Regiospecific Cyclization of β-Methoxyvinyl Trifluoromethyl Ketones with Aminoguanidine: A Convenient Method to Obtain Trifluoromethylated 2-[1H-Pyrazol-1-yl]pyrimidines

Helio Gauze Bonacorso,* Alexandre Pereira Wentz, Nilo Zanatta, Marcos Antonio Pinto Martins

Núcleo de Química de Heterociclos (NUQUIMHIE), Departamento de Química, Universidade Federal de Santa Maria, 97105–900 Santa Maria, RS-Brazil
Fax +55(55)2208031; E-mail: heliogb@base.ufsm.br
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Abstract: The regiospecific one-pot synthesis of a novel series of 6-alkyl(aryl)-2-[3-alkyl(aryl)-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1H-pyrazol-1-yl]-4-trifluoromethylpyrimidines 2 and 6-alkyl(aryl)-2-[3-alkyl(aryl)-2-[3-alkyl(aryl)-5-trifluoromethyl-1H-pyrazol-1-yl]-4-trifluoromethylpyrimidines 3 from 4-alkyl(aryl)-1,1,1-trifluoro-4-methoxyalk-3-en-2-ones 1 and aminoguanidine bicarbonate is reported.

Key words: pyrimidines, pyrazoles, 2-(pyrazolyl)pyrimidines, trifluoromethyl vinyl ketones

Many 2-pyrazolylpyrimidine derivatives are known to exhibit important pharmacological activities.1–4 Studies have been undertaken to examine analgesic, antipyretic and anti-inflammatory activity of these compounds and several of them have been found to be equal or more active than aminopyrine.1,2 For example, 500 ppm of the microcide 2-(3,5-diethyl-1-pyrazolyl)pyrimidine inhibited the proliferation of Pellicularia orizae, Helminthosporium orizae and Helminthosporium sasakii and Pyricularia oryzae on rice.3 It was found that alkyl substitution enhanced the fungicidal activity of the 2-pyrazolylpyrimidines against Pyricularia oryzae and Helminthosporium sigmoideaum irregular, but the activity was impaired by introduction of a phenyl group into the pyrazole ring.4 Among the many derivatives, 4-methoxy-2-[3-methoxy-3-methyl-1H-pyrazol-1-yl]-6-methylpyrimidine (epirizole), which bears a methoxy group at 5-position of the pyrazole and at 4-position of the pyrimidine was reported to be highly active as analgesic and anti-inflammatory.1 On the other hand, many trifluoromethylated 1H-pyrazoles and derivatives are known to exhibit important biological activities in medicinal and agricultural fields.5–10

Since the first 2-(pyrazol-1-yl)pyrimidine was reported in 1963, new methods to obtain these important compounds have been relatively little explored. The classical access to 2-(pyrazol-1-yl)pyrimidine was described by Shirakawa and Tsukikawa1 and involves several steps. The last step of the reaction usually comprises a condensation of β-diketones or alkyl acetoacetate or derivatives thereof with 2-hydrazinopyrimidines.3,4,11,12 In its turn, 2-hydrazinopyrimidines were prepared from pyrimidin-2-ones which were treated with an excess of phosphorous oxychloride followed by nucleophilic substitution of the 2-chloropyrimidine with hydrazine.13 2-Hydrazinopyrimidines were also prepared from the parent 2-methylsulfanyl pyrimidine by nucleophilic substitution of the methanesulfanyl group with hydrazines.14 As an exception of the Shirakawa synthesis, 2-pyrazolylpyrimidines have been obtained by the reaction of 1H-pyrazoles with 2-chloropyrimidines.4

Considering the importance of the 2-(pyrazol-1-yl)pyrimidines due to their prominent biological activity, we were prompted to develop a new and more satisfactory synthetic methods to obtain 2-(5-hydroxy-4,5-dihydro-1H-pyrazol-1-yl)pyrimidines and the corresponding dehydrated 2-(pyrazol-1-yl)pyrimidines.

In recent publications the versatility of the β-alkoxyvinyl-β-aryl[(alkyl)trihalomethyl ketones as readily available building blocks for the regiospecific construction of pyrimidines,15 pyrazoles,16–18 benzodiazepines19 and thiazines20 bearing a trihalomethyl group, have been reported.

The present work reports the regiospecific one-pot synthesis of a new series of 6-alkyl(aryl)-2-[3-alkyl(aryl)-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1H-pyrazol-1-yl]-4-trifluoromethylpyrimidines 2a–h and 6-alkyl(aryl)-2-[3-aldehyde(aryl)-5-trifluoromethyl-1H-pyrazol-1-yl]-4-trifluoromethylpyrimidines 3a, 3d from the reaction of 4-alkyl[(aryl]-1,1,1-trifluoro-4-methoxyalk-3-en-2-ones 1a–h with aminoguanidine bicarbonate.

The synthetic strategy of this work is presented in the Scheme and the most satisfactory yields of the reactions and selected physical properties are presented in the experimental part. The IR and NMR spectral data are shown in Tables 1 and 2.

The β-methoxyvinyl trifluoromethyl ketones 1a–h were prepared according to refs. 21–24. The cyclocondensation reactions of compounds 1a–h with aminoguanidine bicarbonate were carried out in a molar ratio of 2:1 using ethanol as solvent. The reactions were monitored by TLC and the most satisfactory reaction time and temperature was found to be 4 hours at 85–90°C (reflux) for 2a–h. The isolation of the intermediates 2a–h was possible probably due to the presence of a strong electron-withdrawing ef-
The effect of the trifluoromethyl group on the pyrazoline ring. The compounds 3a and 3d were obtained by dehydration of 2a and 2d with sulfuric acid in dichloromethane under reflux for 4 hours. The synthesis of 3d was also performed in a one-step reaction without the isolation of the 4,5-dihydro-pyrazolylpyrimidine 2d when the reaction was carried out with the ketone 1d and aminoguanidine bicarbonate, in a molar ratio 2:1 in ethanol under reflux for 4 hours. Treatment of the crude product with a mixture of sulfuric acid and dichloromethane at reflux temperature and subsequent workup (see experimental) gave 3d.

The unambiguous 1H and 13C NMR chemical shifts assignments of compounds 2a–h, 3a, d were obtained with the help of homonuclear COSY, HMQC and HMBC 2D-NMR experiments and by comparison with NMR data of others pyrazoles and pyrimidines formerly synthesized in our laboratory.

In addition, we have performed reactions using β-alkoxyvinyl trichloromethyl ketones and amino guanidine carbonate in an attempt to obtain the corresponding 4-trichloromethyl analogs of 2 and 3, but the reactions resulted in dark mixtures of unidentified products under similar methodology used for the parent trifluorinated compounds. Evaluation of other conditions to obtain the parent trichloromethylated pyrazolpyrimidine system is now under investigation.

In summary, this work showed a convenient one step procedure which allowed the isolation of a new series of 6-alkyl(aryl)-2-[3-alkyl(aryl)-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1H-pyrazol-l-yl]-4-trifluoromethylpyrimidines 2a–h; General Procedure

To a magnetically stirred solution of 1a–h (5 mmol) in EtOH (25 mL) kept at 20–25°C was added solid amino guanidine bicarbonate (2.5 mmol). The mixture was stirred for 4 h under reflux. The solvent was evaporated and the solid products recrystallized from MeOH.

2a Yield: 85%; mp 69–71°C.
2b Yield: 52%; oil.
2c Yield: 39%; mp 80–82°C.
2d Yield: 55%; mp 182–184°C.
2e Yield: 47%; mp 143–145°C.
2f Yield: 60%; mp 199–201°C.
2g Yield: 50%; mp 217–219°C.
2h Yield: 66%; mp 151–153°C.

6-Alkyl(aryl)-2-[3-alkyl(aryl)-5-trifluoromethyl-1H-pyrazol-l-yl]-4-trifluoromethylpyrimidines 3a, 3d; General Procedure

In a 50 mL flask, a mixture of 2a, 2d (10 mmol) and concd H2SO4 (4 mL, 40 mmol) in CH2Cl2 (20 mL) was magnetically stirred for 4 h under reflux. The mixture was slowly poured into H2O (20 mL) and the solution was extracted with CH2Cl2 (3 × 20 mL). The combined organic fractions were washed with H2O, dried (MgSO4) and the solvent removed in a rotavapor. After keeping 24 h in a refrigerator at 0–5°C the yellow crystals of 3d formed were collected by filtration. Compound 3a was an yellow oil and no further purifica-
Synthesis of Trifluoromethylated 2-[1H-Pyrazol-1-yl]pyrimidines 1507

<table>
<thead>
<tr>
<th>Product</th>
<th>IR (KBr) (cm⁻¹)</th>
<th>δ, J (Hz)</th>
<th>δ, J (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>1595, 1491</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2b</td>
<td>1571, 1489</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2c</td>
<td>1593, 1488</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2d</td>
<td>1592, 1486</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2e</td>
<td>1584, 1485</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2f</td>
<td>1592, 1485</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2g</td>
<td>1590, 1476</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2h</td>
<td>1586, 1490</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The NMR spectra were recorded on a Bruker DPX 400 spectrometer (¹H at 400.13 MHz and ¹³C at 100.62 MHz).*

*Satisfactory elemental analyses obtained: C ±0.42, H ±0.36, N ±0.25. Exception: 2b, C ±2.97, H±0.12, N ±0.79.*
tion was undertaken. Compound 3d was recrystallized from MeOH and 3a was considered pure by elemental analysis.

3a
Yield: 70%; oil.

3d
Yield: 76%; mp 129–131 °C.

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References

Table 2 Selected Spectral Data of Trifluoromethylated 2-[1H-Pyrazol-1-yl]pyrimidines 3a, d

<table>
<thead>
<tr>
<th>Product</th>
<th>IR (KBr) (cm⁻¹)</th>
<th>¹H NMR (DMSO-d₆/TMS)</th>
<th>¹³C NMR (DMSO-d₆/TMS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>1560, 1390</td>
<td>8.01 (s, 1 H, H₂A), 7.09 (s, 1 H, H₂B), 2.76 (s, 3 H, CH₃-A), 2.41 (s, 3 H, CH₃-B)</td>
<td>174.1 (C₆-A), 155.0 (q, J = 36.0, C₅-A), 154.8 (C₇-A), 151.2 (C₈-A), 132.0 (q, J = 40.0, C₅-B), 120.0 (q, J = 274.7, CF₃-B), 119.6 (q, J = 268.6, CF₃-A), 115.6 (C₆-B), 113.5 (C₇-B), 23.8 (CH₃-A), 12.9 (CH₃-B)</td>
</tr>
<tr>
<td>3d</td>
<td>1598, 1475</td>
<td>8.63 (s, 1 H, H₂B), 8.42 (m, 2 H, Ph-A), 8.03 (m, 2 H, Ph-B), 7.92 (s, 1 H, H₂A), 7.63 (m, 3 H, Ph-B), 7.49 (m, 3 H, Ph-B)</td>
<td>168.7 (C₆-A), 156.5 (q, J = 36.5, C₅-A), 155.3 (C₇-B), 152.6 (C₈-A), 134.1, 132.9, 130.4, 129.5, 129.2, 128.9, 128.0, 126.0 (Ar-C), 133.3 (q, J = 40.6, C₅-B), 120.31 (q, J = 275.7, CF₃-B), 119.67 (q, J = 268.7, CF₃-A), 112.1 (C₆-A), 111.3 (C₇-B)</td>
</tr>
</tbody>
</table>

a The NMR spectra were recorded on a Bruker DPX 400 spectrometer (¹H at 400.13 MHz and ¹³C at 100.62 MHz).
b Satisfactory microanalyses obtained: C ± 0.19, H ± 0.16, N ± 0.04.