CHEMISTRY LETTERS, pp. 543-546, 1982. © The Chemical Society of Japan 1982

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 (3), the precursors of trifluoroacetonitrile phenylimine (1), and their reactions with olefins and acetylenes which provide novel routes to 3-trifluoromethylpyrazolines and pyrazoles.[4]

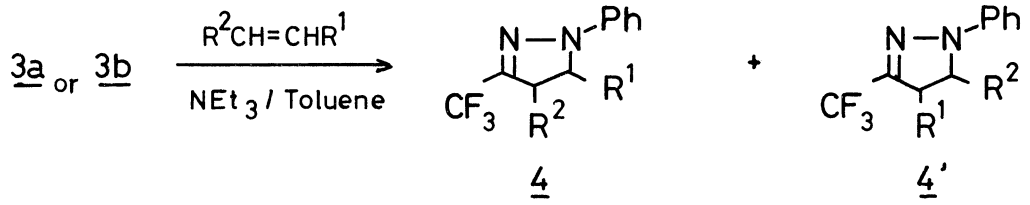
$$CF_3-\overset{\oplus}{C}=N-\overset{\ominus}{N}-Ph$$

1

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

$$CF_3CH(OH)_2 \longrightarrow \underset{2}{CF_3CH=NNHPh} \longrightarrow \underset{\substack{3a: X=Cl \\ 3b: X=Br}}{CF_3\overset{X}{C}=NNHPh}$$

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



The reaction of 3b with methyl propiolate under the same conditions exothermically proceeded to give a mixture consisting of 5-methoxycarbonyl-1-phenyl-3-trifluoromethylpyrazole (5a) and its isomeric 4-methoxycarbonylpyrazole (5a') in the ratio of 76:24 (^{1}H 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 3a with methyl propiolate gave 5a and 5a' in the ratio of 81:19 (^{1}H NMR assay). The reaction of 3b with 2-propynyloxybenzene also gave a mixture of 5b and 5b' in 59 and 13% yields, respectively, whereas that with phenylacetylene afforded only 5-phenylpyrazole 5c along with its linear isomer 6 (see Table 2). 5-Substituted pyrazoles 5a-c were also obtained by dehydrogenation of the corresponding 5-substituted pyrazolines 4 with chloranil.

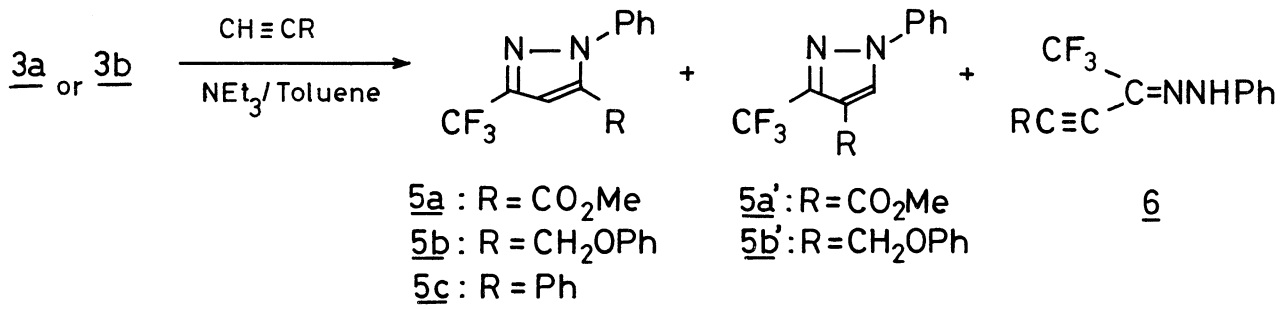


Table 1. Reactions of Halides 3a and 3b with Olefins

$R^2CH=CHR^1$			Conditions		Yields,%[a]		
R^2	R^1	Halides	Temp.(°C)	Time(h)	4[b]	4'[b]	Mp(°C) or bp(°C/mmHg) of 4
H	Ph	3b	80	1.5	97	---[c]	81-82
H	CO_2Me	3a	90	5	85	---[c]	60-61.5
H	OBu	3a	90	12	89[d]	---[c]	oily
H	CH_2OPh	3b	110	6.5	70[e]	9[e]	110.5-112.5
CH_3	CO_2Me	3a	90	16	51[e]	6[e]	120-125/1
Ph	CO_2Me	3a	110	15	26[e]	14[e]	138-139

a) Isolated yields unless otherwise noted. b) Satisfactory analytical data(±0.3% for C,H,N) were obtained for all compounds. c) This means that 4' 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 ^{19}F NMR analyses.

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

		Conditions		Yields,%[a]			Mp(°C) or bp(°C/mmHg)	
R	Halides	Temp.(°C)	Time(h)	5[b]	5'[b]	6[b]	5	5'(6)
CO_2Me	3b	r.t.	2	63	17	---[c]	63	112
	3a	r.t.	1.5	52	12	---[c]		
CH_2OPh	3b	110	2	59	13	---[c]	185-188/4	---[d]
Ph	3b	110	1.5	45	---[c]	24	86-88	(97-99)

a) Isolated yields. b) Satisfactory analytical data(±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 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 1 and dipolarophiles.[8] Effects of trifluoromethyl group on HOMO energy and on LUMO coefficient magnitude of 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.

References

1) a) H. Kimoto and L. A. Cohen, J. Org. Chem., 45, 3831(1980); b) R. Filler, "Adv. in Fluorine Chemistry," Vol.6(1970), p.1; c) R. Filler, Chemtech., 4, 752(1974).

2) a) Y. Kobayashi, I. Kumadaki, and T. Taguchi, Yuki Gosei Kagaku Kyokai Shi, 38, 1119(1980); b) Y. Kobayashi and I. Kumadaki, ibid, 31, 477(1973).

3) a) A. S. Shawali and C. Párkányi, J. Heterocyclic Chem., 17, 833(1980); b) A. Padwa, Angew. Chem. Int. Ed. Ingl., 15, 123(1976); c) R. Huisgen, R. Sustmann, and G. Wallbillich, Chem. Ber., 100, 1786(1967); d) R. Huisgen, M. Seidel, G. Wallbillich, and H. Knupfer, Tetrahedron, 17, 3(1962).

4) H. Gilman, I. Tolman, F. Yeoman, L. A. Woods, D. A. Shirley, and S. Avakian, J. Am. Chem. Soc., 68, 426(1946).

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; ^{1}H NMR(CCl_4, 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 $C_8H_7N_2F_3$, 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., 74, 5422(1952) and K. Tanaka, T. Nakai, and N. Ishikawa, Chem. Lett., 1979, 175.

6) Chloride 3a: bp 72-73°C/ 2 mmHg; ^{1}H NMR(CCl_4, 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} (CF_3). Bromide 3b: bp 74-77°C/ 3 mmHg; ^{1}H NMR(CCl_4, TMS), δ6.8-7.4 (m, aromatic, 5H) and 7.9 (br.s, NH, 1H); IR(film), 3325 (NH), 1600 (C=N and Ph), 1140 cm^{-1} (CF_3).

7) See ref. 3 c).

8) a) K. N. Houk, J. Sims, R. E. Duke, Jr., R. W. Strozier, and J. K. George, J. Am. Chem. Soc., 95, 7287(1973); b) K. N. Houk, J. Sims, C. R. Watts, and L. J. Luskus, ibid, 95, 7301(1973).

(Received January 11, 1982)