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Synthesis of new analgesics based on 4-isopropyl-1-phenyl-3-(trifluoromethyl)pyrazol-5-one

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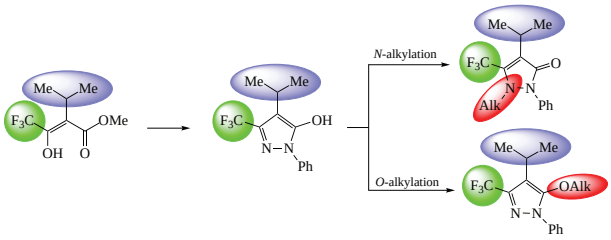
Methyl 4-trifluoro-2-isopropyl-4-oxobutanoate prepared by the improved procedure was cyclized with hydrazines to afford the title pyrazole derivatives. *N*- and *O*-alkylation of 4-isopropyl-1-phenyl-3-(trifluoromethyl)pyrazol-5-ol gave trifluoromethyl analogues of Propyphenazone and 5-alkoxy derivatives. 4-Isopropylpyrazoles containing *O*-butoxy moiety with a terminal trifluoromethyl or acyloxy group were found to demonstrate a promising analgesic activity.



Keywords: 4-isopropyl-3-(trifluoromethyl)pyrazol-5-ols, alkylation, propyphenazone, 5-alkoxypyrazoles, organofluorine compounds, analgesic activity, acute toxicity.

Dedicated to the anniversary of Irina P. Beletskaya, Academician of the Russian Academy of Sciences, a wonderful person, a talented scientist and organizer of science.

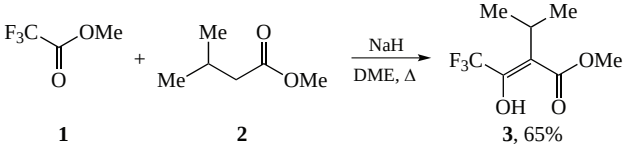
The pyrazole moiety is among the privileged scaffolds in medicinal chemistry,[1–7] largely due to the fact that it underlies the creation of a large family of analgesics-antipyretics of the pyrazolone series.[8] Trifluoromethyl-containing pyrazoles deserve special attention in the development of nonsteroidal anti-inflammatory drugs whose triad of properties includes also analgesic action.[9–11] Such a structural unit is present in selective cyclooxygenase-2 inhibitors Celecoxib and Mavacoxib.

Recently, we have found new applications of trifluoromethyl-substituted pyrazoles for synthesizing analgesics.[12–17] In this context, we suggested methods for chemoselective *N*- and *O*-methylation of 1-phenyl-3-(polyfluoroalkyl)pyrazol-5-ols for the synthesis of MeN- and MeO-derivatives of 1-aryl-3-(polyfluoroalkyl)pyrazol-5-ols as analogues of Antipyrine and Celecoxib, respectively.[14,16] The compounds synthesized, namely CF_3-antipyrine and 5-methoxy-1-phenyl-3-(trifluoromethyl)pyrazole, manifested analgesic activity exceeding that of Analgin in a 'hot plate' test, which determines studies in this area as a promising approach. However, we found no data on the synthesis of a trifluoromethyl analogue of Propyphenazone, though this 4-isopropyl-containing Antipyrine derivative is popular as part of combination drugs for the treatment of headache and rheumatic pain.[18] Compared to other pyrazolone derivatives, Propyphenazone is believed to be the safest because it cannot be converted to potentially carcinogenic nitrosamines due to the lack of an amino group.

In this work, we synthesized new trifluoromethyl-containing analogues of Propyphenazone and studied their analgesic activity. First, we decided to modify the method for synthesizing required methyl 4,4,4-trifluoro-2-isopropyl-3-oxobutanoate that was previously obtained by the reaction of poorly accessible (1-methoxy-3-methylbut-1-en-1-yloxy)trimethylsilane with 4-dimethyl-1-(trifluoroacetyl)pyridinium trifluoroacetate.[19] However, that method involved multiple stages, employed the Schlenk technique and provided low overall yields of ~30%.

In this study (Scheme 1), we obtained oxo ester **3** by the classical Claisen condensation of commercially available methyl esters of trifluoroacetic (**1**) and isovaleric (**2**) acids. Various conditions were tested for its implementation. The conversion of the reactants upon treatment with lithium hydride in hexane or with addition of dimethoxyethane (DME) was as small as ~10–20%. Next, Na and a 60% mineral oil dispersion of NaH as the condensation agents were tested in DME, however, the reaction with sodium led to resinification of the mixture. The optimal conditions for the synthesis of oxo ester **3** were found to be refluxing the reactants in DME for 40 h in the presence of NaH, which provided 65% yield of the desired compound.

To obtain pyrazoles, we performed the cyclization of oxo ester **3** with hydrazines. Its refluxing with hydrazine hydrate in methanol for 3 h resulted in 4-isopropyl-3-trifluoromethyl-1*H*-pyrazol-5-ol **4** (Scheme 2). In contrast, the reaction of oxo ester **3** with phenylhydrazine under the same conditions gave hydrazone **5** that could be detected in the reaction mixture by GC-MS (*m/z* $[M]^+$ 303). Based on the molecular ion mass, compound **5** was formed through condensation of the trifluoroacyl substituent with the amino group of hydrazine. Further refluxing of intermediate **5** in glacial acetic acid led to its



1 **2** **3**, 65%

Scheme 1

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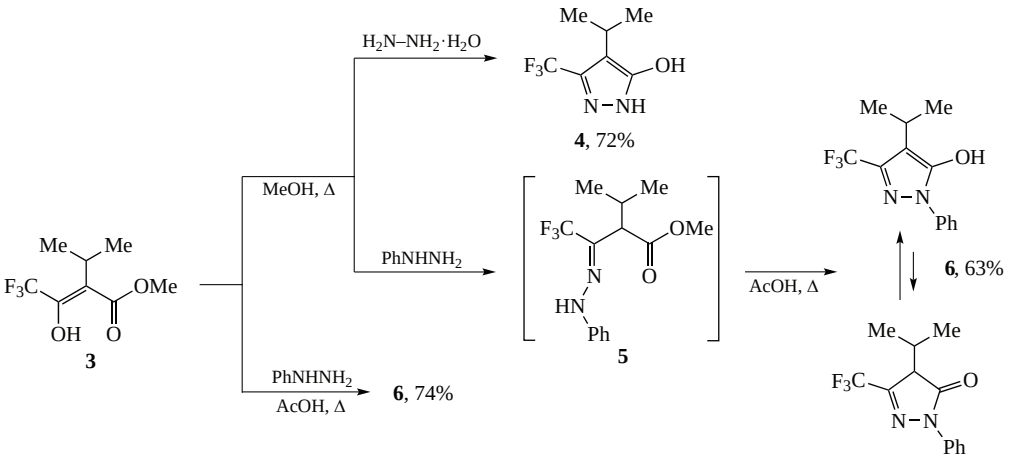
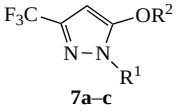


Scheme 2

cyclization into the target 4-isopropyl-1-phenyl-3-trifluoromethyl-1*H*-pyrazol-5-ol **6**. Pyrazole **6** can be obtained in a better yield if the reaction between oxo ester **3** and phenylhydrazine is performed immediately in refluxing glacial acetic acid.

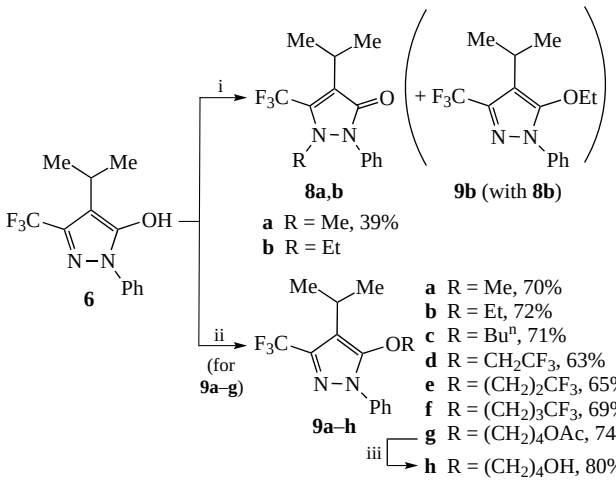
It should be noted that the NMR spectra of pyrazole **4** recorded in $CDCl_3$ contain one set of signals corresponding to the enolic form. In contrast, phenyl-substituted analogue **6** undergoes keto–enol tautomerization in $CDCl_3$ to give two forms in 46 : 54 ratio. However, the spectrum of compound **6** in DMSO-d_6 contains one set of signals belonging to the enolic tautomer. A similar phenomenon was observed earlier for 4-substituted 1-phenyl-3-trifluoromethyl-1*H*-pyrazol-5-ol **7a**[16] that had one form in DMSO-d_6 but three tautomeric forms in $CDCl_3$.



7a–c

a R^1 = Ph, R^2 = H
b R^1 = R^2 = H
c R^1 = Ph, R^2 = Me

Trifluoromethyl-containing analogues of Propyphenazone were obtained using the method that we developed previously for the synthesis of CF_3-antipyrine, *i.e*. by heating 1-phenyl-3-(trifluoromethyl)pyrazol-5-ol **7a** in excess of dimethyl sulfate at 150–160 °C for 5–6 h.[14,16] In this work we found that *N*-methylation of isopropyl containing analogue **6** giving 4-isopropyl-1-methyl-2-phenyl-5-trifluoromethyl-1,2-dihydro-3*H*-pyrazol-3-one **8a** proceeded more efficiently at 100–110 °C within 12 h (Scheme 3), since at higher temperatures



Scheme 3 *Reagents and conditions*: i, R_2SO_4 (excess), 100–110 °C; ii, R_2SO_4 or RHal, K_2CO_3, MeCN, Δ; iii, HCl (gas), MeOH, room temperature.

considerable resinification occurred. A similar reaction with diethyl sulfate affords a mixture of *N*- and *O*-ethyl substituted products **8b** and **9b** in 1 : 1 ratio. Unfortunately, we failed to separate these isomers due to the similarity in their chromatographic mobilities. It should be noted that the selectivity of *N*-alkylation decreases as the alkyl residue is elongated.

We have found previously[16] that *O*-methylation of pyrazol-5-ol **7a** occurred selectively in the presence of a base, therefore, similar conditions were chosen for the *O*-alkylation of pyrazole **6**. Indeed, refluxing pyrazole **6** with dialkyl sulfates in the presence of K_2CO_3 in acetonitrile gave 5-alkoxypyrazoles **9a–c** in good yields. The use of trifluoroalkyl iodides or 4-bromobutyl acetate in a similar reaction led to *O*-alkylated derivatives **9d–g**. Acid hydrolysis of the acetyl group in compound **9g** resulted in 4-hydroxybutoxy-containing pyrazole **9h**.

We explored the analgesic properties of the herein synthesized 4-isopropylpyrazoles **4**, **6** and **9** and compared them with those of Analgin and 4-substituted analogues **7a–c** studied previously (Table 1). It should be noted that, in contrast to CF_3-antipyrine[14] and Propyphenazone, CF_3-propyphenazone **8a** was unstable on long term storage in air or in solutions, and so we failed to analyze its analgesic activity. First, the acute toxicity of the compounds studied was assessed. To this end, a dose of each compound was injected intraperitoneally as a suspension in 1% starch mucus to three CD-1 mice, and their condition was monitored for a period of two weeks.[20,21] It was found for 5-hydroxy derivatives of CF_3-pyrazoles **7a**,**b** that the presence of 4-positioned isopropyl substituent caused a toxicity increase, *viz*. whereas compounds **4** and **6** (Table 1, entries 4, 5) were found to be toxic at a dose of 150 mg kg^{-1}, their 4-unsubstituted analogues **7a**,**b** (entries 1 and 2) showed toxicity at higher doses. The second structural feature affecting the toxicity of these compounds is the presence of hydroxy or alkoxy group at position 5, since 5-alkoxy derivatives **9a–h** (entries 6–13) were less toxic than their 5-hydroxy-substituted analogues **4**, **6**. The nature of the alkyl substituent, including that comprising a hydroxy group in the alkyl chain (**9h**, entry 13), did not have a significant effect on toxicity. Thus, of the samples studied, compounds **4** and **6** containing both 4-positioned isopropyl substituent and 5-positioned hydroxy group showed the greatest toxicity; for this reason, the analgesic effect of these compounds was not tested.

The analgesic activity of pyrazoles **9a–h** was estimated in *in vivo* experiments on SD rats at a dose of 15 mg kg^{-1} using the 'hot plate' test (see Table 1). The compounds were administered intraperitoneally as a suspension in 1% starch mucus. In contrast to 5-methoxypyrazole **7c** (entry 3),[14] its 4-isopropyl-substituted

Table 1 Analgesic activity[a] and acute toxicity of compounds **9a–h**.

Entry	Compound	Analgesic activity: increase in the latency period (%)		Acute toxicity: dose, mg kg^{-1} (number of survived animals from 3 treated)
		1 h	2 h	
1	**7a**[14]	54.5[c]	n/t	300 (1)
2	**7b**[15]	17.7[b]	82.6[c]	150 (3) 300 (0)
3	**7c**[14]	82.9[c]	n/t	300 (3) 600 (3)
4	**4**	n/t	n/t	150 (0) 37 (3)
5	**6**	n/t	n/t	150 (0) 37 (3)
6	**9a**	n/a	n/a	150 (3)
7	**9b**	n/a	56[d]	150 (3)
8	**9c**	n/a	107[d]	150 (3)
9	**9d**	n/a	n/a	150 (3)
10	**9e**	n/a	72[c]	150 (3)
11	**9f**	60[c]	84[e]	150 (3)
12	**9g**	58[b]	85[d]	150 (3)
13	**9h**	n/a	n/a	150 (3)
14	Analgin	59.8 ± 14.9[f]	87.8 ± 26.6[f]	600 (3) LD_{50} 2197 mg kg^{-1} (mice, i/v)[g]

[a] Dose is 15 mg kg^{-1}; n/a is inactive; n/t is not tested; [b] $p < 0.05$; [c] $p < 0.01$; [d] $p < 0.001$; [e] $p < 0.0001$; [f] mean ± standard deviation for three independent experiments. [g] Dipyrone (https://chem.nlm.nih.gov/chemidplus/rn/68-89-3), i/v is intravenous.

analogue **9a** was inactive (entry 6), as was compound **9d** with a short trifluoroethoxy substituent (entry 9). Elongation of the alkoxy substituent in compounds **9b**,**c**,**e**,**f**,**g** resulted in the appearance of a pronounced analgesic effect, which was especially evident in 2 h after administration (entries 7, 8, 10–12). 4-Butoxypyrazole **9c** (entry 8) showed the strongest analgesic effect at this time point. Its analogues **9f**,**g** containing a butoxy moiety with a terminal electron-acceptor group had a pronounced antinociceptive effect (entries 11, 12) at the level of the reference drug, Analgin, at both time points of the measurements. It is interesting to note that replacement of the acyl moiety in compound **9g** with a hydroxyl residue in derivative **9h** resulted in complete activity loss (entry 13).

In summary, we synthesized a series of trifluoromethyl-containing analogues of Propyphenazone and its *O*-alkylated analogues. We demonstrated the applicability of the previously developed methods of selective *O*- and *N*-methylation for the alkylation towards 4-isopropyl-1-phenyl-(3-trifluoromethyl)-pyrazol-5-ol. The instability of trifluoromethyl-substituted Propyphenazone was observed. Biological testing of stable derivatives showed that incorporation of an isopropyl substituent into position 4 of pyrazol-5-ols resulted in an increase in their toxicity, which reduced after replacement of the hydroxyl residue with an alkoxy moiety. Compounds containing a butoxy moiety with a terminal electron-acceptor group showed the greatest activity in the series of *O*-alkoxy derivatives obtained.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.02.014.

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