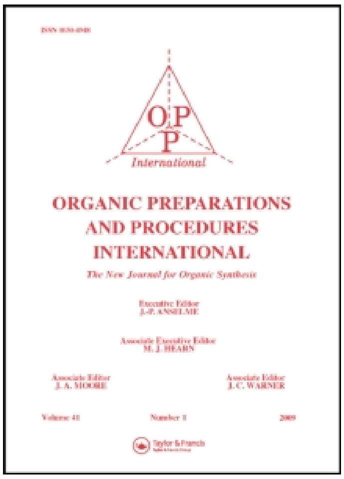

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A NEW, EFFICIENT AND SIMPLE METHOD FOR THE SYNTHESIS OF THIOAMIDES FROM NITRILES

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the desired product **4** as a white solid (24.2 g, 94%), mp. 83-85°C, *lit.*[3] mp. 84-86°C. MS (EI) m/z (%): $[M]^+ = 254$. IR (KBr): 3320, 1748, 1722, 1535, 1066 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.97 (t, 3H, $J = 7.5$ Hz, $CH_2CH_2C\underline{H}_3$), 1.79 (m, 2H, $J = 7.5$ Hz, $CH_2C\underline{H}_2CH_3$), 2.78 (t, 2H, $J = 7.5$ Hz, $C\underline{H}_2CH_2CH_3$), 1.38 (t, 6H, $J = 7Hz$, $CO_2CH_2C\underline{H}_3$), 4.39 (q ,4H, $J = 7Hz$, $CO_2C\underline{H}_2CH_3$), 10.15 (s, 1H, N-H). ^{13}C NMR ($CDCl_3$): δ 166.42, 159.23, 133.51, 62.25, 35.54, 25.59, 15.46, 14.17.

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A NEW, EFFICIENT AND SIMPLE METHOD FOR THE SYNTHESIS OF THIOAMIDES FROM NITRILES

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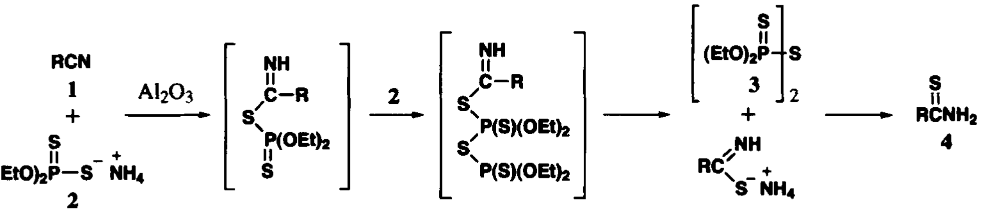
Since organic sulfur compounds have become increasingly useful and important in organic synthesis, the development of convenient and practical methods for the preparation of thioamides is desirable. Thioamides are valuable intermediates useful as building blocks in many areas of chemistry especially in the Hantzsch thiazole synthesis.[1] The following methods have been reported in the literature: (i) three-component condensation of an aldehyde, elemental sulfur and an amine at high temperature and long reaction times,[2] (ii) thionation of the corresponding amide with an electrophilic reagent such as Lawesson's reagent, phosphorous pentasulfide or reaction with a nucleophilic thionating reagent, by electrophilic activation of an amide,[3] (iii) conversion of nitriles to thioamides.[4] Although many different methods have been reported for the preparation of thioamides, the conversion of nitriles to thioamides has so far received comparatively little attention. In general, thiolysis of nitriles involve heating in an alcoholic solution in the presence of an alkali metal hydrogen sulfide or ammonium sulfide under pressure in a closed reactor.[5] The use of alkali-metal hydrogen sulfides or ammonium sulfide can simplify the procedure considerably, but usually requires high pressures and is restricted to very electron-deficient aromatic nitriles. Other reagents, such as thioacids and thioacetamide,[6] and alternative reagents, such as Dowex SH-,[7] diphenylphosphinodithioic acid[8] and sodium trimethylsilanthiolate[9] have been explored; however, each of the starting reagents require for prior synthesis. A new thionation reagent (P_4S_{11})Na_2, prepared *in situ* by reaction of phosphorus decasulfide and sodium sulfide, was also used for conversion of nitriles to thioamides under mild conditions.[10] Recently the use of microwave irradiation for the preparation of thioamides from nitriles by treatment with ammonium sulfide in methanol has also been reported.[11] However, the use of these reagents has drawback which include harsh reaction conditions, expensive reagents and starting materials, and long reaction times. In recent years, the use of reagents and catalysts immobilized on solid supports has received considerable attention.[12] With the advent of green chemistry, the application of microwave energy to accelerate organic reactions is of increasing interest and offers several advantages over conventional techniques.[13] As a part of our efforts to explore the utility of surface-mediated reactions for the synthesis of organic compounds,[14,15] we report herein a new method for the conversion of nitriles to thioamides using a mixture of alumina with ammonium *O,O'*-diethyl dithiophosphate (**2**) under microwave irradiation producing high yields of thioamides (*Scheme 1*, *Table 1*).



a) R = C_6H_5-; b) R = *p*-BrC_6H_4-; c) R = *p*-ClC_6H_4-; d) R = *p*-$NO_2C_6H_4$-; e) R = *m*-ClC_6H_4-;
f) R = 2,4-$Cl_2C_6H_3$-; g) R = CH_3-; h) R = yclohexyl; i) R = *p*-$ClC_6H_4CH_2$-; j) R = *p*-$CH_3OC_6H_4CH_2$-;
k) R = *m*-$CH_3OC_6H_4CH_2$-; l) R = $(C_6H_5)_2CH$-

Scheme 1

We found that a mixture of alumina and ammonium *O,O'*-diethyl dithiophosphate under microwave irradiation is a suitable reagent for the conversion of nitriles to thioamides. As shown in *Scheme 1* and *Table 1*, irradiation of a mixture of aromatic nitriles and ammonium *O,O'*-diethyl dithiophosphate[16] in the presence of alumina afforded the corresponding thioamides in good yields (**4a-4f**). Acetonitrile also reacted to give the thioacetamide in good yield (**4g**) and the reaction also proceeded with other aliphatic nitriles to give corresponding thioamides in good to high yields (**4h-4l**). The reactions were clean with no tar formation. It is important to note the reactions failed after 24 hrs without microwave irradiation. *O,O'*-Diethyl dithiophosphonic anhydride (**3**) was isolated in all conversions (*Scheme 1*).

Table 1. Yields, mps and Combustion Data of Thioamides (**4**) from Nitriles

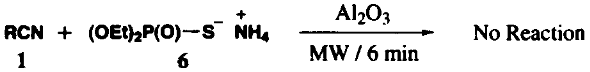
Cmpd.	Yield[a]	mp	*lit.*	Time	Elemental Analysis (Found)		
	(%)	(°C)	(°C)	(min)	C	H	N
4a	75	110-113	117-118[11]	4[b]	----	----	----
4b	78	138-142	----	6	38.91(39.12)	2.80(3.01)	6.48(6.25)
4c	82	115-116	117-118[11]	6	----	----	----
4d	90	159-161	156-159[8a]	4	----	----	----
4e	82	112-114	----	5	48.98(49.10)	3.52(3.75)	8.16(8.04)
4f	68	85-90	----	6	40.79(41.02)	2.45(2.56)	6.80(6.90)
4g	90	114-116	113-114[11]	-[c]	----	----	----
4h	48	109-113	110-115[11]	6	----	----	----
4i	82	97-102	----	6	51.75(51.63)	4.34(4.55)	7.54(7.38)
4j	75	129-132	----	6	59.64(59.52)	6.12(6.10)	7.73(7.61)
4k	78	107-113	----	6	59.64(59.60)	6.12(6.20)	7.73(7.81)
4l	72	144-147	146-149[18]	6	----	----	----

a) Yields refer to pure products after column chromatography. b) Stirred in ethanol for 24 h to give only 30% yield. c) Refluxed in acetonitrile for 6 h.

Table 2. ^{1}H NMR and ^{13}C NMR Data of Compounds **4b, 4e, 4f, 4i, 4j, 4k**

Cmpd.	^{1}H-NMR (δ)	^{13}C-NMR (δ)
4b	7.18 (1H, br,-NH_2) 7.54 (2H, d, 6.7 Hz), 7.74 (2H, d, 6.78 Hz), 7.74 (1H, br, -NH_2)	201.1, 181.7, 140.8, 134.6, 131.8, 129.7, 127.2, 124.8
4e	7.22 (1H, br,-NH_2) 7.35 (1H, t, 7.75 Hz), 7.48 (1H, ddd, 7.75, 1.75, 1.0 Hz), 7.63 (1H, br, -NH_2), 7.72 (1H, ddd, 7.75, 1.75, 1.0 Hz), 7.86 (1H, t, 1.75 Hz)	201.1, 181.7, 140.8, 134.6, 131.8, 129.7, 127.2, 124.8
4f	7.22 (1H, br,-NH_2) 7.28 (1H, dd, 8.5, 2 Hz), 7.40 (1H, d, 2.0 Hz), 7.65 (1H, d, 8.5 Hz), 8.08 (1H, br, -NH_2)	200.1, 181.7, 138.7, 136.4, 131.6, 129.8, 129.0, 127.4
4i	4.48 (2H, s), 6.72 (1H, br,-NH_2) 7.22 (2H, d, 8.0 Hz), 7.35 (1H, d, 8.0 Hz), 7.84 (1H, br, -NH_2)	206.8, 181.7, 133.9, 133.5, 130.7, 129.4, 51.2
4j	3.80 (3H, s), 4.05 (2H, s), 6.72 (1H, br,-NH_2), 6.89 (2H, d, 8.25 Hz), 7.17 (2H, d, 8.25 Hz), 7.76 (1H, br, -NH_2)	159.3, 130.6, 130.5, 126.9, 114.7, 55.3, 51.6
4k	3.80 (3H, s), 4.08 (2H, s), 6.72-6.92 (4H, m), 7.15-7.35 (1H, m), 7.81 (1H, br, -NH_2)	207.1, 181.7, 160.2, 136.2, 130.4, 121.6, 115.0, 113.5, 55.3, 52.1

Recently, we reported that a mixture of alumina/ammonium acetate/sulfur in the presence of diethyl phosphite under microwave irradiation gave ammonium *O,O'*-diethylthiophosphate (**5**) which is a suitable reagent for the synthesis of phosphorothioates of alkyl halides and the conversion of epoxides to thiiranes.[17] Surprisingly, we found that the reaction of nitriles with **5** in the presence of alumina under microwave irradiation failed to give the thioamides or any other product (*Scheme 2*).



Scheme 2

In summary, simple work-up, minimal use of solvents, rapid reaction rates, mild reaction conditions, good yields and the relatively clean reactions make this method an attractive and a useful contribution to present methodologies.

EXPERIMENTAL SECTION

All chemicals were commercial products and distilled or recrystallized before use. All melting points were obtained on a Buchi 510 apparatus and are uncorrected. A commercially available pulse microwave at 2450 MHz (600 W) was used in all experiments. Infrared (IR) spectra were determined using a FT-IR Brucker-Vector 22. NMR spectra were obtained on a DMX-250 Bruker Avance spectrometer in $CDCl_3$. Silica gel column chromatography was carried out on Silica gel 100 (Merck No. 10184). Merck Silica-gel 60 F254 plates were used for preparative TLC. Aluminium oxide 90 active acidic (activity stage I) was used for the reactions (Merck No. 1078). A kitchen-type microwave was used in all experiments.

General Procedure.- Ten mmol of the finely ground reagent was prepared by grinding ammonium *O,O'*-diethyl dithiophosphate (10 mmol, 2.0 g, prepared according to reference 16) and alumina (Al_2O_3, acidic, 2.5 g) in a mortar and pestle until a fine, homogeneous, powder was obtained (5-10 min). The nitrile (5 mmol) was then added to this mixture and ground together until a homogeneous powder was obtained. The mixture was transferred to a round-bottomed flask and then irradiated in a microwave for a total of 4-6 min (each 30-50 seconds period of irradiation followed by mixing) using 300-450 Watts. The mixture was then extracted with 200 mL $CHCl_3$. Any remaining ammonium salt was removed by washing with 100 mL of a saturated aqueous solution of sodium carbonate and then water. The organic phase was dried over sodium sulfate, evaporated to dryness and the resulting solid was chromatographed on silica gel [EtOAc/*n*-hexane (40:60)]. Evaporation of the solvent under reduced pressure gave the pure products in 48-90% yields (compound **3** was isolated as the first eluate of the column chromatography). All the products were isolated as white crystals and gave satisfactory spectral data in agreement with the assigned structures.

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AN IMPROVED PROCEDURE FOR THE ROBINSON ANNULATION REACTION OF SOME CHALCONES CATALYZED BY K_2CO_3 UNDER ULTRASOUND

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One of the highly useful methods for carbon-carbon bond formation is the Michael reaction,[1] which is efficiently catalyzed by alkali metal alkoxides or hydroxides[2] and K_2CO_3.[3] In recent years, a number of efficient catalysts and reagents in heterogeneous media have provided considerable improvement in Michael additions; for instance, montmorillonite/$NiBr_2$,[4] Mg-Al hydrotalcite,[5] zeolite,[6] natural phosphate doped by potassium fluoride,[7] synthetic diphosphate $Na_2CaP_2O_7$ [8] and hydroxy apatite.[9] A large number of organic reactions can be carried out in milder conditions under ultrasound irradiation.[10-15] Recently, addition of acetonitrile to chalcones with K_2O,[12] addition of diethyl acetamidomalonate to chalcones with KOH in the presence of a ephedrine salt[13] and addition of some active methylene compounds to chalcones catalyzed by KOH[14] or KF/basic alumina[15] have been reported under ultrasound irradiation. Herein, we report a modified method for the Robinson Annulation of chalcones with ethyl acetoacetate catalyzed