A CLEAN AND RAPID SYNTHESIS OF 5-AMINOPYRAZOLE-4-CARBOXYLIC ACID ESTERS AND NITRILES USING MONTMORILLONITE K10

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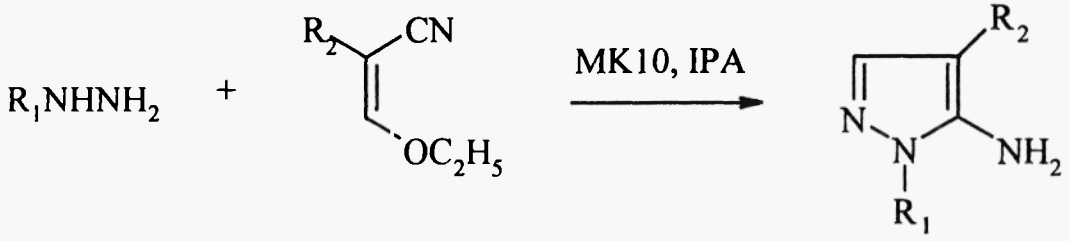
Abstract: A series of 5-aminopyrazole-4-carboxylates (4a-f) and nitriles (5a-f) have been synthesized under heterogeneous catalytic conditions using montmorillonite.

Introduction

Pyrazoles are known for their pharmacological properties such as antipyretic, analgesic and antiinflammatory[1]. A number of pyrazole fused bicyclic and tricyclic heterocycles have been reported to exhibit potential biological activities like phosphodiesterase inhibitors[2], CNS agents[3], benzodiazepine receptor antagonists[4]. Pyrazole ortho amino esters and nitriles are of immense use in the synthesis of these compounds. They also serve as intermediates in agrochemicals pesticides[5] and in the synthesis of desamino pyrazole carboxylates and nitriles[6].



1 **2** $R_2 = CO_2C_2H_5$; **3** $R_2 = CN$ **4** $R_2 = CO_2C_2H_5$; **5** $R_2 = CN$

Scheme 1

Pyrazole ortho amino esters and nitriles are generally synthesized by the reaction of ethyl (ethoxy methylene) cyano acetate or ethoxy methylene malononitrile with phenyl hydrazine or phenyl hydrazine hydrochloride in refluxing ethanol (Scheme-1). The reaction times required range from 15 to 48 hrs. A variety of reaction conditions like sodium acetate in acetic acid[7], in presence of potassium carbonate[8], triethylamine[9] and catalytic amount of acetic acid[4] have been used. However, all these methods suffer from disadvantages like long reaction times[4,9,10] and use of acidic or basic conditions. In view of the present day environmental requirements, there is a need to develop clean and faster methods.

Solid acid catalysts such as clays, are receiving greater attention in recent years and have been used in a number of organic reactions. The advantages of these solid supports are nontoxic, non corrosive economical and environmentally friendly[11]. In continuation of our work on synthesis of heterocycles using solid acid support[12,13], we report herein a clean and rapid method for the synthesis of 5-aminopyrazole carboxylates and nitriles using montmorillonite K10. Thus the reaction of ethoxy methylene cyano acetate (**2**) or ethoxymethylene malononitrile (**3**) with various substituted phenyl hydrazines **1** in refluxing isopropanol in presence of montmorillonite K10 gave the corresponding 5-amino pyrazole carboxylates (**4**) and nitriles (**5**) respectively in good yields and in a lesser reaction times of 1-2 hrs when compared to 15-48 hrs reported in literature. The products are characterized by ^{1}H NMR spectra and by comparison of melting points.

The process reported herein is a clean and rapid method, easy to workup with good yields, purity and above all the catalyst can be recycled for three times without effecting the yields.

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 recorded on a Varian 200 MHz instrument with TMS as internal standard and in $CDCl_3$. Chemical shifts were expressed in δ ppm.

General procedure for the synthesis of 5-amino pyrazole carboxylates (4)

A mixture of phenylhydrazine (**1**, 0.01 mole), ethyl (ethoxy methylene) cyanoacetate (**2**, 0.01 mole), isopropanol (25 ml), montmorillonite K10 (250 mg) was refluxed for 1-2 hrs. At the end of the reaction (as monitored by TLC), the reaction mixture was filtered, solvent removed *in vacuo*, the residue was recrystallized from methanol to give pure **4** as crystalline solid.

General procedure for the synthesis of 5-amino pyrazole carbonitriles (5)

A mixture of phenylhydrazine/hydrazinehydrate (**1**, 0.01 mole), ethoxy methylene malonitrile (**3**, 0.01 mole), isopropanol (25 ml), montmorillonite K10 (250 mg) was refluxed for 1-2 hrs. At the end of the reaction (as monitored by TLC), the reaction mixture was filtered, solvent removed *in vacuo*, the residue was recrystallized from methanol to give pure **5** as crystalline solid.

The yields, melting points and ^{1}H NMR spectral data of compounds prepared according to the above procedure are listed in Table-1.

Table-1: Physical and spectral data of 4 & 5

Compd*	R_1	Yield %	M.p °C(lit)	^{1}H NMR, δ ppm ($CDCl_3$)
4a	C_6H_5	78	98-100(100)[2]	1.26(t, 3H), 4.21(q, 2H), 6.33(s, 2H), 7.54(m, 5H), 7.71(s, 1H)
4b	4-ClC_6H_4	79	148-50(148)[14]	1.25(t, 3H), 4.21(q, 2H), 6.35(s, 2H), 7.71(s, 1H)
4c	4-BrC_6H_4	74	120-22(118)	1.24(t, 3H), 4.22(q, 2H), 6.33(s, 2H) 7.71(s, 1H)
4d	4-$CH_3C_6H_4$	81	112-14(114)[14]	1.24(t, 3H), 2.42(s, 3H), 4.21(q, 2H), 6.21(s, 2H), 7.72(s, 1H)
4e	4-$OCH_3C_6H_4$	76	107-9(110)[14]	1.25(t, 3H), 3.80(s, 3H), 4.21(q, 2H), 6.18(s, 2H), 7.05(d, 2H), 7.41(d, 2H), 7.71(s, 1H)
4f	4-$SO_2CH_3C_6H_4$	84	166-68	1.37(t, 3H), 3.09(s, 3H), 5.49(bs, 2H), 7.82(m, 3H), 8.10(d, 2H)
5a	H	71	169-71(169)[15]	
5b	C_6H_5	72	134-36(138)[15]	5.67(bs, 2H), 7.64(s, 1H), 7.91(m, 5H)
5c	4-ClC_6H_4	85	167-69(167)[15]	5.84(bs, 1H), 7.65(s, 1H), 7.79(d, 2H), 8.01(d, 2H)
5d	4-BrC_6H_4	83	168-70(168)[15]	5.82(bs, 2H), 7.67(s, 1H), 7.81(d, 2H), 8.02(d, 2H)
5e	4-$CH_3C_6H_4$	69	156-58(158)[15]	2.41(s, 3H), 5.71(bs, 2H), 7.66(s, 1H), 7.79(d, 2H), 8.01(d, 2H)
5f	4-$SO_2CH_3C_6H_4$	74	234-36	3.12(s, 3H), 5.68(bs, 2H), 7.66(s, 1H), 7.82(d, 2H), 8.09(d, 2H)

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