# CONVENIENT AND SELECTIVE SYNTHESIS OF 4-TRIFLUOROMETHYLIMIDAZOLES

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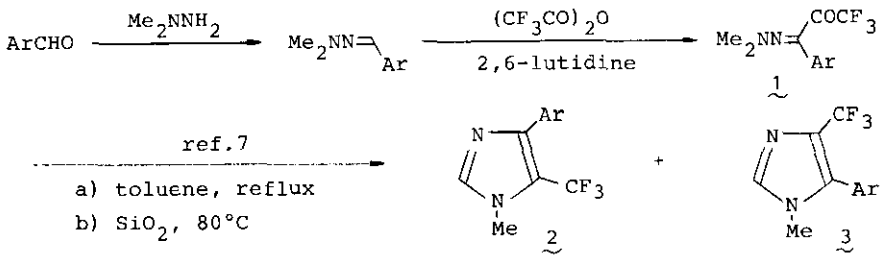
Abstract- Thermally induced cyclization of 3-aryl-1,1,1-trifluoropropane-2,3-dione 2-dimethylhydrazones (5) which can be readily prepared from corresponding arenecarbaldehydes afforded selectively the title compounds (3) in high yields without formation of the regioisomers.

Fluorine-containing heterocycles have increasingly attracted attention of many workers in medicinal and agricultural fields because of their potential biological activity,[1] and development of effective new methods for construction of these compounds is nowadays one of the most important theme of many organic chemists. In these two or three years we have been engaged in the investigation of a series of novel cyclization reactions of trifluoroacetylated dialkylhydrazones leading to various fluorine-containing heterocycles.[2-9]




In the course of these studies interesting facts were observed[2,3] that trifluoroacetylated dimethylhydrazones (1) in refluxing toluene affords predominantly 5-trifluoromethylimidazoles (2) together with a little amounts of their regioisomeric 4-trifluoromethylimidazoles (3), while a mixture of major (3) and minor (2) is obtained when 1 is adsorbed on silica gel and heated at 80°C.[7] This discriminative selectivity attracted our interest and prompted us to synthesize 3 selectively starting from the other new isomeric hydrazones (5).

α-Diketones (4) were readily obtained as monohydrates by acid catalyzed hydrolysis of 1.[2] Addition of 1,1-dimethylhydrazine to 4 immediately gave adducts (4').[10] Unexpectedly these adducts

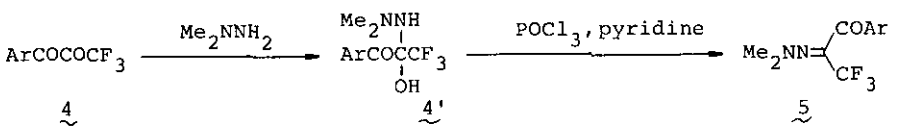


Table 1. Synthesis of 4' and 5.

| Ar | Yield, %[a] | | $^1$H nmr[b] |
|---|---|---|---|
| | 4' | 5 | δ ppm |
| p-$MeOC_6H_4$ | 100 | 59 | 2.98(s, 6H, NMe), 3.84(s, 3H, OMe), 6.89, 7.79(d, J= 9Hz, 4H, Ar) |
| p-Tol | 100 | 83 | 2.40(s, 3H, Me), 2.99(s, 6H, NMe), 7.23, 7.71(d, J= 8Hz, 4H, Ar) |
| Ph | 99 | 81 | 2.99(s, 6H, Me), 7.16-7.90(m, 5H, Ar) |
| p-$ClC_6H_4$ | 99 | 91 | 3.01(s, 6H, NMe), 7.34, 7.71(d, J= 8Hz, 4H, Ar) |
| p-$O_2NC_6H_4$ | 85[c] | 66[d] | 3.09(s, 6H, Me), 7.92, 8.25(d, J= 8Hz, 4H, Ar) |
| o-$MeC_6H_4$ | 100 | 71 | 2.54(s, 3H, Me), 3.07(s, 6H, NMe), 7.00-7.65(m, 4H, Ar) |
| 1-naphthyl | 87 | 52 | 3.08(s, 6H, Me), 7.25-8.05(m, 7H, Ar) |

[a] Isolated yields from 4 in both cases. [b] $^1$H Nmr spectra were recorded at 60 MHz on a JEOL PMX60SI spectrometer using $CDCl_3$ as solvent. [c] Reaction was carried out at 0°C and completed within 30 sec. In this case, obtained 4' was unstable and spontaneously transformed back to 1. Thus freshly prepared 4' was immediately submitted to subsequent reaction leading to 5. [d] Yield is based on $^1$H nmr spectra of crude product. Together with 5, about 15% of 1 was observed in it. Attempted purification of 5 by distillation or column chromatography resulted in formation of some 3 and 1.

gradually and in some cases very rapidly changed back to hydrazones (1) on standing at room temperature. This undesirable reaction was accelerated by the presence of acids such as acetic acid which was used as an effective catalyst for the hydrazone formation. Consequently several attempts to dehydrate 4' gave a mixture of expected 5 and 1. After many trials we found treatment of freshly prepared 4' with $POCl_3$ in the presence of pyridine affords 5 in satisfactory yields. In a typical experiment, 4 (Ar: p-Tol, 2 mmol) in dry $CH_2Cl_2$ (2 ml) was cooled in an ice bath and, then, 1,1-dimethylhydrazine (2.2 mmol) was added dropwise. After stirring for 10 min, the reaction mixture was dried ($MgSO_4$) and $CH_2Cl_2$ was removed in vacuo to afford 4' (Ar: p-Tol). This adducts (4') was then immediately dissolved in dry $CHCl_3$ under nitrogen and with cooling in an ice bath. Dry pyridine (8.8 mmol) and $POCl_3$ (2.4 mmol) were then added and the mixture was warmed to ambient temperature and stirred for 1 h. After addition of $CH_2Cl_2$ (ca. 50 ml), the reaction mixture was poured into 1N HCl (50 ml) and the organic layer was successively washed with water and 10% aq. $Na_2CO_3$. The organic layer was dried over $Na_2SO_4$ and the solvent was removed to give 3-(p-tolyl)-1,1,1-trifluoropropane-2,3-dione 2-dimethylhydrazone (5) (Ar: p-Tol) in 88% yield. Quite similarly several trifluoromethylated hydrazones (5) were successfully prepared (Table 1). Structures of 5 were confirmed by $^1$H nmr and ir spectra, and microcombustion analysis.[11]

Cyclization of 5 to 3 was performed by refluxing it in toluene. For instance, 5 (Ar: Ph, 1 mmol) dissolved in toluene (20 ml) was refluxed for 2 days under nitrogen. Removal of the solvent in vacuo afforded 1-methyl-5-phenyl-4-trifluoromethylimidazole (3) (Ar: Ph) in 93% yield. In other cases in Table 2, corresponding 3 were also obtained in high yields.[12] Worth noting

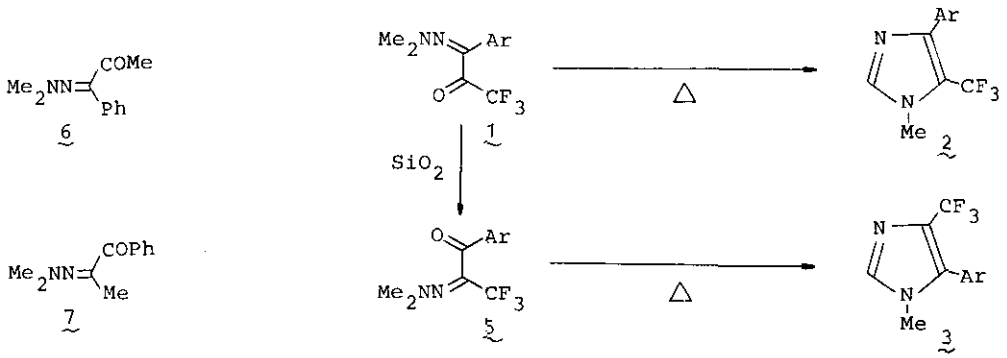
Table 2. Cyclization of 5 to 3.

| Ar | Yield[a] % | mp °C | $^1$H nmr[b] δ, ppm |
|---|---|---|---|
| p-$MeOC_6H_4$ | 96 | 101 | 3.53(s, 3H, NMe), 3.90(s, 3H, OMe), 6.85-7.35(q, J= 9Hz, 4H, Ar), 7.40(s, 1H, CH) |
| p-Tol | 98 | 88 | 2.38(s, 3H, Me), 3.43(s, 3H, NMe), 7.11(s, 4H, Ar), 7.37(s, 1H, CH) |
| Ph | 93 | 110/$_{1Torr}$[c] | 3.43(s, 3H, Me), 7.13-7.50(m, 6H, Ar and CH) |
| p-$ClC_6H_4$ | 82 | 71 | 3.46(s, 3H, Me), 7.06-7.50, 7.46(q and s, J= 8Hz, 5H, Ar and CH) |
| p-$O_2NC_6H_4$ | 52[d] | 150/$_{5Torr}$[c] | 3.54(s, 3H, Me), 7.57, 7.50(s and d, J= 9Hz, 3H, CH and Ar), 8.30(d, J= 9Hz, 2H, Ar) |
| o-$MeC_6H_4$ | 84 | 160/$_{4Torr}$[c] | 2.07 (s, 3H, Me), 3.30(s, 3H, NMe), 7.01-7.45(m, 4H, Ar), 7.49(s, 1H, CH) |
| 1-naphthyl | 63 | 115 | 3.24(s, 3H, Me), 7.20-8.04, 7.58(m and s, 8H, Ar and CH) |

[a] Isolated yield from 5. [b] $^1$H Nmr spectra were recorded at 60 MHz on a JEOL PMX60SI spectrometer using $CDCl_3$ as solvent. [c] Oven temperature of Kugelrohr distillation. [d] Yield calculated from α-diketone (4).

here is formation of none of the regioisomers (2) in any cases. This result is in strong contrast with the thermal cyclization of 1 in the same condition affording 2 as major products with some 3. Identification of 2 was easily performed by comparison of their $^1$H nmr and ir spectra with those of authentic samples prepared by previously reported manner using silica gel as catalyst.[7]

This highly selective conversion of 5 to 3 strongly suggests that the formation of 3 from 1 in our previously reported[7] cyclization of 1 on the surface of silica gel is due to prior isomerization of 1 to 5 in precedence to the cyclization. As for this isomerization, we could not get direct evidence for the intervention of 5. However this view was supported by our recent finding that an analogous isomerization of 6 to 7 occurs with the aid of silica gel as catalyst, though it is a much slower process compared to the case of 1 to 5. Therefore it may be concluded as shown in Scheme 1 that 1 and 5 are thermally cyclized to 2 and 3, respectively, by a common mechanism and when silica gel is used as a catalyst[13] most of 1 is isomerized to 5 before this cyclization.




Scheme 1

Further mechanistic studies for this cyclization is now in progress and will be reported in near future.

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10. $^1$H Nmr ($CCl_4$) δ 2.27 (s, 9H, NMe and ArMe), 3.20-3.50, 5.10-5.50 (br, 2H, NH and OH), 7.19, 8.28 (d, J= 8Hz, 4H, Ar).
11. 5 (Ar:p-Tol): Ir (KBr) 1645 (s), 1600 (s), 1560 (m), 1302 (m), 1237 (m), 1100 (s), 1024 (m), 930 (m) $cm^{-1}$. Anal. Calcd for $C_{12}H_{13}N_2OF_3$: C, 55.81; H, 5.07; N, 10.85; F, 22.07. Found C, 55.61; H, 4.99; N, 10.78; F, 22.32.
12. Structure of 3 was confirmed by comparison of their $^1$H nmr and ir spectral data with authentic samples prepared from 1 by our previously reported method using silica gel (see ref. 7), and some of new compounds were defined by $^1$H nmr and ir spectra and micro combustion analysis. For instance, 3 (Ar: o-Tol): Ir (KBr) 1504 (s), 1403 (s), 1268 (m), 1216 (m), 1171 (s), 1145 (s), 1114 (s), 966 (s), 781 (S), 778 (m), 665 (m) $cm^{-1}$. Anal. Calcd for $C_{12}H_{11}N_2F_3$: C, 60.00; H, 4.62; N, 11.66. Found C, 59.67; H, 4.66; N, 11.38.
13. Even in the absence of silica gel isomerization of 1 to 5 seems to occur in some part, because simple thermal reaction (without silica gel) of 1 afforded a small amount of 3 as a by-product. See ref. 7.


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