Tetrahedron Letters, Vol. 34, No. 32, pp. 5135-5138, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

A FACILE AND CONVENIENT SYNTHESIS OF 5-TRIFLUOROMETHYL-4-PYRIDAZINONES FROM ALDEHYDE DIALKYLHYDRAZONES

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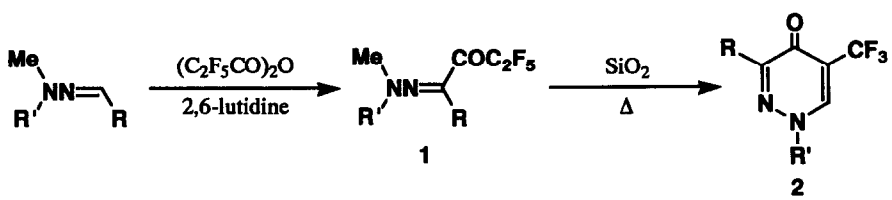
Summary: Several 5-trifluoromethyl-4-pyridazinones were conveniently synthesized by silica gel-mediated cyclization reaction of 1,1,1,2,2-pentafluoroalkan-3,4-dione 4-dialkylhydrazones prepared from aldehyde dialkylhydrazones and pentafluoropropionic anhydride.

Pyridazinone and its derivatives are attractive compounds because of their potential biological activities, and, indeed, some of 4-pyridazinones are used as herbicides.[1] In the course of an extension of our work concerning electrophilic substitution reaction at azomethine carbon atom,[2,3] we found that 1,1,1,2,2-pentafluoroalkan-3,4-dione 4-dialkylhydrazones (**1**) are easily prepared from aldehyde dialkylhydrazones and pentafluoropropionic anhydride, and silica gel-mediated novel cyclization reaction of **1** affords 5-trifluoromethyl-4-pyridazinones (**2**). Now we wish to communicate the facile and convenient synthesis of these new fluorine-containing pyridazinones **2** which are of interest from the view point of pharmacological activity because of their CF_3 functionality.[4]

Quite similarly to the case of previously reported synthesis of 1,1,1-trifluoroalkan-2,3-dione 3-dialkylhydrazones (**1'**), **1** is easily obtainable from aldehyde dialkylhydrazones with the use of pentafluorpropionic anhydride as an acylating reagent instead of trifluoroacetic anhydride for **1'**. Thus obtained **1** adsorbed on silica gel was heated at 70–90°C to give 1-alkyl-5-trifluoromethyl-4-pyridazinones (**2 a - l**) in moderate to good yields. The results are summarized in Table I, in which the yields under optimum conditions are shown. In particular, the reaction of the aliphatic



1 **2**

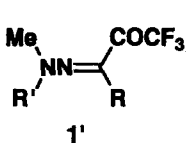
derivatives **1 h - l** proceeded very cleanly to afford the corresponding pyridazinones **2 g - l**, respectively, in excellent yields. On the other hand, some of the aromatic derivatives gave small amounts of by-products together with **2**. For instance, that from the reaction of the dimethylhydrazone **1 d** was the 1-methyl-4-pentafluoroethylimidazole **3 b**(R= *p*-ClC_6H_4)[5] and that from the reaction of the *t*-butyl(methyl)hydrazone **1 f** was 5-pentafluoroethyl-3-oxazoline **4 b**(R= *p*-MeC_6H_4).[6] Formation of these heterocycles are compatible with our previous findings that, under the same conditions, the 1,1,1-trifluoroacetyl derivative **1 a'** afforded mainly the1-methyl-4- trifluoromethyl-

Table I Cyclization Reaction of **1** to **2**.

	Product R	R'	Temp °C	Time h	Yield[a] %	mp[b] °C	^{1}H NMR[c] δ, ppm
2a	Ph	Me	80	24	74	167.0 - 168.0	3.90 (s, 3H, NMe), 7.17 - 7.50 (m, 3H, Ar), 7.85 - 8.15, 7.95 (m and s, 3H, Ar and CH)
2b	*p*-MeC_6H_4	Me	80	24	66	190.5 - 191.5	2.36 (s, 3H, ArMe), 3.92 (s, 3H, NMe), 7.15, 7.98 (d, *J*= 8.2 Hz, 4H, Ar), 7.95 (s, 1H, CH)
2c	*p*-$MeOC_6H_4$	Me	70	24	64	146.0 - 146.5	3.79 (s, 3H, OMe), 3.92 (s, 3H, NMe), 6.86, 8.11 (d, *J*= 8.2 Hz, 4H, Ar), 7.94 (s, 1H, CH)
2d	*p*-ClC_6H_4	Me	80	24	48	189.1 - 190.0	3.93 (s, 3H, NMe), 7.26 (d, *J*= 8.2 Hz, 2H, Ar), 7.92, 8.00 (s and d, 3H, CH and Ar)
2e	*o*-MeC_6H_4	Me	80	24	85	131.5 - 132.0	2.24 (s, 3H, ArMe), 3.81 (s, 3H, NMe), 7.20 (s, 4H, Ar), 8.08 (s, 1H, CH)
2f	*p*-MeC_6H_4	*t*-Bu	70	48	72	147.0 - 148.0	1.65 (s, 9H, *t*-Bu), 2.38 (s, 3H, ArMe), 7.21, 8.10 (d, *J*= 8.2 Hz, 4H, Ar), 8.23 (s, 1H, CH)
2g	Et	*t*-Bu	90	6	96	170/3 Torr[d]	1.22 (t, *J*= 7.2 Hz, 3H, Me), 1.62 (s, 9H, *t*-Bu), 2.80 (q, 2H, CH_2), 8.19 (s, 1H, CH)
2h	*n*-C_7H_{15}	*t*-Bu	90	6	99	185/3 Torr[d]	0.66 - 1.70 (m, 11H, $(CH_2)_4Me$), 1.62 (s, 9H, *t*-Bu), 2.67 (t, *J*= 7.4 Hz, 2H, CH_2), 8.17 (s, 1H, CH)
2i	*i*-Pr	*t*-Bu	90	6	98	59.5 - 60.0	1.21 (d, *J*= 7.0 Hz, 6H, Me), 1.60 (s, 9H, *t*- Bu), 3.50 (hept, 1H, CHMe), 8.10 (s, 1H, CH)

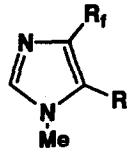
[a] Yields refer to pure isolated compounds. [b] Uncorrected, measured with a Mitamura Riken model 7-12 apparatus. [c] Recorded at 60 MHz on a JEOL PMX 60SI. [d] Oven temperature of Kugelrohr distillation.

imidazole **3 a**,[7] and **1 b'** gave 5-trifluoromethyl-3-oxazoline **4 a**[8] exclusively. However, it is noteworthy that none of pyridazinones occurred in the reactions using the trifluoroacetyl derivatives **1 a'** and **1 b'** as the substrates. This critical difference in reactivity between **1** and **1'** indicates the C-F bonds of the CF_2 group between two electronegative groups CO and CF_3 of **1** are more active than those of the CF_3 group of **1'**.

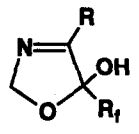


1'

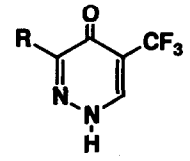
R' ; Me **1a'**
t-Bu **1b'**



R_f ; CF_3 **3a**
C_2F_5 **3b**



R_f ; CF_3 **4a**
C_2F_5 **4b**



R ; *p*-Tol **2j**
Et **2k**
n-C_7H_{15} **2l**
i-Pr **2m**

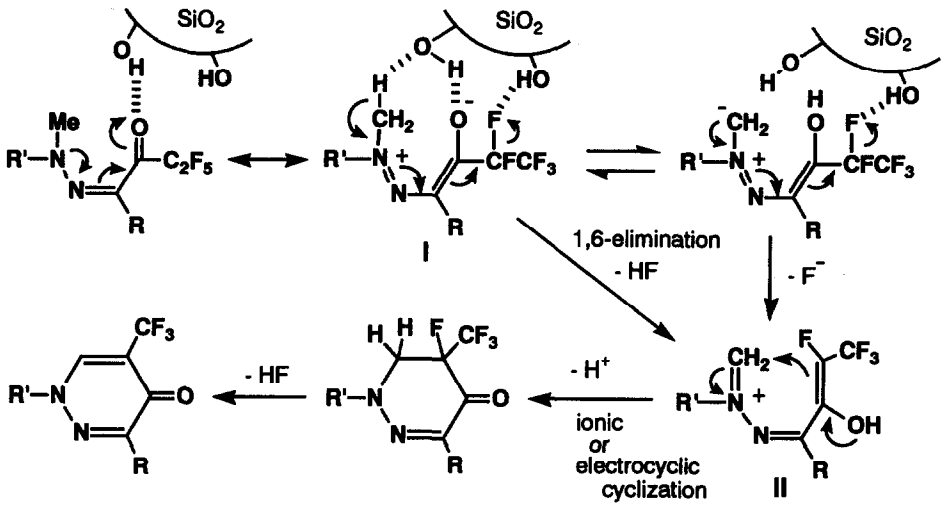
In a typical experiment, a mixture of *p*-tolualdehyde dimethylhydrazone (10 mmol) and 2,6-lutidine (20 mmol) in dry $CHCl_3$ (35 ml) was cooled in an ice bath and, then, pentafluoropropionic anhydride (20 mmol) in dry $CHCl_3$ (5 ml) was added dropwise. After 5h, the mixture was diluted with CH_2Cl_2 (100 ml), and the whole mixture was washed successively with 0.5 N aq. HCl, water, and 1 N aq. Na_2CO_3. The mixture was dried (Na_2SO_4) and the solvent was removed. The residue was recrystallized from *n*-hexane to afford **1 b**[9] in 88% yield. Thus obtained **1 b** (2 mmol) dissolved in CH_2Cl_2 (2 ml), silica gel (6 g: Wakogel C300 after predrying for 3h at 180°C under vacuum) was well mixed, and the CH_2Cl_2 was evaporated to dryness. In an N_2-replaced reaction vessel the mixture was maintained at 90°C for 6 h. The reaction mixture was washed thoroughly with ethyl acetate and silica gel was filtered off. The solvent was removed from the filtrate and fractionation of the residue by silica gel column chromatography afforded **2 b**[10] in 66% yield.

The structures of **2 a - l** were confirmed by IR and ^1H and ^{13}C NMR spectra and micro combustion analysis. In the ^1H and ^{13}C NMR spectra of **2 b**, the pyridazinone ring proton appeared at δ 7.95, and pyridazinone ring C_3, C_4, C_5 and C_6 at δ 155.5, 164.9, 115.1 (q, $^2J_{CF}$= 30.5 Hz), and 141.4 (q, $^3J_{CF}$= 6.1 Hz), respectively.

In the present cyclization reaction, silica gel apparently plays an important role, because the reactions carried out in the absence of silica gel gave none or meager amounts of these pyridazinones. Although sufficient data are not yet available to elucidate the reaction mechanism, one of the possible mechanisms is illustrated in Scheme 1, where silica gel should act as a proton donor toward carbonyl oxygen to stabilize the polarized form (I) and facilitate 1,6-elimination of HF from I to give II.

Finally, *N*-*t*-butyl groups of **2f - l** can be easily removed by heating them at 60°C in 20 N aq. H_2SO_4 to afford **2j - m** in high yields (**2 j**: 84%, **2 k**: 74%, **2 l**: 82%, **2 m**: 94%).

In conclusion, the present cyclization reaction provides a very convenient 3-step synthetic method accessing 5-trifluoromethyl-4-pyridazinones from various aldehydes.



Scheme 1

References and Notes

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5. **3b**: ^{1}H NMR ($CDCl_3$) δ 3.40 (s, 3H, Me), 7.03 - 7.56, 7.49 (q and s, 5H, ArH and CH). *Anal.* Calcd for $C_{12}H_8N_2ClF_5$: C, 46.40; H, 2.60; N, 9.02. Found C, 46.21; H, 2.75; N, 8.96.
6. **4b**: ^{1}H NMR ($CDCl_3$) δ 2.36 (s, 3H, Me), 5.43 (s, 2H, CH_2), 5.70 - 6.20 (br, 1H, OH). *Anal.* Calcd for $C_{12}H_{10}NO_2F_5$: C, 48.82; H, 3.41; N, 4.74; F, 32.18. Found C, 48.70; H, 3.47; N, 4.75; F, 32.21.
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9. **1b**: IR (KBr) 2855 (m), 1652 (s), 1535 (s), 1325 (s), 1222 (s), 1197 (s), 1181 (s), 1122 (s), 1005 (s), 786 (s), 735 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.33 (s, 3H, Me), 3.00 (s, 6H, NMe), 7.01 (s, 4H, ArH).
10. **2b**: IR (KBr) 3040 (m), 1590 (s), 1365 (s), 1340 (s), 1325 (s), 1292 (s), 1208 (s), 1130 (s), 1062 (s), 829 (m), 668 (m) cm^{-1}. *Anal.* Calcd for $C_{13}H_{11}N_2OF_3$: C, 58.21; H, 4.13; N, 10.44; F, 21.25. Found C, 58.06; H, 4.14; N, 10.41; F, 21.37.

(Received in Japan 16 April 1993; accepted 8 June 1993)