PREPARATION OF TRIFLUOROACETONITRILE PHENYLIMINE AND ITS REACTIONS WITH SOME DIPOLAROPHILES

Kiyoshi TANAKA, Seiji MAENO, and Keiryo MITSUHASHI Department of Industrial Chemistry, Seikei University, Musashino-shi, Tokyo 180

Trifluoroaceto-N-phenylhydrazonoyl halides, the precursors of trifluoroacetonitrile phenylimine, prepared by halogenation of trifluoroacetaldehyde phenylhydrazone, react with various olefins and acetylenes in the presence of triethylamine to give 3-trifluoromethylpyrazolines and pyrazoles, respectively. The regioselective results are discussed in terms of HOMO-LUMO interaction of trifluoroacetonitrile phenylimine and dipolarophiles.

The heterocyclic compounds bearing a fluorine atom or a trifluoromethyl group have received current interest because of their pharmacological activity.¹⁾ However, the introduction of such fluorine groups into heterocyclic rings has been limited.²⁾ On the other hand, it is well known that 1,3-dipolar compounds are useful reagents to prepare various heterocyclic compounds.³⁾ In this connection, it is of particular interest to apply the fluorinated 1,3-dipolar compounds as building blocks of the heterocyclic compounds with fluorine groups.

We now wish to report the preparation of trifluoroaceto-N-phenylhydrazonoyl halides $(\underline{3})$, the precursors of trifluoroacetonitrile phenylimine $(\underline{1})$, and their reactions with olefins and acetylenes which provide novel routes to 3-trifluoromethylpyrazolines and pyrazoles.⁴⁾

$$CF_3 - C = N - N - Ph$$

Trifluoroaceto-N-phenylhydrazonoyl chloride (<u>3a</u>) and bromide (<u>3b</u>) were prepared by halogenation of trifluoroacetaldehyde phenylhydrazone (<u>2</u>) which was readily accessible from trifluoroacetaldehyde hydrate and phenylhydrazine.⁵) Treatment of <u>2</u> with N-chloro- and N-bromosuccinimide in dimethylformamide at room temperature afforded <u>3a</u> and <u>3b</u> in 71 and 74% yields, respectively.⁶)

$$\begin{array}{cccc} CF_{3}CH(OH)_{2} & \longrightarrow & CF_{3}CH=NNHPh & \longrightarrow & CF_{3}C=NNHPh \\ & & & & & \\ & & & & \\ & & & \\ & & & & \\ & & & & \\ & & & \\ & &$$

Halides <u>3a</u> or <u>3b</u> reacted with 1-substituted olefins such as styrene, methyl acrylate, and butoxyethylene to afford exclusively 5-substituted 3-trifluoromethyl-2-pyrazolines <u>4</u> in good yields (see Table 1). Only butoxypyrazoline (<u>4</u>: R^2 =H, R^1 =OBu), when separated by column chromatography, decomposed to give 1-phenyl-3-trifluoromethylpyrazole. The reaction of allyloxybenzene with <u>3b</u>, however, gave not only pyrazoline <u>4</u> but also small amount of its isomer <u>4'</u>. These pyrazolines were identified by their spectral data and elemental analyses. ¹H NMR spectra of these pyrazolines show 4-methylene protons coupled with trifluoromethyl group in about 1.5 Hz. On the other hand, the reactions of <u>3a</u> with 1,2disubstituted olefins such as methyl crotonate and cinnamate resulted in formation of both <u>4</u> and <u>4'</u> in the ratios of 90/10 and 64/36, respectively, according to ¹H NMR analyses. These isomers were separated by thin layer chromatography (silica gel, chloroform-hexane) and fully characterized by spectral data and elemental analyses. ¹H NMR spectra show that peaks of 4-methine proton of both isomers are slightly broadened by 3-trifluoromethyl group.



The reaction of <u>3b</u> with methyl propiolate under the same conditions exothermically proceeded to give a mixture consisting of 5-methoxycarbonyl-1-phenyl-3-trifluoromethylpyrazole (<u>5a</u>) and its isomeric 4-methoxycarbonylpyrazole (<u>5a'</u>) in the ratio of 76:24 (¹H NMR analysis). These isomers were separated by column chromatography (silica gel, chloroform-hexane) and identified by their elemental analyses and spectroscopic properties. The similar reaction using <u>3a</u> with methyl propiolate gave <u>5a</u> and <u>5a'</u> in the ratio of 81:19 (¹H NMR assay). The reaction of <u>3b</u> with 2-propynyloxybenzene also gave a mixture of <u>5b</u> and <u>5b'</u> in 59 and 13% yields, respectively, whereas that with phenylacetylene afforded only 5-phenyl-pyrazole <u>5c</u> along with its linear isomer <u>6</u> (see Table 2). 5-Substituted pyrazoles <u>5a-c</u> were also obtained by dehydrogenation of the corresponding 5-substituted pyrazolines <u>4</u> with chloranil.



r- R ² CH=Cl R ²	HR ¹ -, R ¹	Halides	⊢Conditi Temp.(°C)	ons _⊐ Time(h)	rYields,9 4 ^{b)}	^{%a)} ⊣ 4'b)	Mp(°C) or bp(°C/mmHg) of 4
Н	Ph	<u>3b</u>	80	1.5	 97	c)	81-82
н	CO ₂ Me	<u>3a</u>	90	5	85	c)	60-61.5
н	OBu	<u>3a</u>	90	12	89 ^d)	c)	oily
Н	CH ₂ 0Ph	<u>3b</u>	110	6.5	70 ^{e)}	9 ^{e)}	110.5-112.5
CH3	C0 ₂ Me	<u>3a</u>	90	16	51 ^{e)}	6 ^{e)}	120-125/1
Ph	CO ₂ Me	<u>3a</u>	110	15	26 ^{e)}	14 ^{e)}	138-139

Table 1. Reactions of Halides $\underline{3a}$ and $\underline{3b}$ with Olefins

a) Isolated yields unless otherwise noted. b) Satisfactory analytical data($\pm 0.3\%$ for C,H,N) were obtained for all compounds. c) This means that <u>4'</u> was not detected at all. d) Crude yield. Easily decomposed to give 1-phenyl-3-trifluoromethylpyrazole (bp 137-139°C/25 mmHg). e) Yields determined by ¹H or ¹9F NMR analyses.

	- Conditions -			Yields, ^{%a)} —			rMp(°C) or bp(°C/mmHg)¬	
R	Halides	Temp.(°C) Time(h)	<u>5</u> b)	<u>5'</u> b)	<u>6</u> b)	<u>5</u>	<u>5'(6</u>)
CO ₂ Me	<u>3b</u>	r.t.	2	63	17	c)	63	112
	<u>3a</u>	r.t.	1.5	52	12	c)		
CH ₂ OPh	<u>3b</u>	110	2	59	13	c)	185-188/4	d)
Ph	<u>3b</u>	110	1.5	45	c)	24	86-88	(97-99)

Table 2. Reactions of Halides 3a and 3b with Acetylenes (CH=CR)

a) Isolated yields. b) Satisfactory analytical data($\pm 0.3\%$ for C,H,N) were obtained for all compounds. c) This means that compounds were not detected at all. d) MS(m/e),318(M⁺),224(M⁺-PhOH).

It should be noted that the regioselectivity of cycloadditions of trifluoroacetonitrile imine $\underline{1}$ toward olefins and acetylenes shows the similar tendency to that of benzonitrile phenylimine, which, for example, with methyl propiolate, gives a 78:22 mixture of 5- and 4-methoxycarbonylpyrazole.⁷⁾ These results may be interpreted by HOMO-LUMO interaction of $\underline{1}$ and dipolarophiles.⁸⁾ Effects of trifluoro-methyl group on HOMO energy and on LUMO coefficient magnitude of $\underline{1}$ seem to be compensated each other. That is, trifluoromethyl group tends to lower the LUMO and HOMO energy, particularly HOMO energy in this case, causing greater dipole LUMO control of orientation which results in formation of 5- substituted pyrazoles, whereas it decreases the LUMO coefficient of the carbon atom attached to trifluoromethyl group, causing the smaller difference in LUMO coefficient magnitude which weakens dipole LUMO control.

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- 5) Trifluoroacetaldehyde hydrate was obtained by reduction of trifluoroacetic acid with lithium aluminium hydride and a mixture of crude trifluoroacetaldehyde hydrate and phenylhydrazine was stirred at 100°C for 1 h to give trifluoroacetaldehyde phenylhydrazone in 61% yield (based on trifluoroacetic acid): mp 69-73°C; ¹H NMR(CC1₄, TMS), δ 6.5-7.3 (m, aromatic and olefinic, 6H) and 7.6 (br.s, NH, 1H); IR(KBr), 3300 (NH), 1610 (C=N), 1592 cm⁻¹ (Ph); Anal. Calcd for C₈H₇N₂F₃, C, 51.07, H, 3.75, N, 14.89; Found, C, 50.95, H, 3.73, N, 15.38. For the preparation of trifluoroacetaldehyde hydrate and its synthetic utility, see D. R. Husted and A. H. Ahlbrecht, J. Am. Chem. Soc., <u>74</u>, 5422(1952) and K. Tanaka, T. Nakai, and N. Ishikawa, Chem. Lett., <u>1979</u>, 175.
- 6) Chloride <u>3a</u>: bp 72-73°C/ 2 mmHg; ¹H NMR(CCl₄, TMS), δ 6.8-7.4 (m, aromatic, 5H) and 7.8 (br.s, NH, 1H); IR(film), 3340 (NH), 1600 (C=N and Ph), 1150 and 1130 cm⁻¹ (CF₃). Bromide <u>3b</u>: bp 74-77°C/ 3 mmHg; ¹H NMR(CCl₄, TMS), δ 6.8-7.4 (m, aromatic, 5H) and 7.9 (br.s, NH, 1H); IR(film), 3325 (NH), 1600 (C=N and Ph), 1140 cm⁻¹ (CF₃).
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