Synthesis of new trifluoromethyl-containing
1-(3,5-dialkyl-4-hydroxybenzyl)-pyrazole and -pyrazol-5-one
derivatives and their corresponding aroxyls

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Abstract: 3,5-Dialkyl-4-hydroxybenzylhydrazine 1 reacted with hexafluoroacetacetone, and trifluoroacetylacetone yielding the pyrazoles 2 bearing trifluoromethyl and/or methyl substituents in positions 3 and 5. The same hydrazine derivatives 1 afforded the pyrazol-5-ones 3 with trifluoroacetoacetic acid ethyl ester. On oxidation with lead tetraacetate in CH2Cl2, some stable aroxyls were obtained and their ESR spectra are described.

Keywords: fluorination, pyrazole, pyrazolone, trifluoromethyl-1,3-diketones.

INTRODUCTION

Fluorine is the most electronegative element and the van der Waals radius of fluorine is close to that of hydrogen, hence the introduction of a fluorine-containing group into an organic molecule brings about some remarkable changes in its physical and chemical properties.1 Many new fluorinated materials which take advantage of these useful changes, e.g., drugs and agrochemicals, have been designed2 and synthesized.3

Continuing our studies directed toward the synthesis of new fluorine-containing organic compounds,4–7 in the present paper the reactions of hindered phenol-containing hydrazines with hexafluoroacetacetone, trifluoroacetacetone and trifluoroacetacetate ethyl ester are reported.

RESULTS AND DISCUSSION

3,5-Dialkyl-4-hydroxybenzylhydrazine 1, where the 3,5-dialkyl groups are either both t-butyl (series denoted by A) or methyl and t-butyl (series denoted by B), synthe-
sized from hydrazine hydrate and \(N,N\text{-dimethyl-3,5-dialkyl-4-hydroxybenzylamine}\) according to a literature procedure, reacted with hexafluoroacetylacetone, and trifluoroacetylacetone (leading to series denoted by \(a\) and \(b\), respectively) yielding the title pyrazole derivatives \(2a\text{-}b\) bearing trifluoromethyl and/or methyl substituents in positions 3 and 5. The same hydrazine derivatives \(1\) afforded, with trifluoroacetoacetic acid ethyl ester, the title pyrazol-5-one derivatives, which might have the tautomeric structures \(3\) or \(4\) (Scheme 1); actually, in chloroform solution, only the pyrazolonic (lactamic) tautomer \(3\) can be detected by \(\text{H}-\text{NMR spectrometry.}\)

\[
\begin{align*}
\text{2a} & \quad \text{2b} \\
& \quad \text{3} \\
\text{1} & \quad \text{4}
\end{align*}
\]

Scheme 1.

In general, the reaction of monosubstituted hydrazines with unsymmetrical 1,3-diketones can result in the formation of isomeric pyrazoles, depending on the site of initial nucleophilic attack. In the case of trifluoroacetylacetone, enolic species are in equilibrium with the diketone (Scheme 2).

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{O} & \quad \text{CF}_3 \\
\text{H}_3\text{C} & \quad \text{O} & \quad \text{CF}_3 \\
\text{H}_3\text{C} & \quad \text{OH} & \quad \text{CF}_3 \\
\text{H}_3\text{C} & \quad \text{OH} & \quad \text{CF}_3
\end{align*}
\]

Scheme 2.

Contrary to our expectations that condensation of hydrazine \(1\) with trifluoroacetylacetone would yield two regioisomers \(2\) and \(5\) (an undehydrated product in which the \(\text{CF}_3\) group is bonded to a saturated carbon atom), (Scheme 3), the \(\text{F}\) NMR spectra showed that, in the condensation of \(1\) with trifluoroacetylacetone, the
terminal NH₂ group from benzylhydrazine 1 had reacted with the more electrophilic carbonyl, i.e., the –COCF₃, leading to only the pyrazole regioisomer 2.

Compounds 2 and 3 were fully identified by IR, MS, HRMS and ¹H and ¹⁹F NMR spectroscopy.

**IR Spectra**

The infrared absorption spectra of all the above compounds presented the phenolic O–H stretching band at 3630–3650 cm⁻¹ and the aromatic ring vibrations at 1600 and 1485–1500 cm⁻¹. The presence of conjugated C=C and C=N bonds in the pyrazole ring leads to the appearance of two absorption bands at 1500–1600 cm⁻¹. In addition, the pyrazolone derivatives showed C=O stretching bands at 1653 (3A) or 1672 cm⁻¹ (3B).

Table I presents the most characteristic ions in the mass spectra of compounds 2 and 3.

**TABLE I. The most characteristic ions in the mass spectra of compounds 2 and 3**

<table>
<thead>
<tr>
<th>Ion; m/z (relative intensity)</th>
<th>Comp. M⁺</th>
<th>(M–CH₃)⁺</th>
<th>(M–C₅H₄N₂F₃)⁺</th>
<th>(M–C₅H₄N₂F₃O)⁺</th>
<th>(CF₃)⁺</th>
</tr>
</thead>
<tbody>
<tr>
<td>2Aa</td>
<td>422 (30)</td>
<td>407 (100)</td>
<td>219 (13)</td>
<td>203 (20)</td>
<td>57 (13)</td>
</tr>
<tr>
<td>2Bb</td>
<td>380 (35)</td>
<td>365 (100)</td>
<td>177 (20)</td>
<td>161 (67)</td>
<td>57 (5)</td>
</tr>
<tr>
<td>2Ab</td>
<td>368 (53)</td>
<td>353 (100)</td>
<td>219 (13)</td>
<td>203 (45)</td>
<td>57 (8)</td>
</tr>
<tr>
<td>2Bb</td>
<td>326 (60)</td>
<td>311 (90)</td>
<td>177 (30)</td>
<td>161 (100)</td>
<td></td>
</tr>
<tr>
<td>3A</td>
<td>370 (17)</td>
<td>355 (35)</td>
<td>219 (100)</td>
<td>203 (30)</td>
<td>57 (18)</td>
</tr>
<tr>
<td>3B</td>
<td>328 (28)</td>
<td>313 (27)</td>
<td>177 (100)</td>
<td>161 (72)</td>
<td>57 (15)</td>
</tr>
</tbody>
</table>

**¹H-NMR Spectra**

The ¹H and ¹⁹F NMR spectra confirm the structures of all the compounds. The ¹H NMR spectrum of 2 displayed the pyrazole H–C(4) as a singlet in the range δ
6.30–6.87 ppm, indicating that this H is an aromatic pyrazole proton, whereas the 1H NMR spectrum of 3 displayed the H–C(4) as an AB system (doublet at 4.98–5.01 ppm, with the geminal coupling constant $J = 18$ Hz), indicating that these protons are a prochiral CH$_2$ group in an asymmetric environment.

**ESR studies of aroxyl radicals**

On oxidation with lead tetraacetate in dichloromethane, the phenols 2Ab, 3A and 3B were converted into aroxyls, as shown in Schemes 4 and 5.

Hyperfine coupling constants were determined from simulations of the ESR spectra shown in Figs. 1–3, and the results are listed in Table II. The highest spin density is at the para-methylene group, *i.e.*, the hfc’s are 11 Gauss for compound 2Ab and 9.86 Gauss for 3A, taking into account the resonance formulas for the 2Ab-aroxyl and 3A-aroxyl, respectively (Schemes 4 and 5).

| TABLE II. ESR spectral data for the aroxyls of compounds 2Ab, 3A and 3B |
|------------------|----------------|----------------|----------------|----------------|
| Compounds        | $a$(CH$_2$), G | $a$(CH, phenyl), G | $a$(CH), G | $a$(N), G | Linewidth, G |
| 2Ab              | 11.03(2H)      | 1.82(1H)         | 3.10 (1H)   | 0.46         |
| 3A               | 9.86(2H)       | 1.86(2H)         |              | 0.50         |
| 3B               | 6.20(1N)       | 3.14             |              |              |

Scheme 4.

Scheme 5.
In the ESR spectrum of compound 2Ab, presented in Fig. 1, a large triplet (with a large hyperfine coupling constant, \( hfc = 11.03 \) Gauss), due to the two methylene protons, can be recognized. Each component of the main triplet appears as a doublet of triplets, caused by the two magnetically non-equivalent meta-protons of the phenoxy group (\( hfc = 1.82 \) Gauss, 1.62 Gauss), and by the pyrazolyl ring proton H–C(4) which shows a hyperfine splitting constant of 3.10 Gauss. However, this proton splitting was not observed in compound 3A.
In the ESR spectrum of compound 3A (Fig. 2), it is easy to recognize a 1 : 2 : 1 triplet (with a large hyperfine coupling constant, $hfc = 9.86$ Gauss, due to the two methylene protons) of triplets (with a small hyperfine coupling constant, $hfc = 1.86$ Gauss, resulting from the meta-protons of the phenoxyl group). These hyperfine coupling constants and the general splitting pattern are very similar to those observed earlier for related structures.\textsuperscript{12}

For compound 3B, the ESR signal is very weak and poorly resolved (Fig. 3); it shows a broadened triplet ($hfc = 6.20$ Gauss), probably due to the pyrazolic $^{14}$N atom linked to the methylene group, therefore, it is difficult to interpret the spectrum.

The other samples 2Aa, 2Ba and 2Bb showed no detectable ESR signal even when they were prepared and measured at low temperature. In a previous study,\textsuperscript{12} the pyrazole derivative similar to 2Aa, bearing methyl groups (instead of trifluoromethyl groups) in positions 3 and 5 afforded on oxidation with lead tetraacetate in toluene a persistent aroxyl, the ESR spectrum of which showed a triplet (a large coupling constant due to the two methylene protons) of multiplets; each component of the triplet contains nine lines due to slightly different hyperfine couplings: a 1 : 2 : 1 triplet ($hfc = 1.8$ Gauss) caused by the meta-protons of the phenoxyl group, and a 1 : 1 : 1 triplet ($hfc = 1.4$ Gauss) due to the pyrazolic $^{14}$N atom linked to the methylene group. We have no explanation why persistent aroxyls were not obtained in the oxidation of compounds 2Aa, 2Ba and 2Bb.

In summary, six new fluorine-containing heterocycles were synthesized by reaction of 3,5-dialkyl-4-hydroxybenzylhydrazine with hexafluoroacetone, and trifluoroacetylacetone (yielding the pyrazoles bearing trifluoromethyl and/or methyl substituents in positions 3 and 5), and with trifluoroacetoacetic acid ethyl ester (yielding pyrazol-5-ones). All the new heterocycles were characterized.
The ESR spectra of aroxyls obtained by oxidation of phenols 2Ab, 3A and 3B, with Pb(OAc)$_4$ in CH$_2$Cl$_2$ solution, at room temperature, are presented and discussed.

EXPERIMENTAL

Melting points were obtained on a Mel-Temp melting point apparatus and are uncorrected. The IR spectra were obtained on FT/IR-410 Jasco spectrometer. The $^1$H- and $^{19}$F-NMR spectra were recorded, in CDCl$_3$ as a solvent, on a JEOL Datum (400 MHz) spectrometer. The chemical shifts for the $^1$H-NMR spectra are reported in ppm downfield from internal TMS, and those for the $^{19}$F-NMR spectra are given in ppm downfield from internal C$_6$F$_6$. All reactions with air-sensitive compounds were carried out under a nitrogen atmosphere. Column chromatography was conducted on silica gel. GC analyses were performed using a Hitachi G-5000 instrument (flame ionization detector, FID) with a 30 m column NeutraBond.

ESR Measurements

The electron spin-resonance measurements were performed on a Bruker ESP-300 X-band spectrometer with 100 kHz field modulation, 0.2 G modulation amplitude, >10$^4$ receiver gain and 20 mW microwave power. The aroxyl samples were prepared by oxidizing the phenol samples with Pb(OAc)$_4$ in CH$_2$Cl$_2$, at 23 ºC. The dichloromethane solutions were prepared under an argon atmosphere in a Schlenk tube, and were transferred into a quartz ESR tube (2 mm diameter). The calculation of the hyperfine splitting constants was carried out by computer simulation of the ESR spectra with the Bruker WINEPR Simfonia program (version 1.25).

General procedure for the preparation of CF$_3$-containing pyrazoles and pyrazolones

A mixture of 10 mmol 3,5-dialkyl-4-hydroxbenzylhydrazine (1), and 10 mmol CF$_3$-containing 1,3-diketones in 30 mL ethanol was kept for 30 min at room temperature, then refluxed for 10 h (for the syntheses of pyrazoles) and 6 h (for the syntheses of pyrazolones). Water was then added and the aqueous layer was extracted with diethyl ether, dried (Na$_2$SO$_4$), filtered, concentrated, and then purified by flash chromatography on silica gel or by recrystallization.

1-(3,5-Di-t-butyl-4-hydroxybenzyl)-3,5-bis(trifluoromethyl)pyrazole (2Aa). 2Aa was purified by flash chromatography on silica gel, eluting with a 20:1 mixture of hexane and ethyl acetate to give yellow crystals, m.p. 70–71 ºC, yield 63 %. $^1$H-NMR: 1.40 (s, 18H); 5.25 (s, 1H); 5.35 (s, 2H); 6.87 (s, 1H); 7.14 (s, 1H); $^{19}$F-NMR: 99.37 (s, 3F); 102.64 (s, 3F); IR (neat, cm$^{-1}$): 3630–3650 (OH); MS m/z: 422 (M$^+$ + H$^+$). HRMS. Calcd. For C$_{20}$H$_{24}$OF$_6$N$_2$ (m/e): 422.1792; Found: 422.1784.

1-(3,5-Di-t-butyl-4-hydroxybenzyl)-5-methyl-3(trifluoromethyl)pyrazole (2Ab). 2Ab was purified by flash chromatography on silica gel, eluting with a 10:1 mixture of hexane and ethyl acetate to give white crystals, m.p. 115–116 ºC, yield 64 %. $^1$H-NMR: 1.39 (s, 18H); 2.26 (s, 3H); 5.20 (s, 1H); 5.22 (s, 2H); 6.30 (s, 1H); 6.95 (s, 1H); $^{19}$F-NMR: 99.68 (s, 3F); IR (neat, cm$^{-1}$): 3630–3650 (OH); MS m/z: 368 (M$^+$ + H$^+$). HRMS. Calcd. For C$_{20}$H$_{27}$OF$_3$N$_2$ (m/e): 368.2075; Found: 368.2084.

1-(3-t-Butyl-4-hydroxy-5-methylbenzyl)-3,5-bis(trifluoromethyl)pyrazole (2Ba). 2Ba was purified by recrystallizations from n-heptane, white crystals, m.p. 70 ºC, yield 56 %. $^1$H-NMR: 1.38 (s, 9H); 2.22 (s, 3H); 4.80 (s, 1H); 5.34 (s, 2H); 6.87 (s, 1H); 6.95 (s, 1H); 7.10 (d, J = 1.70 Hz, 1H); $^{19}$F-NMR: 99.44 (s, 3F); IR (neat, cm$^{-1}$): 3630–3650 (OH); MS m/z: 380 (M$^+$ + H$^+$). HRMS. Calcd. For C$_{17}$H$_{18}$OF$_6$N$_2$ (m/e): 368.2075; Found: 368.2084.

1-(3-t-Butyl-4-hydroxy-5-methylbenzyl)-3-(trifluoromethyl)pyrazole (2Bb). 2Bb was purified by recrystallizations from n-heptane, white crystals, m.p. 114–116 ºC, yield 65 %. $^1$H-NMR: 1.36 (s, 9H); 2.19 (s, 3H); 2.23 (s, 3H); 4.77 (s, 1H); 5.20 (s, 2H); 6.30 (s, 1H); 6.76 (s, 1H); 6.94 (d, J
1-(3,5-Di-t-butyl-4-hydroxybenzyl)-3-(trifluoromethyl)pyrazol-5-one (3A). 3A was purified by recrystallizations from n-heptane, white crystals, m.p. 219–221 °C, yield 66 %. 1H-NMR: 1.38 (s, 18H); 3.27 (s, 2 H); 5.01 (d, J = 18 Hz, 2H); 5.72 (s, 1H); 5.73 (s, 1H); 6.95 (s, 1H); 19F-NMR: 101.17 (s, 3 F); IR (neat, cm−1): 3630–3650 (vOH); 1653 (vC=O); MS m/z: 370 (M+). HRMS. Calcd. for C19H25OF3N2 (m/e): 370.1866; Found: 370.1868.

1-(3-t-Butyl-4-hydroxy-5-methylbenzyl)-3-(trifluoromethyl)pyrazol-5-one (3B). 3B was purified by recrystallizations from n-heptane, white crystals, m.p. 186–192 °C, yield 64 %. 1H-NMR: 1.38 (s, 9H); 2.14 (s, 3 H); 3.30 (s, 2H); 4.98 (d, J = 18 Hz, 2H); 5.73 (s, 1H); 6.83 (s, 1H); 6.93 (d, J = 1.70 Hz, 1H); 19F-NMR: 101.24 (s, 3F); IR (neat, cm−1): 3630–3650 (vOH); 1672 (vC=O); MS m/z: 328 (M+). HRMS. Calcd. for C16H19OF3N2 (m/e): 328.1398; Found: 328.1383.

REFERENCES