl ether was added to the reaction mixture. The mixture was washed with water and brine, dried over magnesium sulfate, and evaporated to leave a residue which was placed on a column (silica gel) and eluted to give the pyrazole **3**. Product was further purified by recrystallization. The isoxazoles **7** were similarly prepared from **5** and β-diketones.

Decarboxylation of 3a and 8a. A mixture of **3a** (1.59 g, 5.6 mmol) in ethanol (25 cm^3) and 10% aqueous sodium carbonate (50 cm^3) was refluxed for 12 h. After the solvent was removed, the resulting mixture was washed with diethyl ether and dissolved in water. The aqueous solution was acidified with concd hydrochloric acid, extracted with diethyl ether, and dried over magnesium sulfate. Removal of the solvent left a solid (1.03 g). A mixture of thus obtained solid and 0.1 g of copper powder in 3 cm^3 of quinoline was heated at 190°C for 3 h and evaporated under reduced pressure to leave a residue. The residue was chromatographed on silica gel and eluted with hexane–ethyl acetate (5:1) to give 0.41 g (32%) of **4** which was further purified by preparative GLC; ^{1}H NMR ($CDCl_3$) δ=2.30 (s, 3H), 6.37 (s, 1H), 7.4 (s, 5H), IR (neat) 1590 (Ph), 1170,1130 cm^{-1} (CF_3).

Found: C, 58.57; H, 3.96; N, 12.37%. Calcd for $C_{11}H_9F_3N_2$: C, 58.41; H, 4.01; N, 12.38%.

Similar treatment of **8a** provided **10** which was collected by distillation (64%) and purified by preparative GLC. ^{1}H NMR ($CDCl_3$) δ=2.52 (s, 3H), 6.25 (s, 1H), IR (neat) 3150 (CH), 1185, 1145 cm^{-1} (CF_3).

Found: C, 39.72; H, 2.31; N, 9.28%. Calcd for $C_5H_4F_3NO$: C, 39.75; H, 2.67; N, 9.27%.

Reaction of 5 with Methyl Acetoacetate. After the similar procedures to the above using **5** (5.00 g, 18.8 mmol), methyl acetoacetate (5.95 g, 51.3 mmol), and sodium methoxide (2.77 g, 51.3 mmol), the solvent was removed to leave a residue. The residue was extracted with chloroform and then with ethyl acetate. The chloroform layer was washed with water, dried over magnesium sulfate, and evaporated. The resulting residue was distilled to give 3.44 g of a mixture of **8a** (24% yield) and methyl acetoacetate in the ratio of 17:83 (boiling range, 74—76°C/25 mmHg, 1 mmHg=133.322 Pa). The isoxazole **8a** was further separated by preparative GLC. On the other hand, the ethyl acetate layer was evaporated to give a residue which was dissolved in water. The aqueous solution was acidified with concd hydrochloric acid and extracted with diethyl ether. The extracts were dried over magnesium sulfate and evaporated to leave an oily matter which was sublimed under reduced pressure to give 0.57 g (16%) of **9**; mp 96—98°C (recrystallized from chloroform), ^{1}H NMR ($CDCl_3$–DMSO-d_6) δ=2.53 (s), 9.3 (br. s), IR(KBr) 3340 (OH), 1730 (C=O), 1150 cm^{-1} (CF_3), MS (CI, *m/z*) 196 $(M+H)^+$, 224 $(M+Et)^+$.

Found: C, 32.91; H, 2.60; N, 6.34%. Calcd for $C_6H_4F_3NO_3 \cdot 1.3H_2O$[7]: C, 32.98; H, 3.04; N, 6.41%.

In a similar manner, the reaction with ethyl acetoacetate or methyl benzoylacetate was performed and the results are summarized in Table 1.

References

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7) Since the isoxazole **9** is hygroscopic and easily sublimed under reduced pressure, the complete drying was impossible.