A CONVENIENT SYNTHESIS OF 4,5-BIS(TRIFLUOROMETHYL)-PYRIDAZINES

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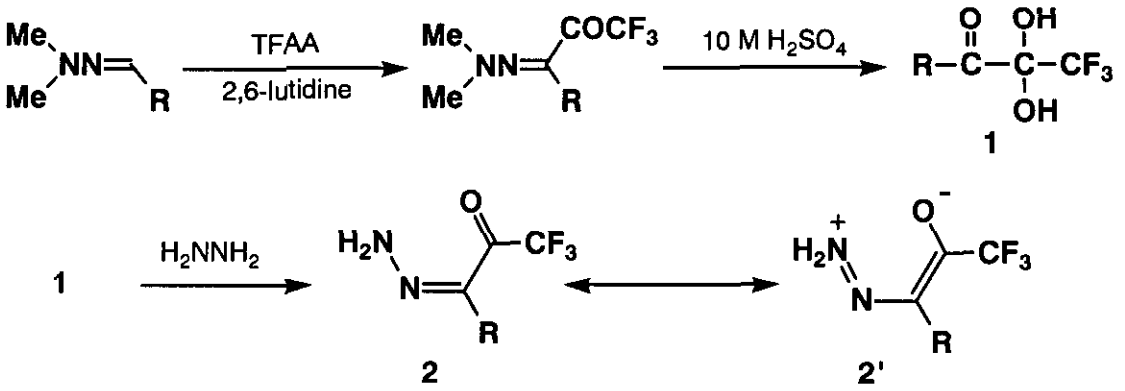
Abstract - Acid catalyzed selfcondensation of 3-hydrazono-1,1,1-trifluoroalkan-2-ones (**2**) prepared from 1,1,1-trifluoroalkan-2,3-diones (**1**) and 100% hydrazine hydrate afforded 4,5-bis(trifluoromethyl)-pyridazines (**3**) in satisfactory yields.

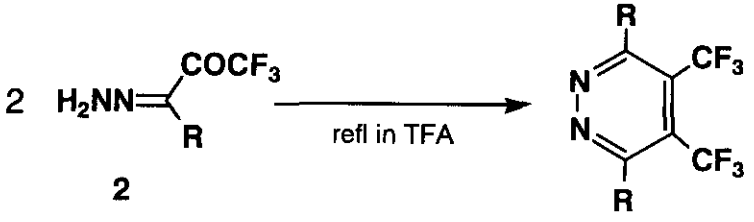
Fluorine-containing heterocycles are one of the most fascinating targets for synthetic organic chemists because of their potentially high biological activities.[1] On the other hand, many synthetic derivatives of pyridazine show remarkable physiological activities.[2] For example, some of pyridazinones are known as a plant growth inhibiter.[3] In previous paper[4] we presented a new facile synthetic method for 5-trifluoromethyl-4-pyridazinones from aldehyde *N*,*N*-dimethylhydrazones. In this paper we wish to report a convenient synthesis of "symmetric" pyridazines bearing two trifluoromethyl groups from diketones (**1**).

By usual manner,[5] trifluoroacetylation of aldehyde dimethylhydrazones with the use of TFAA, and subsequent hydrolysis of obtained 3-dimethylhydrazono-1,1,1-trifluoroalkan-2-ones in hot 10M H_2SO_4 gave **1** as monohydrates, respectively. Reaction of diketones (**1**) with 100% hydrazine hydrate in MeOH afforded the corresponding 1,1,1-trifluoro-3-hydrazonoalkan-2-ones (**2**) in quantitative yields. No isomeric 1,1,1-trifluoro-2-hydrazonoalkan-3-ones were detected under the reaction conditions we examined. Direct formation of **2** by *C*-trifluoroacetylation of aldehyde hydrazones prepared from aldehydes and hydrazine hydrate resulted in failure because of preferential *N*-trifluoroacetylation strongly preventing *C*-trifluoro-



acetylation at azomethine carbon atom. Thus obtained monohydrazones (**2**) are characterized by strong push-pull type electronic structure indicated above and expected as a good building block for construction of several fluorine-containing heterocycles.

A solution of **2** in TFA (0.2 - 2 mL / 1 mmol of **2**) was refluxed for 2 h - 1 d . After distillation of TFA, the residue was dissolved in CH_2Cl_2, washed with aq. K_2CO_3, and dried over Na_2SO_4. Evaporation of the solvent afforded 4,5-bis(trifluoromethyl)pyridazines (**3**) as brown solid or viscous oil. After silica gel column chromatography (benzene), pure **3a** - **d** were obtained in the yields listed in Table. When the reaction was carried out in the absence of TFA, **3** was not obtained at all. The structure of pyridazines (**3**) were confirmed on the basis of ^1H and ^{13}C NMR, and IR spectra, and micro combustion analysis.[6,7] In ^{13}C NMR spectra of **3b** in $CDCl_3$, only two signals of pyridazine ring carbon atoms appear at 126.0 ($^2J_{CF}$=19.6 Hz) and 158.3 ppm, and single quartet assignable to trifluoromethyl carbon atoms at 122.1 ppm ($^1J_{CF}$= 277.1 Hz), indicating symmetrical structure of **3b**. Another possible isomers 3,5-



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R	2, 3
Ph	a
p-Tol	b
p-ClC$_6$H$_4$	c
p-MeOC$_6$H$_4$	d

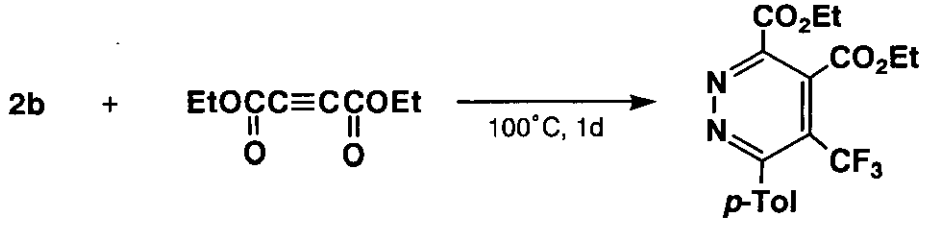
Table. Synthesis of Pyridazines (**3**) from Monohydrazones (**2**).

substrate	reaction conditions TFA[a] mL/mmol	time h	product	yield[b] (%)	^{1}H NMR ($CDCl_3$/TMS)[c] δ
2a	2	20	**3a**	52	7.35 - 7.67 (m, 10H, ArH)
2b	2	24	**3b**	48	2.47 (s, 6H, Me), 7.11 - 7.62 (AA'BB'q, J=8.0 Hz,8H, ArH)
2c	1	20	**3c**	7.5	7.41, 8.10 (d, J=8.2 Hz, 8H, ArH)
	0.2	2[d]		35	
2d	2	24	**3d**	51	3.84 (s, 6H, OMe), 6.99, 7.57 (d, J=8.4 Hz, 8H, ArH)

a) Amounts of TFA (mL) used for 1 mmol of **2**. b) Yield refer to isolated compounds.
c) ^{1}H NMR spectra were recorded at 60 MHz on a JEOL PMX60SI. d) Reaction was carried out at room temperature.

bis(trifluoromethyl)pyridazines could not be detected in any case of the reactions in Table. One of the most reasonable mechanism for present pyridazine formation reaction is that *via* [4+2] type cycloaddition process between two molecules of hydrazone (**2**) characterized by polarized dienic canonical form **2'**. TFA should enhance the dienic character of **2** to more extent by protonation at carbonyl oxygen atom of **2**.

We also examined cycloaddition reaction of **2** with dimethyl acetylenedicarboxylate (DMAD). Reaction of **2** (R= *p*-Tol) with two molar equivalents of DMAD afforded expected cycloaddition product (**4**)[8] in 62% yield. The reaction proceeded smoothly in the absence of acid catalyst.



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Detailed reaction mechanism for present pyridazine formation reaction from **2** to **3** as well as an extension of this synthetic method to preparations of general "symmetric" pyridazines are

now under investigation and will be reported in near future.

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6. For instance, **3b**: pale yellow crystals, mp 195.0 - 196.0°C (cyclohexane / benzene); ^{13}C NMR ($CDCl_3$/ TMS) δ 21.4 (Me), 122.1 ($^1J_{CF}$=277.1 Hz, CF_3), 125.8 ($^2J_{CF}$=36.7 Hz, C4 and C5), 129.3, 129.4 (C2' and C3' of *p*-Tol), 133.8 (C1' of *p*-Tol), 140.4 (C4' of *p*-Tol), 158.3 (C3 and C6); IR (KBr) 2960 (w), 1375 (s), 1235 (s), 1190 (s), 1140 (s), 1110 (m), 1030 (m) cm^{-1}. Anal. Calcd for $C_{20}H_{14}N_2F_6$: C, 60.61; H, 3.56; N, 7.07. Found: C, 60.47; H, 3.57; N, 7.31.
7. ^{13}C NMR spectra were recorded at 59.5 MHz on a Bruker AC250 and IR spectra were taken with a Hitachi model G3.
8. **4**: pale yellow crystals, mp 176.2 - 177.0°C (cyclohexane / benzene); ^{1}H NMR ($CDCl_3$/ TMS) δ 2.46 (s, 3H, Ar**Me**), 3.93, 4.05 (s, 6H, OMe), 7.15 - 7.67 (AA'BB'q, J=8 Hz, 4H, ArH); ^{13}C NMR ($CDCl_3$/ TMS) δ 21.4 (Ar**Me**), 53.9, 54.0 (OMe), 122.0 ($^1J_{CF}$=277.0 Hz, CF_3), 124.3 ($^2J_{CF}$= 33.7 Hz, **C**CF_3), 129.3 (C2' and C3' of *p*-Tol), 131.3 (CF_3C-**C**-CO_2Me), 132.5 (C1' of *p*-Tol), 140.9 (C4' of *p*-Tol), 146.9 (N-**C**-CO_2Me), 160.8 (*p*-Tol-**C**-N), 163.3, 163.9 (C=O); IR (KBr) 2960 (w), 1740 (s), 1551 (w), 1437 (m), 1389 (m), 1280 (s), 1241 (s), 1224 (s), 1193 (s), 1140 (s), 1112 (m), 1046 (m) cm^{-1}. Anal. Calcd for $C_{16}H_{13}N_2O_4F_6$: C, 54.24; H, 3.70; N, 7.91; F, 16.09. Found: C, 53.94; H, 3.56; N, 7.75; F, 15.78.

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