# 4- and 5-Trifluoromethylimidazoles. Novel Cyclization of Trifluoroacetylated Aldehyde Dimethylhydrazones

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Thermally induced cyclization reaction of trifluoroacetylated arylaldehyde dimethylhydrazones **1** in refluxing toluene afforded 1-methyl-4-aryl-5-trifluoromethylimidazoles **2** in good yields. In contrast thermal cyclization of **1** in the presence of silica gel gave regioisomeric 1-methyl-4-trifluoromethyl-5-aryl-imidazoles **5** as major products. These reactions could be extended to the syntheses of related several 1,4,5-trisubstituted imidazoles.

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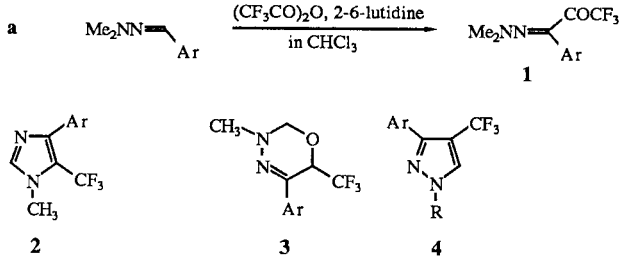
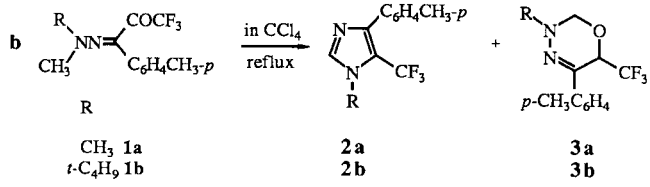
For the last few years we have been engaged in the investigation of electrophilic substitution reaction at azomethine carbon atoms of aldehyde hydrazones [1,2]. For example, dimethylhydrazones of a number of aromatic aldehydes were successfully acylated at their azomethine carbon atoms with trifluoroacetic anhydride (TFAA) to give the corresponding trifluoroacetylated hydrazones **1** in high yields [1]. In the course of an extension of this work it was found that there took place three different types of




interesting cyclization reactions of **1**. The first is a thermally induced cyclization which affords 3-methyl-5-aryl-6-trifluoromethyl-3,6-dihydro-2*H*-1,3,4-oxadiazines **3** as a major product together with 1-methyl-4-aryl-5-trifluoromethylimidazoles **2** as a minor one [1]. The second is a silica gel catalyzed cyclization (no solvent, rt) of **1** to give **3** as a sole product [3]. The last one which was found most recently is a TFAA-pyridine mediated cyclization of **1** to afford 1-alkyl-3-aryl-4-trifluoromethylpyrazoles **4** [4]. Fluorine containing heterocycles, in spite of their synthetic difficulties by conventional methods in fair yields, have attracted particular interests of many organic chemists because of their potentially high physiological activities [5]. As for ourselves the above mentioned cyclizations of **1** seemed quite attractive, by which syntheses of several different types of heterocycles bearing the trifluoromethyl group can be readily achieved starting from commercially available aldehydes by only three steps. Since we already succeeded in selective conversion of **1** to oxadiazine derivatives **3** [3] and pyrazoles **4** [4], the next target is to establish a method for selective cyclization of **1** to imidazoles **2** in high yields. This situation prompted us to study thermally induced cyclization of **1** leading to **2** in more detail. We now wish to report here the results.

As reported in our preceding paper [1] the major product of thermal reaction of **1** in refluxing carbon tetrachloride for 16 ~ 114 hours is dihydro-2*H*-oxadiazine **3**. This thermal reaction was reexamined in more detail with the use of **1a** under several conditions. After 4 days in refluxing carbon tetrachloride, **1a** was converted to the corresponding imidazole **2a** and oxadiazine **3a** in a ratio

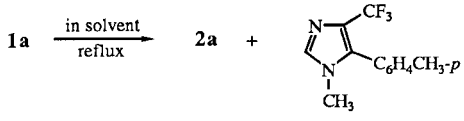



of 39:61. The cyclization of *t*-butyl methyl derivative **1b** under the same reaction conditions proceeded more slowly and, in contrast to the case of **1a**, afforded the corresponding **2b** and **3b** in a ratio of 83:17, where imidazole **2b** became the major product. This is presumably due to enhanced steric hindrance, and dihydrooxadiazine formation may be particularly sensitive to it. In fact, silica gel catalyzed cyclization of **1b** to **3b** proceeded very slowly [3] compared to the case of **1a** to **3a**. Then we examined this thermal cyclization reaction of **1a** in a variety of solvents under reflux conditions. Interestingly, as is shown in Table 1, reactions carried out in the solvents of higher boiling points (> 100°, entries 5, 6) did not afford **3a**, and in polar solvents (entries 4, 5) in contrast to the cases of non-polar solvents (entries 1, 3) formation of **3a** was also suppressed completely. In these cases yields of **2a** much increased and at the same time unexpected 4-trifluoromethylimidazole **5a**, the regioisomer of **2a**, was also produced as a minor product. The structure of **5a** was con-

firmed by ir, $^1$H- and $^{13}$C-nmr spectra, and micro combustion analysis. In acetonitrile (entry 4) appreciable amounts of 1,2-diketone **6** was obtained together with imidazoles **2a** and **5a**. The reaction carried out in toluene gave the best yields of imidazoles, which were 8:2 regioisomeric mixture of **2a** and **5a**.

Table 1

Thermal Cyclization of Dimethylhydrazone **1a** in Various Solvents [a]




**5a**

\+ **3a** + *p*-$CH_3C_6H_4COCOCF_3$

**6**

| Entry | Solvent [c] | Recovery of **1a** | Ratio (%) [b] **2a** | **5a** | **3a** | **6** [d] |
|---|---|---|---|---|---|---|
| 1 | $CCl_4$ | 0 | 39 | 0 | 61 | 0 |
| 2 | $C_6H_6$ | 36 | 10 | 7 | 26 | 21 |
| 3 | *n*-$C_7H_{16}$ | 0 | 28 | 0 | 72 | 0 |
| 4 | $CH_3CN$ | 0 | 62 | 18 | 0 | 20 |
| 5 | DME [e] | 0 | 64 | 36 | 0 | 0 |
| 6 | $CH_3C_6H_5$ | 0 | 80 | 20 | 0 | 0 |

[a] Under a nitrogen atmosphere **1a** (0.5 mmole) in the solvent (10 ml) was refluxed for 2 days. [b] The product ratio was calculated on the basis of the $^1$H-nmr spectra. [c] All solvents were dried over molecular sieves 3A, 1/16 before use. [d] This compound was obtained as a monohydrate at the trifluoroacetyl carbonyl group. [e] Reaction was carried out in sealed tube at 120°.

The cyclization of a series of substrates **1c-f** in refluxing toluene afforded the corresponding imidazoles **2c-f** and **5c-f** (equation 1). In all cases the main products were 5-trifluoromethyl isomers **2c-f**, which were more than three times, and in some cases more than ten times, as much as the corresponding 4-trifluoromethyl regioisomers **5c-f**. In particular, cyclization of *t*-butylmethylhydrazone **1b** and phenylmethylhydrazone **1g** occurred with complete selectivity to afford only 5-trifluoromethyl isomers, **2b** (99%) and **2g** (88%), respectively.

Imidazoles **2a** and **5a** were obtained much more quickly by heating **1a** in a sealed tube without solvent. The reaction completed within 5 minutes and the isomeric ratios of **2a** to **5a** in the products were 87:13 (140°), 81:19 (170°) and 74:26 (200°). Apparently heating at higher temperatures favors formation of **5a**. However neat reactions did not proceed so cleanly as those carried out in toluene, and considerable amounts of unidentified materials were observed in any cases.

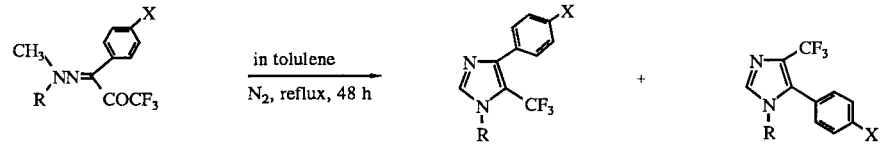
Table 2

Thermal Cyclization of Dimethylhydrazone **1a** in the Presence of Catalysts [a]


| Entry | Catalyst | Eq. | Time (days) | ratio (%) [b] **1a** | **2a** | **5a** | **3a** |
|---|---|---|---|---|---|---|---|
| 1 | *p*-$CH_3C_6H_4SO_3H$ | 0.2 | 4 | 0 | 18 | 0 | 82 |
| 2 | $CH_3CO_2H$ | 1.0 | 4 | 0 | 21 | 0 | 79 |
| 3 | 2,6-lutidine | 1.0 | 2 | 37 | 19 | 0 | 43 |
| 4 | $SiO_2$ [c] | 520 mg | 4 | 0 | 42 | 58 | 0 |
| 5 | $Al_2O_3$ [d] | 520 mg | 1 | 31 | 16 | 0 | 53 |
| 6 | molecular sieves [e] | 520 mg | 3 | 35 | 22 | 0 | 43 |

[a] Compound **1a** (0.2 mmole), carbon tetrachloride (4 ml). Entries 4-6 were carried out under a nitrogen atmosphere. Inorganic supports were dried for 2 hours at 180° under vacuum and carbon tetrachloride was dried over molecular sieves 3A, 1/16 before use. [b] Product ratios were calculated on the basis of $^1$H-nmr spectra. [c] Wakogel C-300; Wako Chemical Co. [d] Woelm Acid TLC; ICN Phamaceuticals GmbH & Co. [d] Molecular sieves 4A, 1/16; Nakarai Chemical Co.

Equation 1




| R | X | | | |
|---|---|---|---|---|
| $CH_3$ | $CH_3$ | **1a** | **2a** (80:20) | **5a** |
| *t*-$C_4H_9$ | $CH_3$ | **1b** | **2b** (100:0) | **5b** |
| $CH_3$ | H | **1c** | **2c** (93:7) | **5c** |
| $CH_3$ | $CH_3O$ | **1d** | **2d** (91:9) | **5d** |
| $CH_3$ | Cl | **1e** | **2e** (81:19) | **5e** |
| $CH_3$ | $NO_2$ | **1f** | **2f** (75:25) | **5f** |
| Ph | $CH_3$ | **1g** | **2g** (100:0) | **5g** |

Thus transformation from **1a** to **2a** was achieved fairly selectively under toluene reflux conditions but the regio isomer **5a** always appeared as a minor product. Therefore the thermal cyclization reaction of **1a** was then examined in the presence of some catalysts. These reactions were carried out in refluxing carbon tetrachloride because no **5a** was found in this condition (see Table I). Two kinds of acids, 2,6-lutidine [6] and three inorganic supports shown in Table 2 were chosen as catalysts. Unfortunately, selectivity toward **2a** was not improved at all and the proportion of **3a** in the products rather increased in some cases.

However, an interesting case was found incidentally, when the reaction was performed in the presence of silica gel (entry 4). Only in this case formation of **3a** was completely suppressed, and instead formation of **5a** increased surprisingly. This result is completely different from those with the use of alumina (entry 5) or molecular sieves 4A (entry 6) as a catalyst. Since most of the 4-trifluoromethyl isomers **5** can be easily isolable by column chromatography, these results indicate thermal cyclization reaction of **1a** in the presence of silica gel becomes a rather suitable method for selective synthesis of **5a**. Therefore we tried the cyclization of **1a** in the presence of silica gel in refluxing *n*-heptane, benzene, toluene and ethanol. As is shown in Table 3 **5a** was predominantly obtained when *n*-heptane or toluene was used as a solvent (entries 2 and 4). In these cases the selectivity toward **5a** was obviously enhanced compared to the case in carbon tetrachloride. In contrast, the formation of **5a** was least in the case of the reaction carried out in refluxing ethanol (entry 5). This can be attributed to the minimized interaction between the substrate and silica gel surface in a polar solvent such as ethanol (Table 3). Heating of **1a** adsorbed on silica gel at 80° without any solvent afforded the highest selectivity toward **5a** (75%, entry 6), and the reaction proceeded much more rapidly then using solvents. Therefore under this condition the reaction of a series of substrates, **1c-f** was then examined. In all cases as is shown in equation 2, 4-trifluoromethylimidazoles **5c-f** were obtained predominantly together with minor amounts of the corresponding 5-trifluoromethyl isomers **2c-f**. Selectivity for 4-trifluoromethyl derivatives **5** was more than 60% and these **5a-f** could be isolated easily by column chromatography. Therefore this is a useful method for the preparation of **5**. As for pathway from **1** to **5**, it is evident that **5a** is not formed by isomerization of **2a** because **2a** was not unchanged at all under the reaction conditions of equation 2. Without solvent at room temperature **1** adsorbed on silica gel is completely converted to **3** (but not to **5** at all) [3]. Therefore it may be probable that **5** should be formed from **3** after prior cyclization of **1** to **3**. However this pathway also seems impossible because attempted heating of **3** in the presence of silica gel either with and without solvent afforded **2** preferentially. Hydrazono group migration from the azomethine carbon to the trifluoroacetyl carbonyl carbon of **1** on a silica gel surface followed by cyclization to **5** as illustrated in Scheme 1 is one of the possible pathways, though we have not succeeded in detection of the assumed intermediate **1'** as yet. Detailed mechanistic studies of the transformations from **1** to **2** and to **5** are now in progress.

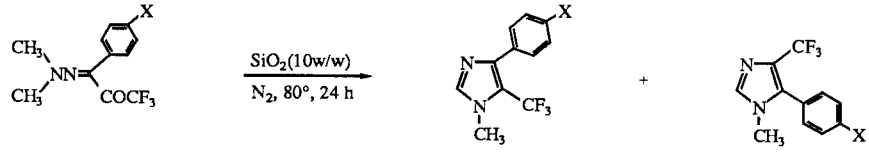
Table 3

Thermal Cyclization of Dimethylhydrazone **1a** in the Presence of Silica Gel [a]

| Entry | Solvent | Time (days) | Ratio (%) [b] 2a | 5a | 3a |
|---|---|---|---|---|---|
| 1 | $CCl_4$ | 4 | 42 | 58 | 0 |
| 2 | *n*-$C_7H_{16}$ | 4 | 32 | 68 | 0 |
| 3 | $C_6H_6$ | 4 | 53 | 47 | 0 |
| 4 | $CH_3C_6H_5$ | 2 | 27 | 73 | 0 |
| 5 | $C_2H_5OH$ | 4 | 71 | 12 | 17 |
| 6 | none | 1 | 25 | 75 | 0 |

[a] All reactions were carried out under a nitrogen atmosphere. **1a** (0.5 mmole); silica gel (1.3 g, Wakogel C-300); solvent (10 ml). Entries 1~5 were carried out under reflux conditions and entry 6 was performed at 80°. Silica gel was dried for 2 hours at 180° under vacuum and solvents were dried over molecular sieves 3A, 1/16 before use. [b] Product ratios were calculated on the basis of $^1$H-nmr.

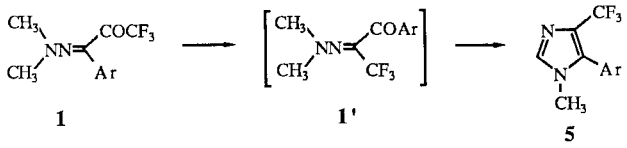
Equation 2




eq 2

| X | | | | |
|---|---|---|---|---|
| H | 1c | 23 | : | 77 |
| $CH_3$ | 1a | 25 | : | 75 |
| $CH_3O$ | 1d | 38 | : | 63 |
| Cl | 1e | 32 | : | 68 |
| $NO_2$ | 1f | 37 | : | 63 |

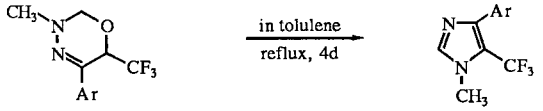
Scheme 1



1 1' 5

Prompted by the finding of the conversion from **3** to **2** as stated above, oxadiazine derivative **3a** was heated in refluxing toluene and found that **3a** was converted gradually to **2a** even in the absence of silica gel. The reaction proceeded very cleanly, but more slowly than that of **1a** to either **2a** or **5a** in refluxing toluene and, after four days, all **3a** was transformed solely to **2a**. None of **5a** was detected in the crude product. This selective transformation was also successful with **3c** and **3d**. However, under the same conditions **3e** afforded **2e** and **5e** in the ratio of 78:11 together with 11% recovery of **3e**, and **3f** remained intact even after 7 days. In refluxing carbon tetrachloride no reaction occurred in all cases. Since we already established a selective and convenient method [3] for conversion of **1** to **3**, tandem transformation **1**→**3**→**2** should be a useful method for the selective synthesis of **2a**, **2c** and **2d**.

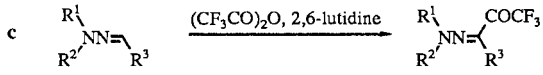
Equation 3



eq 3

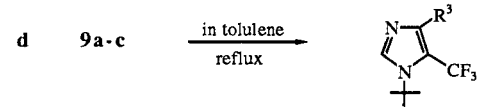
| Ar | | |
|---|---|---|
| *p*-$CH_3C_6H_4$ | **3a** | **2a** 86% |
| $C_6H_5$ | **3c** | **2c** 95% |
| *p*-$CH_3OC_6H_4$ | **3d** | **2d** 92% |

We could not examine the thermal cyclization of aliphatic aldehyde dimethylhydrazones **7** because **7** could not be prepared by direct trifluoroacetylation of aliphatic aldehyde dimethylhydrazones [2]. However aliphatic aldehyde diisopropylhydrazones were readily converted to the corresponding trifluoroacetylated hydrazones **8** [7]. Similarly, trifluoroacetylation of aliphatic aldehyde *t*-butyl(methyl)-hydrazones was also successful to afford **9a-c** in high



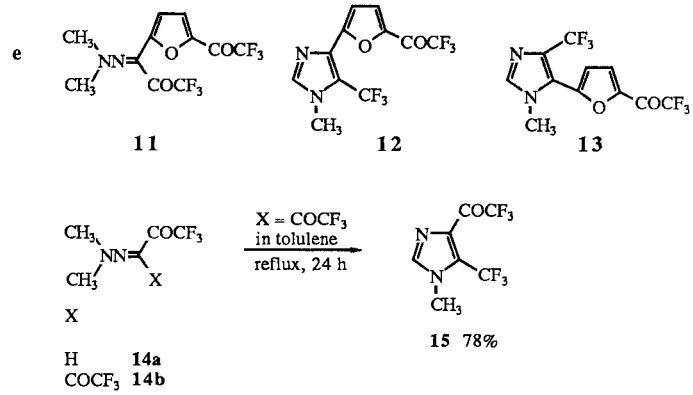
| $R^1$ | $R^2$ | $R^3$ | |
|---|---|---|---|
| $CH_3$ | $CH_3$ | alkyl | **7** |
| *i*-$C_3H_7$ | *i*-$C_3H_7$ | alkyl | **8** |
| $CH_3$ | *t*-$C_4H_9$ | $C_2H_5$ | **9a** |
| $CH_3$ | *t*-$C_4H_9$ | *i*-$C_3H_7$ | **9b** |
| $CH_3$ | *t*-$C_4H_9$ | $C_6H_5CH_2$ | **9c** |

yields. Although attempted thermal reaction of **8** ($R^3$ = Et) gave neither imidazoles nor any other definite products, **9a-c** were readily converted to the corresponding 5-trifluoromethylimidazoles **10a-c** by heating them in refluxing toluene. It seems of interest to note here that the cyclization of **9a-c** proceeded more rapidly than that of **1** to **2** and to **5** and that only 5-regioisomers were produced without any formation of the 4-isomers. 4-Trifluoromethylimidazoles could not be obtained from **1b** and **9a-c** even under the conditions of Table 3 with the use of silica gel.



| $R^3$ | Time | |
|---|---|---|
| $C_2H_5$ | 4h | **10a** (43%) |
| *i*-$C_3H_7$ | 16h | **10b** (81%) |
| $C_6H_4CH_2$ | 24h | **10c** (18%) |

Cyclization reaction of **11** occurred very rapidly. The reaction completes within 2 hours in refluxing carbon tetrachloride to afford the corresponding two imidazoles **12** and **13** in a ratio of 4:1. Dimethylhydrazone **14b** bearing two trifluoroacetyl groups could be converted solely to **15** in 78% yield be heating it in refluxing toluene, whereas corresponding hydrazone **14a** bearing only one trifluoroacetyl group did not give any imidazoles at all in spite of our many efforts.

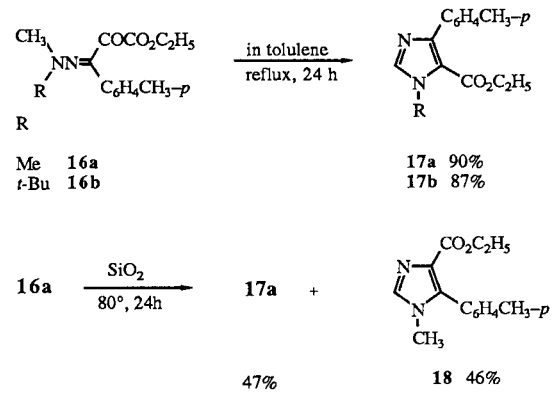


11 12 13

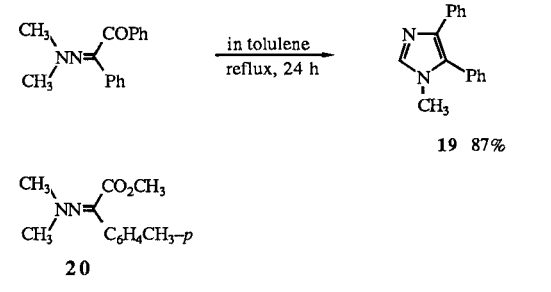
| X | | |
|---|---|---|
| H | **14a** | |
| $COCF_3$ | **14b** | |

**15** 78%

This thermal cyclization was extended to dialkylhydrazones bearing other acyl groups. Dimethyl and *t*-butyl(methyl)hydrazones bearing ethoxyglyoxyl group (**16a** and **16b**) in refluxing toluene gave the corresponding 5-ethoxycarbonylimidazoles **17a** and **17b**, respectively, in excellent yields. Possible regioisomers 4-ethoxycarbonylimidazoles were not detected in both cases. On the other hand when **16a** adsorbed on silica gel was heated for 24 hours at 80°, **17a** and its regioisomer **18** were obtained in a ratio of about 1:1 similar to the case of trifluoroacetyl




derivatives. Benzil monodimethylhydrazone in refluxing toluene afforded the corresponding imidazole **19** in 87% yield [8]. However, under similar conditions this cyclization did not occur at all with the corresponding methoxycarbonyl derivative **20**, which was prepared by haloform type cleavage of **1a** followed by esterification by diazomethane. Isomerization between syn and anti isomers of **20** was a sole reaction we could observe.




Structures of newly synthesized imidazoles were confirmed by $^1$H- and $^{13}$C-nmr and ir spectra, and micro combustion analysis. In particular, $^{13}$C-nmr spectra were very helpful for structural determination. $^{13}$C-Parameters for representative imidazoles are summarized in Table 4 together with those for related compounds. Direct C-H coupling constants larger than 205 Hz were observed for all imidazole ring C2 nuclei. Such large C-H coupling constants for sp$^2$ carbon nuclei are characteristic to imidazole ring C2 atom placed between two nitrogen atoms but not expected for isomeric pyrazole ring carbons. For instance, ring carbons of a series of ten pyrazoles bearing trifluoromethyl group synthesized independently [4,11] exhibited smaller $^1J_{CH}$, among which the largest one (195 Hz) was that for the C5 atom of 1-methyl-3-trifluoroacetyl-4-trifluoromethylpyrazole. Even in this case it is more than 10 Hz smaller than any $^1J_{CH}$ at C2 atom of the imidazoles in Table 4. These data clearly indicate that newly synthesized heterocycles are surely imidazoles but not pyrazoles.

The *N*-methyl carbon of **2a** appears at 33.5 ppm down field from TMS as a somewhat broadened signal owing to long range or (and) through space C-F coupling. Also the $^1$H nmr spectrum of **2a** exhibited a broadened *N*-methyl proton signal due to C-F coupling. Similar C-F couplings were neither observed with $^{13}$C- nor with $^1$H-nmr spectra of **5a**. This is in agreement with the assigned structures for **2a** to be 5-trifluoromethylimidazole and for **5a** to be 4-trifluoromethylimidazole. As is seen in Table 4, all ring carbon atoms directly attached to trifluoromethyl group appears as a quartet, with the geminal coupling constants of 35-40 ppm. This quartet in **2a** (at 116.5 ppm) is more shielded than that in **5a** (at 128.8 ppm). In *N*-methylimidazole the C5 atom is about 9 ppm more shielded than the C4 atom. These facts also support the structures of **2a** and **5a**.

Convenient and versatile synthetic routes readily accessible to variously substituted imidazoles involving 4-tri-

Table 4

$^{13}$C Parameters for Imidazoles [a] δ, ppm

| | C2 | ($^1J_{CH}$) | C4 | ($^2J_{CF}$) | C5 | ($^2J_{CF}$) | others |
|---|---|---|---|---|---|---|---|
| **2a** | 140.5 | (209 Hz) | 145.1 | | 116.5 | (39.1 Hz) | 33.5 ($CH_3$), 121.7 ($CF_3$) |
| **5a** | 137.6 | (211 Hz) | 128.8 | (37.4 Hz) | 133.0 [b] | | 31.2 ($CH_3$), 122.2 ($CF_3$) |
| **10b** | 137.8 | (208 Hz) | 153.6 [c] | | 114.8 | (38.5 Hz) | 58.8, 30.8 (*t*-Bu) [d] 122.5 ($CF_3$), 27.0 (CH) [e] |
| **15** | 140.9 | (215 Hz) | 135.5 [f] | | 127.2 | (35.4 Hz) | 34.5 ($CH_3$), 116.3, 119.8 ($CF_3$), 174.7 (CO) |
| **17a** | 141.2 | (207 Hz) | 149.3 | | 119.0 | | 34.9 ($CH_3$) |
| 1-methylimidazole | | | | | | | |
| | 137.7 | (205 Hz) | 129.0 [g] | | 120.2 [h] | | 32.6 ($CH_3$) |

[a] The $^{13}$C-nmr spectra were recorded at 22.5 MHz on a JEOL FX90Q spectrometer with tetramethylsilane as an internal standard. [b] $^3J_{CF}$ = 2.2 Hz. [c] $^3J_{CF}$ = 2.2 Hz. [d] C-F Through-space coupling (2.8 Hz) was observed for the methyl carbon atoms. [e] Long range coupling, $^4J_{CF}$ or C-F through-space coupling (2.9 Hz) was observed for the methine carbon atom. [f] $J_{CF}$ = 4.9 Hz. [g] $^1J_{CH}$ = 188 Hz. [h] $^1J_{CH}$ = 189 Hz.

fluoromethyl- and 5-trifluoromethylimidazoles from aldehydes only by three or four steps have been developed. The mechanism of these fascinating cyclization reactions are now under elucidation and will be reported in the near future.

## EXPERIMENTAL

All $^1$H-nmr spectra were recorded at 60 MHz on a JEOL PMX60SI spectrometer in deuteriochloroform solutions (unless otherwise noted) containing tetramethylsilane as an internal standard. The $^{13}$C-nmr spectra were measured in deuteriochloroform with a JEOL FX90Q spectrometer with tetramethylsilane as an internal standard. Infrared spectra was taken with a Hitachi model G3 spectrophotometer. Preparative tlc was carried out with the use of Merk Kieselgel 60 $PF_{254}$. Micro combustion analyses for all new compounds isolated were in satisfactory agreement with the calculated values (C ±0.35, H ±0.28, N ±0.30, F ±0.28, Cl ±0.10%).

General Procedure for the Preparation of Aldehyde *t*-Butylmethylhydrazones.

To an aqueous solution of *t*-butylhydrazine hydrochloride (100 mmoles) and sodium acetate (100 mmoles) in water (50 ml) was added aldehyde (100 mmoles), and the mixture was stirred for 5 hours. In the case of phenylacetaldehyde, *t*-butylhydrazine hydrochloride (110 mmoles) and sodium hydroxide (100 mmoles) in place of sodium acetate was used, and benzene (100 ml) was added as a solvent. Reaction mixture was poured into 1*M* sodium hydroxide and then extracted with three portions of ether (80 ml x 3). Combined extracts were dried over magnesium sulfate and the solvent was removed. To this was added iodomethane (200 mmoles) in ether (20 ml). In the case of phenyl acetaldehyde hydrazone, 2,6-lutidine (100 mmoles) was also added. The mixture was stirred for 6 hours, poured into an excess of 1*M* sodium hydroxide, and extracted with three portions of dichloromethane (80 ml x 3). The combined organic layers were dried over magnesium sulfate, the solvent was removed, and the residue was purified by Kugelrohr distillation. The yields are as follows – *p*-tolualdehyde *t*-butyl(methyl)hydrazone, 71%; propionaldehyde *t*-butyl(methyl)hydrazone, 59%; isobutylaldehyde *t*-butyl(methyl)hydrazone, 67%; phenylacetaldehyde *t*-butyl(methyl)hydrazone, 61%.

Acylated Hydrazones **1a-f**, **9a-c**, **11**, **14a-b**, **16a-b**, and **20**.

Trifluoroacetylated hydrazones **1a-f**, **9a-c**, **11** and **14a-b** were prepared according to the manner reported earlier [1,2,3].

1,1,1-Trifluoro-3-(*p*-tolyl)propane-2,3-dione 3-methyl(phenyl)hydrazone (**1g**).

This compound was obtained as yellow crystals (*n*-hexane), mp 85°; $^1$H-nmr: δ 6.90-7.50 (m, 9H, aryl), 3.08 (s, 3H, $NCH_3$), 2.34 (s, 3H, $CH_3$).

1,1,1-Trifluoropentane-2,3-dione 3-[*t*-Butyl(methyl)hydrazone] (**9a**).

This compound was obtained as a yellow oil; $^1$H-nmr: δ 3.12 (s, 3H, $NCH_3$), 2.62 (q, 2H, $CH_2$), 1.30 (s, 9H, *t*-$C_4H_9$), 1.07 (t, 3H, $CH_3$).

1,1,1-Trifluoro-4-methylpentane-2,3-dione 3-[*t*-Butyl(methyl)hydrazone] (**9b**).

This compound was obtained as a yellow oil; $^1$H-nmr: δ 6.76-7.26 (m, 5H, $C_6H_5$), 4.00 (s, 2H, $CH_2$), 2.95 (s, 3H, $NCH_3$), 1.25 (s, 9H, *t*-$C_4H_9$).

1,1,1-Trifluoro-4-phenylbutane-2,3-dione 3-[*t*-Butyl(methyl)hydrazone] (**9c**).

This compound was obtained as a yellow oil; $^1$H-nmr: δ 3.02, 2.98 (s and hept, 4H, $NCH_3$ and CH), 1.29 (s and d, 15H, *t*-$C_4H_9$ and $CH_3$).

Ethyl 3-(*p*-Tolyl)-3-dimethylhydrazono-2-oxopropionate (**16a**) and Ethyl 3-(*p*-Tolyl)-3-[*t*-butyl(methyl)hydrazono]-2-oxopropionate (**16b**).

To an ice-cooled mixture of hydrazone (5 mmoles) and pyridine (10 mmoles) in dry acetonitrile (8 ml) was added dropwise ethyl chloroglyoxylate (6 mmoles) dissolved in dry acetonitrile (2 ml) with continuous stirring. After 8 hours, dichloromethane (80 ml) was added and the mixture was washed with 1*M* hydrochloric acid, with water and finally with aqueous sodium carbonate. The organic layer was dried over magnesium sulfate, and the solvent was removed. *p*-Tolualdehyde which was produced together with the desired hydrazone was distilled off under reduced pressure (40°/2 Torr). Recrystallization of the residue afforded **16a** (69%) and **16b** (59%).

Hydrazone **16a**.

This compound was obtained as yellow crystals (diethyl ether), mp 70°; $^1$H-nmr: δ 7.02 (s, 4H, aryl), 4.20 (q, 2H, $CH_2$), 2.92 (s, 6H, $NCH_3$), 2.32 (s, 3H, $CH_3$), 1.33 (t, 3H, $CH_2CH_3$).

Hydrazone **16b**.

This compound was obtained as yellow crystals (diethyl ether), mp 114°; $^1$H-nmr: δ 7.05 (s, 4H, aryl), 4.25 (q, 2H, $CH_2$), 2.61 (s, 3H, $NCH_3$), 2.30 (s, 3H, $CH_3$), 1.32, 1.29 (t and s, 12H, $CH_2CH_3$ and *t*-$C_4H_9$).

Methyl *p*-Tolyldimethylhydrazonoacetate (**20**).

To a methanolic solution of **1a** (10 mmoles in 44 ml of methanol) was added saturated aqueous potassium hydroxide (*ca.* 15*N*, 4.52 ml) and the mixture was stirred for 16 hours. After evaporation of methanol, resulted solution was neutralized to *ca.* *p*H 6 with 1*M* hydrochloric acid and extracted with two portions of ether (50 ml x 2). The extracts were dried over magnesium sulfate. To this was added dropwise an ethereal solution of diazomethane prepared from *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (33 mmoles), 40% aqueous potassium hydroxide (20 ml) and ether (50 ml). After quenching excess diazomethane by addition of acetic acid, the mixture was washed with aqueous sodium carbonate and dried over magnesium sulfate. Ether was evaporated to afford **20** (38%) as a yellow oil, $^1$H-nmr: δ 7.02 (s, 4H, aryl), 3.70 (s, 3H, $OCH_3$), 2.79 (s, 6H, $NCH_3$), 2.30 (s, 3H, $CH_3$).

Cyclization Reaction of Dimethylhydrazone **1a** and *t*-Butyl(methyl)hydrazone **1b** in Carbon Tetrachloride.

In carbon tetrachloride (10 ml) was dissolved **1a** or **1b** (0.5 mmole) and the mixture was refluxed for 4 days under a nitrogen atmosphere. After removal of carbon tetrachloride, there was obtained a mixture (123 mg) of **2a** and **3a** (39:61) from **1a**, and that (141 mg) of **2b** and **3b** (79:16) from **1b**.

Cyclization Reaction of Dimethylhydrazone **1a** in Various Solvents (refer Table I).

With the use of **1a** (0.5 mmole) and appropriate solvents (10

ml), reaction and workup were carried out quite similarly. Reaction time was 48 hours in all cases. Crude products were analyzed by $^1$H-nmr spectroscopy. Yields were as follows - entry 2, 123.2 mg; entry 3, 114.0 mg; entry 4, 101.6 mg; entry 5, 118.9 mg; entry 6, 106.1 mg.

Cyclization Reaction of Hydrazones **1b-g** in Toluene.

With the use of **1b-g** (0.5 mmole) and toluene (10 ml) reaction and work-up were performed quite similarly. Reaction time was 48 hours in all cases. From **1b** there was obtained 139.6 mg (99%) of **2b**. From **1c** a mixture (99.8 mg) of **2c** and **5c** (93:7) was obtained, Fractionation by preparative tlc (benzene:ethyl acetate/8:2) afforded 58.8 mg (52%) of **2c** and 4.5 mg (4%) of **5c**. From **1d** there was obtained a mixture (132.1 mg) of **2d** and **5d** (91:9). Fractionation by preparative tlc (benzene:ethyl acetate, 6:4) gave 80.7 mg (63%) of **2d** and 6.4 mg (5%) of **5d**. From **1e** there was obtained a mixture (116.5 mg) of **2e** and **5e** (81:19). Fractionation by preparative tlc (benzene:ethyl acetate/8:2) afforded 84.7 mg (65%) of **2e** and 11.7 mg (9%) of **5e**. From **1f** there was obtained a mixture (134.8 mg) of **2f** and **5f** (75:25). Fractionation by preparative tlc (benzene:ethyl acetate/8:2) gave 78.6 mg (58%) of **2f** and 24.4 mg (18%) of **5f**. From **1g** there was obtained 159.1 mg of crude **2g**, which was purified by preparative tlc (benzene:ethyl acetate/9:1) to afford 133.5 mg (88%) of **2g**.

1-(*t*-Butyl)-4-(*p*-tolyl)-5-trifluoromethylimidazole (**2b**).

This compound was obtained as pale yellow crystals (*n*-hexane), mp 117°; ir (potassium bromide): 1505, 1391, 1284, 1150, 1120, 1105 cm$^{-1}$; $^1$H-nmr (carbon tetrachloride): δ 7.00-7.67 (m, 5H, aryl and CH), 2.40 (s, 3H, $CH_3$), 1.73 (s, 9H, $t$-$C_4H_9$).

*Anal.* Calcd. for $C_{15}H_{17}F_3N_2$: C, 63.82; H, 6.07; N, 9.92; F, 20.19. Found: C, 63.89; H, 6.02; N, 9.85; F, 19.93.

1-Methyl-4-(*p*-anisyl)-5-trifluoromethylimidazole (**2d**).

This compound was obtained as colorless crystals (*n*-hexane), mp 58°; ir (potassium bromide): 1504, 1407, 1254, 1202, 1170, 1100, 1049, 1033, 834 cm$^{-1}$; $^1$H-nmr: δ 7.46 (d and s, 3H, aryl and CH), 6.76 (d, 2H, aryl), 3.80 (s, 3H, $OCH_3$), 3.77 (s, 3H, $CH_3$).

*Anal.* Calcd. for $C_{12}H_{11}F_3N_2O$: C, 56.25; H, 4.33; N, 10.93; F, 22.24. Found: C, 56.38; H, 4.28; N, 10.92; F, 22.07.

1-Methyl-4-(*p*-chlorophenyl)-5-trifluoromethylimidazole (**2e**).

This compound was obtained as a colorless oil (Kugelrohr distillation; oven temperature 130°/2 Torr); ir (potassium bromide): 1475, 1400, 1320, 1272, 1168, 1103, 1053, 955, 829 cm$^{-1}$; $^1$H-nmr: δ 7.52 (s, 1H, CH), 7.38 (s, 4H, aryl), 3.77 (s, 3H, $CH_3$).

*Anal.* Calcd. for $C_{11}H_8ClF_3N_2$: C, 50.69; H, 3.09; N, 10.79; F, 21.87. Found: C, 50.69; H, 3.19; N, 10.63; F, 21.69.

1-Methyl-4-(*p*-nitrophenyl)-5-trifluoromethylimidazole (**2f**).

This compound was obtained as yellow crystals (*n*-hexane-benzene), mp 98°; ir (potassium bromide): 1515, 1356, 1170, 1110, 1080, 1056, 856 cm$^{-1}$; $^1$H-nmr: δ 8.12 (d, 2H, aryl), 7.60 (d, 2H, aryl), 7.50 (s, 1H, CH), 3.78 (s, 3H, $CH_3$).

*Anal.* Calcd. for $C_{11}H_8F_3N_3O_2$: C, 48.72; H, 2.97; N, 15.49; F, 21.02. Found: C, 48.99; H, 2.84; N, 15.48; F, 20.92.

1-Phenyl-4-(*p*-tolyl)-5-trifluoromethylimidazole (**2g**).

This compound was obtained as orange crystals (*n*-hexane), mp 111°; ir (potassium bromide): 1496, 1249, 1170, 1109, 1092, 837, 768, 694 cm$^{-1}$; $^1$H-nmr: δ 7.03-7.69 (m, 10H, aryl and CH), 2.37 (s, 3H, $CH_3$).

*Anal.* Calcd. for $C_{17}H_{13}F_3N_2$: C, 67.55; H, 4.34; N, 9.27; F, 18.85. Found: C, 67.46; H, 4.30; N, 9.14; F, 18.79.

Cyclization Reaction of 1,1,1-Trifluoro-3-(*p*-tolyl)propane-2,3-dione 3-Dimethylhydrazone (**1a**) in a Sealed Tube.

In a φ6 mm glass sealed tube **1a** (0.5 mmole) was heated for 5 minutes at 140° (oil bath temperature). Reactions at 170° and 200° were also carried out quite similarly. Crude materials were analyzed by $^1$H-nmr spectroscopy. Yields and ratios (**2a:5a**) are as follows- 110 mg, 87:13 (140°); 109 mg, 81:19 (170°); 102 mg, 74:26 (200°).

Cyclization Reaction of **1a** in the Presence of Catalyst (Table II).

Method A (for entries 1-3).

To a solution of **1a** (0.2 mmole) in carbon tetrachloride (4 ml) was added an appropriate catalyst (*p*-toluenesulfonic acid: 0.04 mmole, acetic acid: 0.2 mmole, 2,6-lutidine: 0.2 mmole). The mixture was refluxed for 2-4 days. In the cases of entries 1 and 2, the mixture was washed with aqueous sodium carbonate and dried over magnesium sulfate, and the solvent was evaporated. In the case of entry 3, 2,6-lutidine and carbon tetrachloride was removed under vacuum.

Method B (for entries 4-6).

An inorganic support (520 mg, wakogel C-300 silica gel; woelm Acid TLC alumina; Nakarai Chemical Co. molecular sieves 4A 1/16) previously dried for 2 hours at 180° under vacuum and **1a** (0.2 mmole) was placed in a nitrogen replaced reaction vessel. To this was added carbon tetrachloride (4 ml) and the mixture was refluxed for 1-4 days with continuous stirring. The inorganic support was filtered off and washed thoroughly with ether. The washings and the filtrate were combined and the solvent was removed. Products were analyzed by $^1$H-nmr spectroscopy. Yields are as follows - entry 1: 47.7 mg (**2a:3a** = 18:82), entry 2: 50.8 mg (**2a:3a** = 21:79), entry 3: 48.3 mg (**1a:2a:3a** = 37:19:43), entry 4: 46.9 mg (**2a:5a** = 42:58), entry 5: 35.1 mg (**1a:2a:3a** = 31:16:53), entry 6: 47.2 mg (**1a:2a:3a** = 35:22:43).

Cyclization Reaction of **1a** in the Presence of Silica Gel (Table III).

Except for the case of entry 6 reactions were carried out according to Method B. Appropriate solvents (10 ml) were used together with **1a** (0.5 mmole) and silica gel (1.3 g). The following method C was employed for entry 6.

Method C.

To **1a** (0.5 mmole) in benzene (5 ml) was added dry (180°, 2 hours, 0.1 torr) silica gel (1.3 g, see method B). The mixture was stirred well for 5 minutes and the solvent was removed under vacuum. Thus obtained pale yellow powder was heated for 24 hours at 80° under nitrogen atmosphere. To this was added ethanol (20 ml) and the mixture was stirred for 5 minutes. Silica gel was filtered off and washed with ethanol (30 ml). The filtrate and the washings were combined, dried over magnesium sulfate and the solvent was evaporated. Products were analyzed by $^1$H-nmr spectroscopy. Yields were as follows - entry 2, 99.3 mg (**2a:5a** = 32:68); entry 3, 99.0 mg (**2a:5a** = 53:47); entry 4, 108.1 mg (**2a:5a** = 27:73); entry 5, 128.8 mg (**2a:5a:3a** = 71:12:17); en-

try 6, 106.9 mg (**2a**:**5a** = 25:75). In the case of entry 6 fractionation by preparative tlc (benzene:ethyl acetate/8:2) afforded 13.1 mg (11%) of **2a** and 74.1 mg (62%) of **5a**.

1-Methyl-4-trifluoromethyl-5-(*p*-tolyl)imidazole (**5a**).

This compound was obtained as colorless crystals (*n*-hexane-heptane), mp 87-88.5°; ir (potassium bromide): 1510, 1406, 1275, 1218, 1170, 1145, 1108, 964, 825 $cm^{-1}$; $^1$H-nmr: $\delta$ 7.37 (s, 1H, CH), 7.11 (s, 4H, aryl), 3.43 (s, 3H, $NCH_3$), 2.38 (s, 3H, $CH_3$).

*Anal.* Calcd. for $C_{12}H_{11}F_3N_2$: C, 60.00; H, 4.62; N, 11.66; F, 23.73. Found: C, 60.26; H, 4.61; N, 11.54; F, 23.81.

Cyclization Reaction of Dimethylhydrazones **1c-f** Adsorbed on Silica Gel.

Reaction was carried out according to method C. From **1c** a mixture (109.1 mg) of **2c** and **5c** (23:77), from **1d** a mixture (114.3 mg) of **2d** and **5d** (38:63), from **1e** a mixture (112.4 mg) of **2e** and **5e** (32:68), and from **1f** a mixture (93.8 mg) of **2f** and **5f** (37:63) were obtained. Fractionation by preparative tlc afforded; 15.4 mg (14%) of **2c** and 65.5 mg (58%) of **5c** (benzene:ethyl acetate/8:2), 20.8 mg (16%) of **2d** and 61.3 mg (48%) of **5d** (benzene:ethyl acetate/7:3), 23.1 mg (18%) of **2e** and 58.2 mg (45%) of **5e** (benzene:ethyl acetate/8:2), and 29.7 mg (22%) of **2f** and 47.0 mg (35%) of **5f** (benzene:ethyl acetate/8:2).

1-Methyl-4-trifluoromethyl-5-phenylimidazole (**5c**).

This compound was obtained as pale yellow oil (Kugelrohr distillation; oven temperature 110°/1 Torr); ir (potassium bromide): 1505, 1405, 1214, 1170, 1142, 1108, 965, 780 $cm^{-1}$; $^1$H-nmr: $\delta$ 7.13-7.50 (m, 6H, aryl and CH), 3.43 (s, 3H, $CH_3$).

*Anal.* Calcd. for $C_{11}H_9F_3N_2$: C, 58.41; H, 4.01; N, 12.38; F, 25.20. Found: C, 58.37; H, 4.02; N, 12.32; F, 25.14.

1-Methyl-4-trifluoromethyl-5-(*p*-anisyl)imidazole (**5d**).

This compound was obtained as colorless crystals (*n*-hexane), mp 100-101°; ir (potassium bromide): 1617, 1510, 1402, 1289, 1248, 1148, 1105, 1018, 956, 832 $cm^{-1}$; $^1$H-nmr: $\delta$ 7.40 (s, 1H, CH), 6.85-7.35 (q, 4H, aryl), 3.90 (s, 3H, $OCH_3$), 3.53 (s, 3H, $NCH_3$).

*Anal.* Calcd. for $C_{12}H_{11}F_3N_2O$: C, 56.25; H, 4.33; N, 10.93; F, 22.24. Found: C, 56.48; H, 4.23; N, 10.88; F, 22.21.

1-Methyl-4-trifluoromethyl-5-(*p*-chlorophenyl)imidazole (**5e**).

This compound was obtained as colorless crystals (*n*-hexane), mp 69-71°; ir (potassium bromide): 1487, 1403, 1172, 1129, 1107, 1092, 961, 834 $cm^{-1}$; $^1$H-nmr: $\delta$ 7.06-7.50, 7.46 (q and s, 5H, aryl and CH), 3.46 (s, 3H, $CH_3$).

*Anal.* Calcd. for $C_{11}H_8ClF_3N_2$: C, 50.69; H, 3.09; N, 10.79; Cl, 13.60. Found: C, 50.96; H, 3.13; N, 10.66; Cl, 13.56.

1-Methyl-4-trifluoromethyl-5-(*p*-nitrophenyl)imidazole (**5f**).

This compound was obtained as pale yellow oil (Kugelrohr distillation; oven temperature 150°/5 Torr); ir (potassium bromide): 1603, 1517, 1340, 1153, 1113, 968, 857 $cm^{-1}$; $^1$H-nmr: $\delta$ 8.30 (d, 2H, aryl), 7.57, 7.50 (s and d, 3H, CH and aryl), 3.54 (s, 3H, $CH_3$).

*Anal.* Calcd. for $C_{11}H_8F_3N_3O_2$: C, 48.72; H, 2.97; N, 15.49; F, 21.02. Found: C, 49.07; H, 3.08; N, 15.30; F, 20.82.

Conversion of 5-Aryl-6-trifluoromethyl-3,6-dihydro-2*H*-1,3,4-oxadiazines **3a**, **3c** and **3d** to 1-Methyl-4-aryl-5-trifluoromethylimidazoles **2a**, **2c** and **2d**.

A solution of oxadiazine derivative (0.5 mmole) in toluene (10 ml) was refluxed for 4 days under nitrogen atmosphere. Removal of the solvent gave 103.0 mg (86%) of **2a**, 117.9 mg (92%) of **2d**, and 123.5 mg (95%) of **2e**.

Cyclization Reaction of Hydrazones **9a**, **9b**, **9c**, **14b**, **16a**, **16b**, **20**, and Benzil Monodimethylhydrazone in Toluene.

A solution of substrate (1 mmole) in toluene (20 ml) was refluxed for 24 hours (4 hours in the case of **9a** and 16 hours in the case of **9b**) under nitrogen atmosphere. Removal of the solvent gave crude materials. Purification by Kugelrohr distillation afforded 94.7 mg (43%) of **10a**, 189.8 mg (81%) of **10b**, 191.9 mg (78%) of **15** [12], 219.9 mg (90%) of **17a**, and 248.8 mg (87%) of **17b**. Fractionation by preparative tlc (benzene/ethyl acetate = 9/1) followed by Kugelrohr distillation gave 50.8 mg (18%) of **10c**. Recrystallization from carbon tetrachloride gave 203.6 mg (87%) of **19**. In the case of **20** (one isomer only) [13], a mixture (219.1 mg) of two isomers of **20** (ratio = 48:52) [14] was obtained.

1-(*t*-Butyl)-4-ethyl-5-trifluoromethylimidazole (**10a**).

This compound was obtained as a yellow oil (Kugelrohr distillation; oven temperature 110°/4 Torr); ir (potassium bromide): 2940, 1685, 1545, 1142, 1105 $cm^{-1}$; $^1$H-nmr: $\delta$ 7.58 (s, 1H, CH), 2.62 (q, 2H, $CH_2$), 1.64 (s, 9H, *t*-$C_4H_9$), 1.20 (t, 3H, $CH_3$).

*Anal.* Calcd. for $C_{10}H_{15}F_3N_2$: C, 54.54; H, 6.86; N, 12.72. Found: C, 54.26; H, 6.58; N, 12.65.

1-(*t*-Butyl)-4-isopropyl-5-trifluoromethylimidazole (**10b**).

This compound was obtained as a yellow oil (Kugelrohr distillation; oven temperature 110°/1.5 Torr); ir (potassium bromide): 2965, 1378, 1280, 1209, 1145, 1103, 1030 $cm^{-1}$; $^1$H-nmr: $\delta$ 7.60 (s, 1H, CH), 2.80-3.45 (hept, 1H, C*H*$CH_3$), 1.67 (s, 9H, *t*-$C_4H_9$), 1.25 (d, 6H, $CH_3$).

*Anal.* Calcd. for $C_{11}H_{17}F_3N_2$: C, 56.40; H, 7.31; N, 11.96; F, 24.33. Found: C, 56.36; H, 7.46; N, 12.12; F, 24.26.

1-(*t*-Butyl)-4-benzyl-5-trifluoromethylimidazole (**10c**).

This compound was obtained as a pale yellow oil (Kugelrohr distillation; oven temperature 140°/1 Torr); ir (potassium bromide): 1560, 1304, 1264, 1130, 1104, 1041 $cm^{-1}$; $^1$H-nmr: $\delta$ 7.63 (s, 1H, CH), 7.15 (s, 5H, aryl), 4.04 (s, 2H, $CH_2$), 1.64 (s, 9H, *t*-$C_4H_9$).

*Anal.* Calcd. for $C_{15}H_{17}F_3N_2$: C, 63.82; H, 6.07; N, 9.92; F, 20.19. Found: C, 63.98; H, 6.17; N, 9.74; F, 20.01.

1-Methyl-4-trifluoroacetyl-5-trifluoromethylimidazole (**15**).

This compound was obtained as colorless crystals (Kugelrohr distillation; oven temperature 105°/3 Torr), mp 60°; ir (hydrate form on potassium bromide) 3120-3500, 1520, 1180, 1120 $cm^{-1}$; $^1$H-nmr: $\delta$ 7.59 (s, 1H, CH), 3.89 (s, 3H, $CH_3$).

*Anal.* Calcd. for $C_7H_4F_6N_2O$: C, 34.16; H, 1.64; N, 11.38; F, 46.32. Found: C, 33.92; H, 1.82; N, 11.68; F, 46.25.

1-Methyl-4-(*p*-tolyl)-5-ethoxycarbonylimidazole (**17a**).

This compound was obtained as a yellow oil (Kugelrohr distillation; oven temperature 230°/2 Torr); ir (potassium bromide): 2960, 1690, 1535, 1502, 1368, 1205, 1093 $cm^{-1}$; $^1$H-nmr: $\delta$ 7.02-7.67, 7.54 (q and s, 5H, aryl and CH), 4.21 (q, 2H, $CH_2$), 3.83 (s, 3H, $NCH_3$), 2.37 (s, 3H, $CH_3$), 1.20 (t, 3H, $CH_2CH_3$).

*Anal.* Calcd. for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.54; H, 6.70; N, 11.33.

1-(*t*-Butyl)-4-(*p*-tolyl)-5-ethoxycarbonylimidazole (**17b**).

This compound was obtained as a pale yellow oil (Kugelrohr distillation; oven temperature 240°/1 Torr); ir (potassium

bromide): 2970, 1710, 1537, 1493, 1368, 1170, 1050 $cm^{-1}$; $^1H$-nmr: δ 7.68 (s, 1H, CH), 7.05-7.50 (q, 4H, aryl), 4.25 (q, 2H, $CH_2$), 2.46 (s, 3H, $CH_3$), 2.71 (s, 9H, $t$-$C_4H_9$), 1.15 (t, 3H, $CH_2CH_3$).

*Anal.* Calcd. for $C_{17}H_{22}N_2O_2$: C, 71.30; H, 7.74; N, 9.78. Found: C, 70.97; H, 7.49; N, 9.66.

1-Methyl-4,5-diphenylimidazole (**19**).

This compound was obtained as colorless crystals (carbon tetrachloride), mp 161° (lit 158-159°) [10]; $^1H$-nmr: δ 6.93-7.50 (m, 11H, aryl and CH), 3.30 (s, 3H, $CH_3$).

Cyclization Reaction of 2-(3',3',3'-trifluoro-1'-dimethylhydrazono-2'-oxopropyl)-5-trifluoroacetylfuran (**11**).

A solution of **11** (1 mmole) in carbon tetrachloride (20 ml) was refluxed for 5 hours under nitrogen atmosphere. The solvent was removed and the residue (270 mg) including **12** and **13** (8:2) was fractionated by preparative tlc (cyclohexane:ethyl acetate/3:7) to give 100.8 mg (32%) of **12** and 49.8 mg (16%) of **13**.

1-Methyl-4-(5'-trifluoroacetylfuran-2'-yl)-5-trifluoromethylimidazole (**12**).

This compound was obtained as a pale yellow oil (Kugelrohr distillation; oven temperature 150°/3 Torr); ir (potassium bromide): 1685, 1474, 1267, 1130, 993, 874 $cm^{-1}$; $^1H$-nmr: δ 7.52 (s and d, 2H, CH of furan and imidazole), 6.88 (d, 1H, CH of furan), 3.86 (s, 3H, $CH_3$).

*Anal.* Calcd. for $C_{11}H_6F_6N_2O_2$: C, 42.32; H, 1.94; N, 8.97; F, 36.52. Found: C, 42.54; H, 1.93; N, 9.20; F, 36.39.

1-Methyl-4-trifluoromethyl-5-(5'-trifluoroacetylfuran-2'-yl)imidazole (**13**).

This compound was obtained as pale orange crystals (diethyl ether), mp 125°; ir (potassium bromide): 1686, 1464, 1318, 1248, 1203, 1149, 1133, 1004, 880 $cm^{-1}$; $^1H$-nmr: δ 7.54, 7.50 (s and d, 2H, CH of furan and imidazole), 6.93 (d, 1H, CH of furan), 3.79 (s, 3H, $CH_3$).

*Anal.* Calcd. for $C_{11}H_6F_6N_2O_2$: C, 42.32; H, 1.94; N, 8.97; F, 36.52. Found: C, 42.14; H, 1.90; N, 8.74; F, 36.80.

Cyclization Reaction of Ethyl 3-(*p*-Tolyl)-3-dimethylhydrazono-2-oxopropionate (**16a**) Adsorbed on Silica Gel.

According to method C **16a** (1 mmole) adsorbed on silica gel (1 g) was reacted. Thus obtained mixture (232.9 mg) of **17a** and **18** (1:1) was fractionated by preparative tlc (benzene:ethyl acetate/8:2) to afford 114.9 mg (47%) of **17a** and 112.3 mg (46%) of **18**.

1-Methyl-4-ethoxycarbonyl-5-(*p*-tolyl)imidazole (**18**).

This compound was obtained as pale yellow crystals (cyclohexane), mp 116-117°; ir (potassium bromide): 3090, 1708 (CO), 1505, 1378, 1162 $cm^{-1}$; $^1H$-nmr: δ 7.36 (s, 1H, CH), 7.11 (s, 4H, aryl), 4.13 (q, 2H, $CH_2$), 3.43 (s, 3H, $NCH_3$), 2.36 (s, 3H, $CH_3$), 1.20 (t, 3H, $CH_2CH_3$).

*Anal.* Calcd. for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.58; H, 6.62; N, 11.36.

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[6] In our previous report (ref 1) it was mentioned that thermal cyclization reaction of **1c** in carbon tetrachloride in the presence of 2,6-lutidine resulted in preferential formation of imidazole **2c**. Afterwards this result was found not to be so reproducible; the ratio of **2c** and the corresponding oxadiazine **3c** varies considerably in each experiment and 2,6-lutidine is not a good catalyst for preferential formation of **2a**.

[7] This is owing to the blocking effect of the two isopropyl groups. Otherwise, undesirable *N*-trifluoroacetylation occurs exclusively, which is the case of aliphatic aldehyde dimethylhydrazones.

[8] The Russian group (ref 9) reported that treatment of benzil with 1,1-dimethylhydrazine at 110° or heating benzil monodimethylhydrazone with cupric sulfate at 130° gave 1-methyl-3,4-diphenylpyrazole. Later on, the US group (ref 10) pointed out that this product is not the above pyrazole but imidazole **19**.

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[11] Unpublished results. Direct C-H coupling constants at ring carbons of representative pyrazoles bearing trifluoromethyl group are as follows - 1-methyl-3-(*p*-tolyl)-4-trifluoromethylpyrazole (188 Hz at C5), 1-(*t*-butyl)-3-(isopropyl)-4-trifluoromethylpyrazole (187 Hz at C5), 1-methyl-3-(trifluoromethyl)-4-phenylpyrazole (188 Hz at C5), 1-methyl-4-phenyl-5-trifluoromethylpyrazole (189 Hz at C3), 1-methyl-3-phenyl-5-trifluoromethylpyrazole (179 Hz at C4), 1-methyl-3-(trifluoromethyl)-5-phenylpyrazole (179 Hz at C4), 1-methyl-3-(trifluoroacetyl)-4-trifluoromethylpyrazole (195 Hz at C5), 1-methyl-3-(trifluoromethyl)-4-trifluoroacetylpyrazole (194 Hz at C5). Synthesis of these pyrazoles were reported (refs 1 and 4) or will be reported in near future.

[12] This compound is easily hydrated at the carbonyl group by atmospheric moisture. Hydrated **15** was difficultly soluble in chloroform and there was observed an equilibrium between **15** and its hydrate in acetone.

[13] Structural determination of the *E* and *Z* isomers for this compound is under study.

[14] The ratio is that of (starting material):(isomerized product). The latter exhibits *O*-methyl and *N*-methyl protons at 3.98 and 2.60 ppm, respectively, in the $^1H$-nmr spectra.