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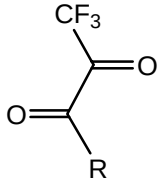
A CONVENIENT SYNTHESIS OF TRIFLUOROMETHYLPYRIDAZINES FROM 3-HYDRAZONO-1,1,1-TRIFLUOROALKAN-2-ONES

Yasuhiro Kamitori* and Tomoko Sekiyama

Department of Chemical Science and Engineering, Faculty of Engineering, Kobe University, Kobe 657-8501, Japan, e-mail: kamitori@cx.kobe-u.ac.jp

Abstract – 3-Hydrazono-1,1,1-trifluoroalkan-2-ones readily obtained from aldehyde dialkylhydrazones reacted with acetylacetone to afford the corresponding 4-acetyl-3-methyl-5-trifluoromethylpyrizazines in good yields. The reaction with ethyl acetoacetate also gave the corresponding pyridazines. These reactions proceeded successfully in the absence of any catalyst.

Fluorine-containing heterocycles are very attractive targets for synthetic organic chemists because of their potentially high physiological activities.[1-4] 1,1,1-Trifluoro-2,3-alkanediones (**1**), easily obtained from aldehyde dialkylhydrazones,[5] are an excellent synthetic intermediate accessible a variety of organofluorine compounds including heterocycles bearing trifluoromethyl substituent.[6-7] Similarly, 3-hydrazono-1,1,1-trifluoro-2-alkanones (**2**)[8] are thought to be an effective intermediate for construction of some fluorine-containing heterocycles such as pyridazine derivatives. Indeed, we found that bis(trifluoromethyl)pyridazines (**3**) can be prepared from **2** in the presence of TFA.[9] These facts prompted us to examine reactions of hydrazones (**2**) with various organic reactants. In this paper, we wish to report the results of reactions of **2** with acetylacetone and related compounds.



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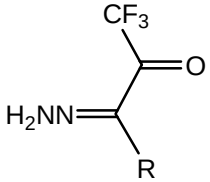

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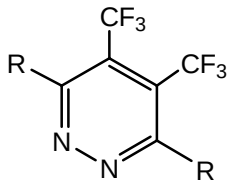
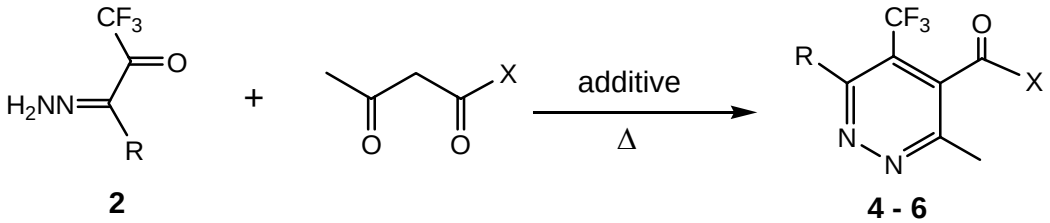


3

Bayer and coworkers reported the reaction of 3-aminoacrolein with alkane-1,3-diones affording pyridine derivatives.[10] They employed NH_4OAc as an effective catalyst for this reaction. Accordingly, we tried the reaction of hydrazones (**2**) corresponding to an aza-analogue of 3-aminoacrolein with acetylacetone under similar conditions at first.



2

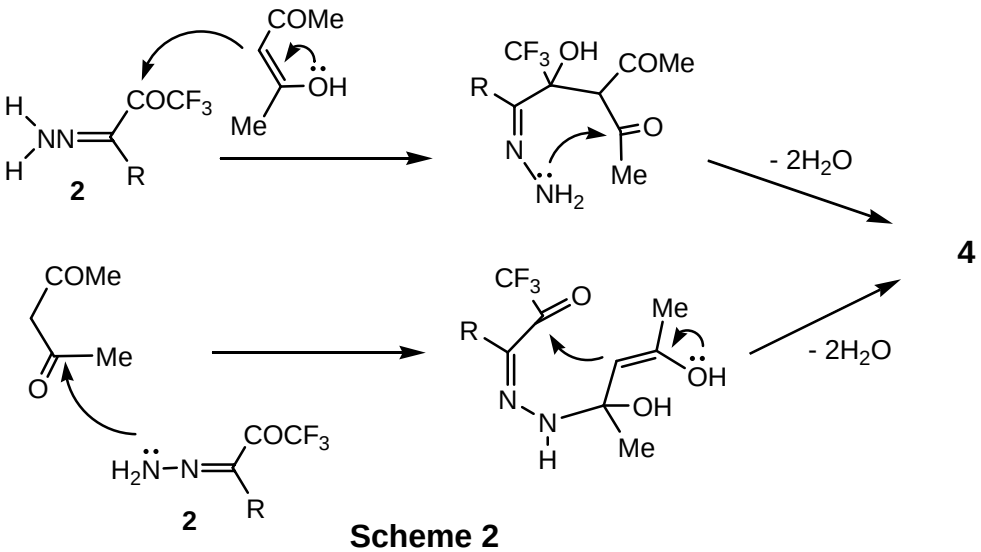
R	
p-MeC_6H_4	**2a**
p-$MeOC_6H_4$	**2b**
p-ClC_6H_4	**2c**

4 - 6

R	X	
p-MeC_6H_4	Me	**4a**
p-$MeOC_6H_4$	Me	**4b**
p-ClC_6H_4	Me	**4c**
p-MeC_6H_4	OEt	**5a**
p-$MeOC_6H_4$	OEt	**5b**
p-ClC_6H_4	OEt	**5c**
p-MeC_6H_4	Ph	**6a**

Scheme 1

In the presence of catalytic amounts of NH_4OAc, 3-aryl-3-hydrazono-1,1,1-trifluoropropan-2-ones (**2a** and **2c**) and 1.2 molar amounts of acetylacetone were allowed to react for 16 h at 110°C. After workup, the corresponding pyridazines (**4a** and **4c**) were obtained in 57 and 54% yields, respectively. Similarly **2a** reacted successfully with ethyl acetoacetate to afford the corresponding pyridazines (**5a**) in 60% yield. In contrast, the reaction of **2a** with 1-phenyl-1,3-butanedione did not proceed at all, and the corresponding pyridazines (**6a**) could not be obtained in spite of our any effort.



Scheme 2

Table 1. Synthesis of Pyridazines (**4 - 6**) from 3-Hydrazono-1,1,1-trifluoroalkan-2-ones (**2**).

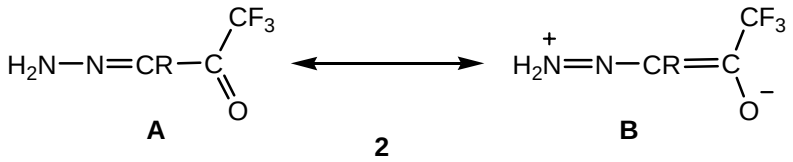
Entry	Reactants[a]	Additive[b]	Solvent	Temp. (°C)	Time (h)	Product	Yield (%)[c]
1	**2a** + AA	NH_4OAc	none	110	16	**4a**	57
2	**2c** + AA	NH_4OAc	none	110	16	**4c**	54
3	**2a** + EA	NH_4OAc	none	110	16	**5a**	60
4	**2a** + BA	NH_4OAc	none	110	16	**6a**	0
5	**2a** + AA	KOH[d]	DMF	20	24	**4a**	0
6	**2a** + AA	(*iso*-Pr)$_2$NEt[e]	MeCN	20	24	**4a**	0
7	**2a** + AA	(*iso*-Pr)$_2$NEt[f]	none	110	16	**4a**	0
8	**2a** + AA	none	none	110	16	**4a**	91
9	**2a** + EA	none	none	110	16	**5a**	68
10	**2a** + AA	none	toluene	reflux	24	**4a**	92
11	**2b** + AA	none	toluene	reflux	24	**4b**	87
12	**2c** + AA	none	toluene	reflux	24	**4c**	80
13	**2a** + EA	none	toluene	reflux	24	**5a**	76
14	**2b** + EA	none	toluene	reflux	24	**5b**	72
15	**2c** + EA	none	toluene	reflux	24	**5c**	70
16	**2a** + BA	none	toluene	reflux	30	**6a**	9

a) AA= acetylacetone, EA= ethyl acetoacetate, BA= 1-phenyl-1,3-butanedione. b) For Entries 1 - 4, NH_4OAc (0.216 equiv.) was used. c) Isolated yield after preparative TLC. d) KOH (1 equiv.) was used. e) (*iso*-Pr)$_2$NEt (1.2 equiv.) was used. f) (*iso*-Pr)$_2$NEt (0.258 equiv.) was used.

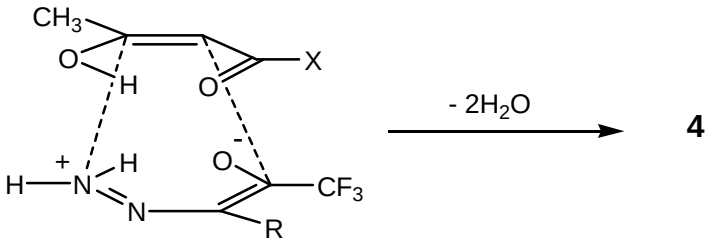
Such cyclization reaction of **2** to pyridazine (**4**) seems to be induced by nucleophilic attack of enolized acetylacetone toward carbonyl carbon atom of hydrazones (**2**) or that of terminal nitrogen atom of **2** toward one of the carbonyl carbons of acetylacetone as illustrated in Scheme 2. If these are true, the addition of base should accelerate the reaction. Therefore we tried the reaction of hydrazone (**2a**) with acetylacetone in the presence of KOH as well as di(*iso*propyl)ethylamine instead of NH_4OAc. However, attempted reactions yielded no pyridazine (**4a**) and most of **2a** was recovered unchanged. From these results we speculated that the present cyclization reaction should be mediated thermally rather than catalytically. Consequently we tried the reaction of hydrazones (**2**) with acetylacetone in the absence of any additive.

A neat mixture of hydrazone (**2a**) and 1.2 molar amounts of acetylacetone was heated at 110°C. After 16 h, the corresponding pyridazine (**4a**) was obtained in 91 % yield. The reaction using ethyl acetoacetate under the similar conditions afforded the corresponding pyridazine (**5a**) in 68 % yield. These yields are considerably higher than those obtained by the reactions in the presence of NH_4OAc.

In order to optimize yield, we tried the reaction of hydrazone (**2a**) with acetylacetone under several conditions. The best result was obtained when a mixture of **2a** and 1.2 molar amounts of acetylacetone was refluxed for 24 h in toluene. Under these conditions, pyridazine (**4a - c**) were obtained in 80 - 92% yields, respectively. Quite similarly, the reaction of **2a - c** with ethyl acetoacetate afforded the corresponding pyridazines (**5a - c**) in 70 - 76% yield. Even the reaction of **2a** with 1-phenyl-1,3-butanedione that gave no pyridazine in the presence of NH_4OAc proceeded to some extent affording the corresponding pyridazine (**6a**)[11] in 9% yield.



An azaenamine structure together with strongly electron withdrawing trifluoroacetyl group in hydrazones (**2**) results in a considerable contribution of highly polarized canonical structure **B** and, consequently, the enhanced dienic character in **2**. Hetero Diels-Alder type [4+2] cycloaddition of **2** with enolized acetylacetone followed by dehydration (Scheme 3) is one of the possible mechanism for the present pyridazine formation reaction.[12,13] Steric hindrance owing to phenyl group in the transition state of such [4+2] cycloaddition reaction might be the reason why the reaction of **2** with 1-phenyl-1,3-butanedione (X= Ph) proceeds sluggishly.



Scheme 3

In conclusion, hydrazones (**2**) readily obtained from aldehyde dimethylhydrazones were found to react with acetylacetone as well as ethyl acetoacetate without any additive to afford the corresponding trifluoromethylpyridazines (**4** and **5**) in high yields. Mechanistic study for the present cyclization reaction and examinations in order to synthesize another type of fluorine-containing heterocycles starting from hydrazones (**2**) are now in progress.

EXPERIMENTAL

Melting points were determined with a Mitamura Riken model 7-12 apparatus and uncorrected. ^1H NMR spectra were recorded at 60 MHz on a JEOL PMX 60SI. All NMR spectra were measured in $CDCl_3$

containing TMS as an internal standard. IR spectra were taken with a Hitachi model G3. 3-Hydrazono-1,1,1-trifluoro-2-alkanones (**2a - c**) were prepared according to a literature method.[5,9]

Typical procedure for the reaction of 2 with dicarbonyl compounds (acetylacetone, ethyl acetoacetate, and 1-phenyl-1,3-butanedione) in the presence of NH_4OAc

To a mixture of **2a** (345 mg, 1.5 mmol) and acetylacetone (180 mg, 1.8 mmol) was added NH_4OAc (25 mg, 0.324 mmol). The mixture was heated for 16 h at 110°C in a sealed tube. After cooling, the mixture was pored into CH_2Cl_2 (100 mL), and the whole mixture was washed with water (100 mL) and dried over Na_2SO_4. Removal of the solvent and fractionation of the residual materials by preparative TLC (benzene / EtOAc = 7 / 3) afforded 251 mg (57%) of 1-(3-methyl-6-*p*-tolyl-5-trifluoromethylpyridazin-4-yl)ethanones (**4a**).

In the cases of the reactions using ethyl acetoacetate and 1-phenyl-1,3-butanedione, the raw products were purified by preparative TLC (benzene / EtOAc = 9 / 1).

The reactions in the absence of NH_4OAc (Entries 8 and 9) were carried out quite similarly without addition of NH_4OAc.

In the case of the reaction under basic conditions (Entry 7), di(*iso*propyl)ethylamine (50 mg, 0.387 mmol) was used instead of NH_4OAc.

Typical procedure for the reaction of 2a with acetylacetone at 20°C under basic conditions

To a solution of **2a** (345.3 mg, 1.5 mmol) and acetylacetone (180 mg, 1.8 mmol) in MeCN (4.5 mL) was added di(*iso*propyl)ethylamine (233 mg, 1.8 mmol), and the mixture was stirred for 20 h at 20°C. The reaction mixture was poured into CH_2Cl_2 (100 mL), and the whole mixture was washed with water (100 mL) and dried over Na_2SO_4. After removal of the solvent, **2a** (323.1 mg, 1.404 mmol) was recovered (Entry 6).

In the case of Entry 5, the reaction was carried out quite similarly with the use of KOH (85%, 99 mg, 1.5 mmol) and DMF (4.5 mL) instead of di-(*iso*propyl)ethylamine and MeCN, respectively. After workup, **2a** (319.5 mg, 1.388 mmol) was recovered.

General procedure for the reaction of 2 with dicarbonyl compounds (acetylacetone, ethyl acetoacetate, and 1-phenyl-1,3-butanedione) in toluene

A mixture of **2a - c** (1.5 mmol) and dicarbonyl compounds (1.8 mmol) dissolved in toluene (3 mL) was stirred for 24 h under reflux. Removal of the solvent and fractionation of the residual materials by preparative TLC (benzene / EtOAc = 7 / 3 for **4a - c**, and benzene / EtOAc = 9 / 1 for **5a - c** and **6a**) gave the corresponding pyridazines (**4a - c**, **5a - c**, and **6a**).

1-(3-Methyl-6-*p*-tolyl-5-trifluoromethylpyridazin-4-yl)ethanone (4a): colorless crystals (cyclo-

hexane), mp 130.5 - 131.0°C: ^{1}H NMR δ 2.43 (s, 3H, *p*- C**H**$_3$C$_6$H$_4$), 2.60 (s, 3H, COCH$_3$), 2.76 (s, 3H, 3-CH$_3$), 7.20 - 7.63 (q, *J*= 8.6 Hz, 4H, *p*- CH$_3$C$_6$**H**$_4$); IR (KBr) ν 1717 (s, C=O), 1393 (s), 1364 (s), 1210 (m), 1171, 1151 (s, CF$_3$) cm^{-1}. *Anal*. Calcd for $C_{15}H_{13}N_2OF_3$: C, 61.22; H, 4.45; N, 9.52; F, 19.37. Found: C, 61.04; H, 4.63; N, 9.51; F, 19.16.

1-[6-(4-Methoxyphenyl)-3-methyl-5-trifluoromethylpyridazine-4-yl]ethanone (4b): pale brown crystals (cyclohexane), mp 126.0 -126.5°C: ^{1}H NMR δ 2.57 (s, 3H, COCH$_3$), 2.73 (s, 3H, 3-CH$_3$), 3.85 (s, 3H, OCH$_3$), 7.06, 7.56 (d, *J*= 8.8 Hz, 4H, *p*-CH$_3$OC$_6$**H**$_4$); IR (KBr) ν 1710 (s, C=O), 1391 (s), 1366 (m), 1250 (s), 1210 (s), 1174, 1141 (s, CF$_3$) cm^{-1}. *Anal*. Calcd for $C_{15}H_{13}N_2O_2F_3$: C, 58.07; H, 4.22; N, 9.03. Found: C, 58.33; H, 4.07; N, 8.78.

1-[6-(4-Chlorophenyl)-3-methyl-5-trifluoromethylpyridazine-4-yl]ethanone (4c): pale brown crystals (cyclohexane), mp 111.0 - 111.5°C: ^{1}H NMR δ 2.60 (s, 3H, COCH$_3$), 2.76 (s, 3H, 3-CH$_3$), 7.47 (s, 4H, *p*-ClC$_6$H$_4$); IR (KBr) ν 1720 (s, C=O), 1394 (s), 1361 (s), 1206 (s), 1176, 1142 (s, CF$_3$) cm^{-1}. *Anal*. Calcd for $C_{14}H_{10}N_2OClF_3$: C, 53.43; H, 3.20; N, 8.90. Found: C, 53.29; H, 3.16; N, 8.82.

Ethyl 3-methyl-6-*p*-tolyl-5-trifluoromethylpyridazine-4-carboxylate (5a): pale brown crystals (*n*-hexane), mp 68.5 - 69.0°C: ^{1}H NMR δ 1.42 (t, *J*= 7.2 Hz, 3H, CH$_2$C**H**$_3$), 2.43 (s, 3H, *p*-C**H**$_3$C$_6$H$_4$), 2.86 (s, 3H, 3-CH$_3$), 4.52 (q, *J*= 7.2 Hz, 2H, C**H**$_2$CH$_3$), 7.21 – 7.68 (q, *J*= 8.1 Hz, 4H, *p*-CH$_3$C$_6$**H**$_4$); IR (KBr) ν 1748 (s, C=O), 1396 (s), 1309 (m), 1236 (s), 1182, 1135 (s, CF$_3$) cm^{-1}. *Anal*. Calcd for $C_{16}H_{15}N_2O_2F_3$: C, 59.26; H, 4.66; N, 8.64; F, 17.57. Found: C, 59.28; H, 4.61; N, 8.57; F, 17.46.

Ethyl 6-(4-methoxyphenyl)-3-methyl-5-trifluoromethylpyridazine-4-carboxylate (5b): pale brown crystals (cyclohexane), mp 56.5 - 57.5°C: ^{1}H NMR δ 1.38 (t, *J*= 7.2 Hz, 3H, CH$_2$C**H**$_3$), 2.85 (s, 3H, 3-CH$_3$), 3.87 (s, OCH$_3$), 4.53 (q, *J*= 7.2 Hz, 2H, C**H**$_2$CH$_3$), 7.10, 7.64 (d, *J*= 8.4 Hz, 4H, *p*-CH$_3$OC$_6$**H**$_4$); IR (KBr) ν 1744 (s, C=O), 1395 (s), 1233 (s), 1185, 1138 (s, CF$_3$) cm^{-1}. *Anal*. Calcd for $C_{16}H_{15}N_2O_3F_3$: C, 56.47; H, 4.44; N; 8.23. Found: C, 56.26; H, 4.53; N, 7.97.

Ethyl 6-(4-chlorophenyl)-3-methyl-5-trifluoromethylpyridazine-4-carboxylate (5c): colorless crystals (cyclohexane), mp 87.5 - 89.0°C: ^{1}H NMR δ 1.40 (t, *J*= 7.2 Hz, 3H, CH$_2$C**H**$_3$), 2.87 (s, 3H, 3-CH$_3$), 4.56 (q, *J*= 7.2 Hz, 2H, C**H**$_2$CH$_3$), 7.57 (s, 4H, *p*-ClC$_6$H$_4$); IR (KBr) ν 1747 (s, C=O), 1392 (s), 1243 (s), 1182, 1140 (s, CF$_3$) cm^{-1}. *Anal*. Calcd for $C_{15}H_{12}N_2O_2ClF_3$: C, 52.26; H, 3.51; N, 8.13. Found: 52.28; H, 3.56; N, 8.08.

(3-Methyl-6-*p*-tolyl-5-trifluoromethylpyridazin-4-yl)phenylmethanone (6a): yellow oil, bp 160°C/3 torr (oven temperature of Kugelrohr): ^{1}H NMR δ 2.43 (s, 3H, *p*-C**H**$_3$C$_6$H$_4$), 2.62 (s, 3H, 3-CH$_3$), 7.16 - 7.87 (m, 9H, *p*-CH$_3$C$_6$**H**$_4$ and Ph); IR (KBr) ν 1675 (s, C=O), 1385 (s), 1263 (s), 1174, 1139 (s, CF$_3$) cm^{-1}. *Anal*. Calcd for $C_{20}H_{15}N_2OF_3$: C, 67.41; H, 4.24; N, 7.86. Found: C, 67.59; H, 4.55; N, 7.63.

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8. Hydrazones (**2**) could not be obtained by direct trifluoroacetylation of aldehyde hydrazones ($H_2NN=CHR$) because of exclusive trifluoroacetylation at terminal nitrogen. Therefore it was necessary to prepare **2** from aldehyde dialkylhydrazones *via* diketone (**1**).
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11. Frequency of the C=O absorption band in IR spectra of **6a** being 42 cm^{-1} lower than that of **2a** reveals that **6a** is (3-methyl-6-*p*-tolyl-5-trifluoromethylpyridazin-4-yl)phenylmethanone and not 1-(3-phenyl-6-*p*-tolyl-5-trifluoromethylpyridazin-4-yl)ethanone.
12. On the basis of the density functional calculation (pBP/DN**), the activation energy for [4+2] cycloaddition of **2** (R=Ph) with enolized acetylacetone (Scheme 3) was estimated as 32 Kcal/mol. Calculations were accomplished using the computer program package PC SPARTAN pro (Wavefunction, Inc). About pBP/DN**, see: A. D. Becke, *Phys. Rev. A*, 1988, **38**, 3089; J. P. Perdew, *Phys. Rev. B*, 1986, **33**, 8822.
13. Our calculations predict that inverse demand type hetero Dield-Alder reaction should occur between **2** (R= Ph) and acetylacetone enol. Optimized orbital fitting of HOMO of acetylacetone enol with LUMO of **2** suggests the regiochemistry of the transition state structure shown in Scheme 3.