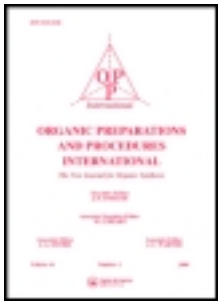

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A CLEAN AND RAPID SYNTHESIS OF 5-AMINO AND 5-ALKOXYCARBONYLPYRAZOLES USING MONTOMORILLONITE UNDER ACID FREE CONDITIONS

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A CLEAN AND RAPID SYNTHESIS OF 5-AMINO AND 5-ALKOXYCARBONYLPYRAZOLES USING MONTOMORILLONITE UNDER ACID FREE CONDITIONS

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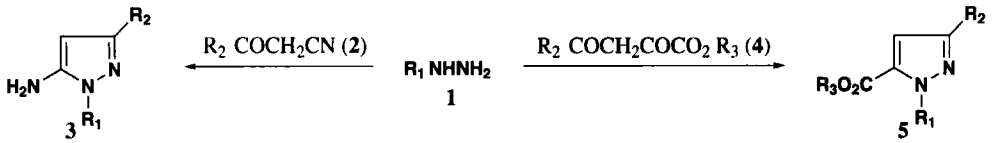
5-Aminopyrazoles are compounds of considerable medicinal interest as they exhibit antiinflammatory and antipyretic properties.[1] These derivatives are also useful intermediates in the synthesis of several fused pyrazoles of potential biological interest.[2, 3] 5-Alkoxycarbonyl pyrazoles are also important intermediates in the synthesis of agrochemicals, microbiocides, plant growth regulators[4] and anticoagulant factor Xa inhibitors.[5] The most common method of synthesizing 5-aminopyrazoles involves the condensation of β-ketonitriles (**2**) with hydrazines (**1**) under a variety of conditions. These include refluxing **2** with **1** in ethanol for 8-16 hrs and reaction of **1** with **2** in presence of large excess of hydrochloric acid.[6] Cyclization of **2** with **1** in refluxing ethanol in presence of triethylamine[7] and 10% acetic acid have also been reported.[8] However, all these methods suffer from certain disadvantages like long reaction times,[9] strongly acidic[6] or basic conditions.[7]

The use of heterogeneous catalysts such as clays has gained much importance during recent years in synthetic organic chemistry because they are economical eco-friendly and selective.[10] Montomorillonite K10 has been extensively used in various organic condensation reactions as a solid acidic catalyst.[11,12] In continuation of our work on synthesis of heterocyclic templates by simple methods,[13,14] we report herein the synthesis of 5-amino and 5-alkoxycarbonylpyrazoles in presence of montomorillonite as solid acid support.



3: a) R_1 = H, R_2 = C_6H_5; b) R_1 = H, R_2 = 4-$CH_3C_6H_4$; c) R_1 = H, R_2 = 4-$CH_3OC_6H_4$; d) R_1 = H, , R_2 = 4-ClC_6H_4, e) R_1 = R_2 = C_6H_5; f) R_1 = C_6H_5, R_2 = 4-$CH_3C_6H_4$; g) R_1 = C_6H_5, R_2 = 4-$CH_3OC_6H_4$; h) R_1 = C_6H_5, R_2 = 4-FC_6H_4; i) R_1 = $CH_2C_6H_5$, R_2 = C_6H_5

5: a) R_1 = H, R_2 = CH_3, R_3 = C_2H_5; b) R_1 = H, R_2 = C_6H_5, R_3 = C_2H_5 ; c) R_1 = R_2 = C_6H_5, R_3 = CH_3 d) R_1 = C_6H_5, R_2 = 4-$CH_3SC_6H_4$, R_3 = CH_3; e) R_1 = C_6H_5, R_2 = 2-Thienyl, R_3 = CH_3

The synthesis of 5-aminopyrazoles **3** were carried out by refluxing β-ketonitriles (**2**) with hydrazines (**1**) in refluxing isopropanol in presence of montomorillonite. It is interesting to note that the reaction times required are dramatically reduced to less than 1 hr, compared to 6-8 hrs when the same reaction is carried out in refluxing ethanol with or without the presence of acetic acid. This method could be applied for the synthesis of a variety of 1,3-substituted 5-aminopyrazoles (*Table 1* **3a-i**). 1,3-Diaryl-pyrazole-5-carboxylates (**5**) are obtained as the major isomer when this reaction is extended to pyruvates. Thus various **5** are obtained when pyruvates (**4**) are reacted with hydrazine hydrate / arylhydrazine (**1**) in refluxing isopropanol in presence of montomorillonite in a short reaction time (<1 hr) when compared to refluxing in acetic acid as per reported methods.[5]

In conclusion, a clean, high yielding and rapid method for the synthesis of 5-amino and 5-alkoxycarbonylpyrazoles using montomorillonite K10 as solid acid support has been developed. The scope and generality of present method of making aminopyrazoles and pyrazolecarboxylates in the presence of montomorillonite under acid free conditions is evident from the reaction of different benzoylacetonitriles and pyruvates with alkyl and arylhydrazines. This method is superior to reported methods, as the reaction is quick, easy to work up, the use of less expensive reagents and does not involve corrosive acids.

EXPERIMENTAL SECTION

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on Perkin Elmer System 2000 FT IR spectrometer in KBr pellets. ^{1}H NMR spectra were obtained on a Varian 200 MHz instrument with TMS as internal standard and in $CDCl_3$. Chemical shifts are expressed in δ ppm. Montomorillonite was purchased from Lancaster.

Synthesis of 5-Aminopyrazoles 3, General Procedure.- To a mixture of β-ketonitrile (**2**, 0.01 mole), hydrazine hydrate/alkylhydrazine/arylhydrazine (0.01 mole), in isopropanol (25 mL) montomorillonite K10 (0.5 gm) was added. The reaction mixture was refluxed for 30-60 minutes. At the end of the reaction as monitored by TLC (Hexane : ethyl acetate, in the ratio of 2:1), the reaction mixture was cooled and filtered, solvent removed and the residual solid was recrystallized from methanol to give pure **3** as crystalline solids (*Table 1*).

TABLE. Yields, mps, Spectral Data of **3** & **5**

Cmpd	Yield[a] (%)	mp (°C)	*lit.* mp (°C)	^{1}H NMR Data (δ) ppm $CDCl_3$
3a	76	124-126	(125)[15]	4.28(bs, 3H), 5.86(s, 1H), 7.22-7.65(m, 5H)
3b	73	145-147	(147)[15]	2.35(s, 3H), 5.61(bs, 3H), 5.87(s, 1H), 7.40(m, 2H), 7.44(m, 2H)
3c	78	141-142	(141)[15]	3.78(s, 3H), 4.45(bs, 3H), 5.84(s, 1H), 7.36(d, 2H), 7.41(d, 2H)
3d	79	172-173	(173)[15]	4.27(bs, 3H), 5.85(s, 1H), 7.21-7.59(m, 4H)
3e	78	124-126	(126)[9]	3.84(bs, 2H), 5.94(s, 1H), 7.34-7.83(m, 10H)
3f	73	172-173	(171)[16]	2.37(s, 3H), 3.68(bs, 2H), 5.82(s, 1H), 7.08-7.59(m, 9H)
3g	74	185-187	(186)[6]	3.78(s, 3H), 4.45(bs, 2H), 5.82(s, 1H), 6.82(d, 2H), 7.32-7.71(m, 7H)
3h	72	148-150	(148)[17]	3.69(bs, 2H), 5.84(s, 1H), 7.21-7.73(m, 9H)
3i	71	123-125	(125-6)[18]	3.91(bs, 2H), 5.28(s, 2H), 5.98(s, 1H), 7.03-7.38(m, 10H)
5a	67	79-81	(81-83)[4]	1.41(t, 3H), 2.25(s, 3H), 4.38(q, 2H), 6.31(s, 1H), 12.18(bs, 1H)
5b	71	138-140	(139-40)[4]	1.42(t, 3H), 4.36(q, 2H), 6.92(s, 1H), 7.21-7.76(m, 5H), 12.79(bs, 1H)
5c	74	106-108	(108)[18]	3.97(s, 3H), 7.06(s, 1H), 7.24-7.34(m, 10H)
5d	69	102-104	*b*	2.46(s, 3H), 3.78(s, 3H), 7.05(s, 1H), 7.26-7.41(m, 9H)
5e	68	115-117	*c*	3.94(s, 3H), 7.07(s, 1H), 7.16(m, 1H), 7.27-7.36(m, 5H), 7.53(m, 2H)

a) Yields are based on pure crystallized compounds; b) *Anal.* Calcd. for $C_{18}H_{16}N_2O_2S$; C, 66.66; H, 4.93; N, 8.64; Found: C, 66.47; H, 5.06; N, 8.73%; c) *Anal.* Calcd. for $C_{15}H_{12}N_2O_2S$; C, 63.38; H, 4.22; N, 9.85; Found: C, 63.42; H, 4.36; N, 9.62.

Synthesis of 1,3-Diaryl-5-methoxycarbonylpyrazoles 5.- To a mixture of pyruvate (**4**, 0.01 mole), phenylhydrazine (0.01 mole) **1**, in isopropanol (25 mL) montomorillonite K10 (0.5 gm) was added. The reaction mixture was refluxed for 30-60 minutes. At the end of the reaction as

monitored by TLC (Hexane : ethyl acetate, in the ratio of 3:1), the reaction mixture was cooled and filtered, solvent removed and the residual solid was recrystallized from methanol to give pure **5** as crystalline solids (*Table 1*).

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