Synthesis of Aminopyrazoles from α- Oxoketene *O,N*-Acetals Using Montmorillonite K-10/Ultrasound

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Received 14 January 2003

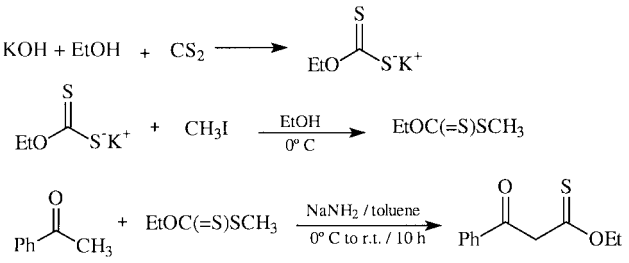
Abstract: 5(3)-Amino-3(5) phenylpyrazoles **3a**–**f** have been conveniently prepared by condensation of α-oxoketene *O,N*-acetals **2a**–**g** with hydrazine using montmorillonite K-10 as solid support under sonication.

Key words: aminopyrazoles, α-oxoketene *O,N*-Acetals, β-oxothioxo ester, montmorillonite K-10

The synthesis of heterocyclic compounds using the methodology of reactions on solid supports has been an objective of study in our laboratories. We reported previously the synthesis of a series of pyrazoles from β-enamino compounds using this methodology,[1–3] where the amino group was lost during the formation of the pyrazole rings. In this study, we have succeeded in obtaining pyrazoles while keeping the amino group intact, a worthwhile product since aminopyrazoles are useful biologically active compounds.[4,5]

The strategy used in this work to prepare aminopyrazoles involves the cyclization of α-oxoketene *O,N*-acetals with hydrazine in heterogeneous media, using montmorillonite K-10 and ultrasound sonication. The α-oxoketene *N,N*-; *N,S*-; *S,S*-; and *O,N*-acetals have been proven to be versatile intermediates in the construction of a large number of heterocycles,[6–14] however, very few examples are reported starting from α-oxoketene *O,N*-acetals. In this work the α-oxoketene *O,N*-acetals **2a**–**g** were obtained through the reaction of β-oxothioxo ester **1** and primary amines. The β-oxothioxo ester **1** was prepared according to reported procedures[15–17] by the reaction of potassium hydroxide with carbon disulfide in ethanol to give potassium *O*-ethyl dithiocarbonate followed by alkylation with methyl iodide resulting in *S*-methyl *O*-ethyl dithiocarbonate in 85% yield (Scheme 1). The described methods for the ethoxythiocarbonylation of enolates with *S*-methyl *O*-ethyl dithiocarbonate use sodium *tert*-butoxide or sodium amide as base.[16,17] We tested the reaction on acetophenone with *S*-methyl *O*-ethyl dithiocarbonate with these two types of bases; using sodium amide in toluene gave better yields.

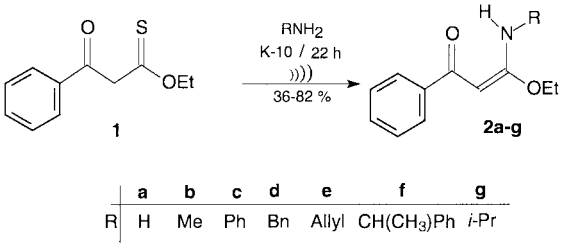
The procedure for the condensation of the primary amines with β-oxothioxo esters for the synthesis of α-oxoketene



Scheme 1

O,N-acetals has been reported in the literature.[17] The regiochemistry of these reactions shows strong dependence on the reaction medium and reaction conditions. When the reaction is carried out with formic acid under reflux in toluene, β-oxothioxo esters are obtained. Without formic acid, a mixture of α-oxoketene *O,N*-acetals and enaminothio esters are obtained.

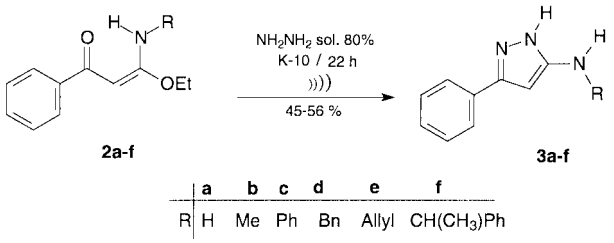
In view of these limitations we decided to study these reactions using the methodology of solid supported reactions, using montmorillonite K-10 as a solid support and sonication under solvent free conditions, without the use of any acid. A series of α-oxoketene *O,N*-substituted acetals **2a**–**g** were obtained selectively by dispersing *O*-ethyl 3-oxo-3-phenylpropanethioate (**1**) and primary amines on montmorillonite K-10 under ultrasound (Scheme 2).



Scheme 2

The cyclization of α-oxoketene *O,N*-substituted acetals **2a**–**f** with 80% hydrazine hydrate on montmorillonite K-10 under ultrasound, afforded 5(3)-amino-substituted 3(5)-phenyl 1*H*- pyrazoles **3a**–**f** (Scheme 3). Using these conditions, the ring closure process occurs according the Baldwin's rules[18] resulting in the allowed 5-*exo-trig* products. The reaction is considered to proceed by the initial attack of hydrazine at C-β, with loss of the OEt group followed by cyclization.

Synthesis 2003, No. 8, Print: 05 06 2003.
Art Id.1437-210X,E;2003,0,08,1160,1162,ftx,en;M00103SS.pdf.



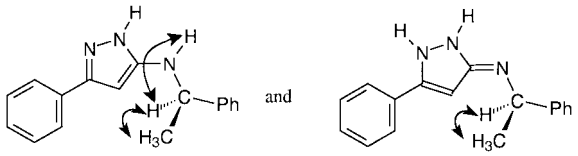
Scheme 3

The structures of the products were unambiguously established based on the ^{1}H and ^{13}C NMR spectra by DEPT 135, HMQC and HMBC experiments. For the aminopyrazole **3f** [R = (*R*)-(+)-1-phenylethylamine], two tautomeric forms were observed in the ^{1}H NMR spectrum (Figure 1). Duplicate signals (see Table 1) in ^{1}H NMR spectrum were observed for the hydrogen of the chiral group [C*H*(CH_3)Ph] as a quintet (5.24 ppm) and a quartet (4.53 ppm) corresponding to the forms **3f** and **3f′**, respectively. In the ^{13}C NMR spectrum, the carbon of the chiral group [*C*H(CH_3)Ph] exhibits different chemical shifts for the tautomeric forms, 47.59 ppm for **3f** and 54.75 ppm for **3f′**, while the carbon of the methyl group appears at 21.62 ppm and at 24.45 ppm for **3f** and **3f′**, respectively. These assignments were confirmed by HMQC and HMBC experiments. The relative proportion of the tautomers has been established on the basis of ^{1}H NMR spectrum, resulting in a ratio of 1:1 for **3f** and **3f′**.

Table 1 α-Oxoketene *O*,*N*-Acetals **2a**–**g** and 5(3)-Amino-3(5)-phenylpyrazoles **3a**–**f** Prepared

Product[a]	Yield[b] (%)	mp (°C)	^{1}H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS) δ
2a	78	75–78	1.27 (t, 3 H, *J* = 7.0), 4.02 (q, 2 H, *J* = 7.0), 5.38 (s, 1 H), 7.36–7.86 (m, 5 H), 6.32 (br, 1 H),10.27 (br, 1 H)	13.89, 63.58, 74.70, 126.44, 127.79, 130.13, 140.52, 169.57, 187.51
2b	40	53–54	1.40 (t, 3 H, *J* = 7.0), 2.90 (d, 3 H, *J* = 5), 4.15 (q, 2 H, *J* = 7.0), 5.40 (s, 1 H), 7.40 (m, 3 H), 7.80 (m, 2 H), 10.90 (br, 1 H)	14.90, 26.30, 64.10, 73.80, 126.40, 127.90, 129.90, 140.90, 168.90, 186.20
2c	36	74–76	1.50 (t, 3 H, *J* = 7.0), 4.28 (q, 2 H, *J* = 7.0), 5.56 (s, 1 H), 7.09–7.90 (m, 10 H), 13.16 (br, 1 H)	14.11, 64.89, 75.30, 121.37, 123.79, 126.63, 128.11, 128.80, 130.33, 137.50, 140.31
2d	60	71–73	1.26 (t, 3 H, *J* = 7.0), 4.02 (q, 2 H, *J* = 7.0), 4.44 (d, 2 H, *J* = 6.0), 5.39 (s, 1 H), 7.19–7.87 (m, 10 H), 11.43 (br, 1 H)	13.94, 43.69, 64.14, 73.80, 126.34, 126.88, 126.95, 127.76, 128.22, 129.93, 137.90, 140.59, 168.12, 186.30
2e	45	51–52	1.40 (t, 3 H, *J* = 7.0), 3.95 (m, 2 H), 4.15 (q, 2 H), 5.25 (m, 2 H), 5.40 (s, 1 H), 7.40 (m, 3 H), 7.80 (m, 2 H), 11.50 (br, 1 H)	14.20, 42.30, 64.20, 73.90, 115.80, 126.40, 127.90, 130.00, 133.70, 140.80, 168.30, 186.50
2f	67	oil	1.25 (t, 3 H, *J* = 7.0), 1.56 (d, 3 H, *J* = 6.8), 4.05 (q, 2 H, *J* = 7.0), 4.95 (m, 1 H, *J* = 6.8), 5.36 (s, 1 H), 7.22–7.87 (m, 10 H), 11.46 (d, 1 H)	13.95, 23.43, 50.22, 64.16, 73.97, 125.55–143.99, 167.45, 186.45
2g	82	oil	1.20 (d, 6 H, *J* = 6.5), 1.29 (t, 3 H, *J* = 7.0), 3.85–4.06 (m, 1 H), 5.32 (s, 1 H), 7.32–7.86 (m, 5 H), 11.03 (d, 1 H)	14.60, 23.40, 42.46, 64.53, 73.90, 126.83, 128.30, 130.33, 141.39,168.12, 186.21
3a	45	108–109	4.28 (br, 3 H), 5.86 (s, 1 H), 7.22–7.65 (m, 5 H)	9.27, 125.41, 128.23, 128.83, 130.35, 145.77, 154.21
3b	54	122–124	2.80 (s, 3 H), 5.80 (s, 1 H), 6.91 (br, 2 H), 7.23–7.59 (m, 5 H)	31.76, 87.38, 125.43, 127.97, 128.68, 130.86, 146.14, 157.58
3c	56	153–154	6.30 (s, 1 H), 6.83–7.59 (m, 10 H), 6.29 (br, 2 H)	92.21, 115.93, 120.17, 125.55, 128.48, 128.94, 129.27, 130.02, 143.17, 145.39, 151.37
3d	45	oil	4.46 (s, 1 H), 5.98 (s, 1 H), 7.07 (br, 2 H), 7.43–7.85 (m, 10 H)	49.18, 87.72, 125.43, 126.98, 127.38, 127.94, 128.37, 128.61, 130.67, 139.49, 146.07, 156.42
3e	50	101–102	3.70–3.73 (m, 2 H), 5.05–5.10 (m, 1 H), 5.15–5.25 (m, 1 H), 5.80 (s, 1 H), 5.83–5.91 (m, 1 H), 7.23–7.58 (m, 5 H)	47.75, 87.72, 115.79, 125.44, 127.92, 128.63, 130.80, 135.66, 146.10, 156.23
3f	51	oil	1.61 (d, 3 H, *J* = 6.8), {1.57 (d, 3 H, *J* = 6.8)}, 5.24 (quint, 1 H, *J* = 6.8), {4.53 (q, 1 H, *J* = 6.8)}, 5.64 (s, 1 H), 5.95 (br, 1 H), 7.17–8.13 (m, 10 H)[c]	21.62 {24.45}, 47.59 {54.75}, 88.55, 125.33–130.70, 142.52 {145.20}, 154.35 {160.28}[c]

[a] All compounds gave satisfactory elemental analyses: C ±0.20, H ±0.14; N ±0.18.
[b] Yield of pure isolated product.
[c] Chemical shifts given in braces refer to duplicated signs belonging to **3f′**.



3f 3f '

Figure 1 Structure of tautomeric forms **3f** and **3f'**

These results demonstrate that the use of the methodology with montmorillonite K-10 is a valuable improvement over the classical methods due to the availability of the acid sites, milder conditions, and higher selectivity.

Melting points were determined with a Microquímica APF-301 apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 200 spectrometer in $CDCl_3$/TMS. Elemental analyses were carried out on a Vario CHN-standard analyzer. An ultrasound bath (water), Thornton 50-60 Hz, 110/220 V, 1.0 amps was used. The temperature of the water bath never exceeded 35 °C.

α-Oxoketene *O*,*N*-Acetals 2a–g; General Procedure

O-Ethyl 3-oxo-3-phenylpropanethioate (**1**; 208 mg, 1 mmol) in CH_2Cl_2 (1 mL) was dispersed on montmorillonite K-10 (0.3 g, Fluka). Then the corresponding amine (1.2 mmol) was added dropwise and the mixture was placed in ultrasound bath for 22 h. The products were extracted by washing the montmorillonite K-10 with CH_2Cl_2; the CH_2Cl_2 solution was dried ($MgSO_4$), filtered and the solvent was removed in vacuo to yield the crude products. The purification was performed by flash column chromatography on silica gel (Aldrich 230–400 mesh) using hexane–EtOAc (20%) as eluent (see Table 1).

5(3)-Amino-Substituted 3(5)-Phenyl-1*H*-pyrazoles 3a–f; General Procedure

Hydrazine hydrate (80%, 2 mmol) was added dropwise to the appropriate α-oxoketene *O*,*N*-acetal **2** (1 mmol) in CH_2Cl_2 (1 mL) dispersed on montmorillonite K-10 (0.3 g, Fluka), and the mixture was placed in ultrasound bath for 22 h. The product was extracted by washing the montmorillonite K-10 with CH_2Cl_2; the CH_2Cl_2 solution was dried ($MgSO_4$), filtered, and the solvent was removed in vacuo to yield the crude product. Compounds **3a**, **3b**, and **3d** were purified by recrystallization from diisopropyl ether, and **3c**, **3e**, and **3f** were purified by flash column chromatography on silica gel (Aldrich 230–400 mesh) CH_2Cl_2–EtOAc (10%) as eluent to give analytically pure pyrazoles (Table 1).

Acknowledgments

We are grateful to the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Brazil and Fundação de Amparo a Pesquisa do Estado do Rio Grande do Sul (FAPERGS-01/0506.6) for financial support and to FAPERGS (D.H) and CNPq-PIBIC for fellowships to D.M.H., J.K.R and L.C.T. We thank Dr. Robert Burrow for helpful comments on the manuscript.

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