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Microwave-Assisted Neat Reaction Technology for Regioselective Thiocyanation of Substituted Anilines and Indoles in Solid Media

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An efficient and solvent -free approach for regioselective thiocyanation of various substituted anilines and indoles is described. The reaction performed both on and off the alumina surface under microwave conditions. Microwave irradiation reactions under solvent-free conditions resulted in a "green-chemistry" procedure, by which thiocyanation was achieved. In comparison to other reported methods for regioselective thiocyanation of anilines and indoles on the focus of reaction times, yields and usage of oxidizing agents, the present method shows considerable advantages.

Keywords: Solvent-free, Regioselective thiocyanation, Microwave irradiation, Anilines, Indoles

INTRODUCTION

In recent years, the use of expensive and hazardous reagents and organic solvents was being avoided by the increasing applications of eco-friendly reagents, solid state procedures, solvent-free reactions and microwave irradiation techniques. Microwave assisted solid supported procedure offers several advantages over the traditional heating, such as accelerating the rate of reaction and high selectivity in products [1]. Because of these properties, microwave assisted solid supported reactions are playing significant role in industrial sector.

The thiocyano anilines and indoles are playing increasingly imperative role in the sulfur containing chemistry [2a]. Thiocyanation approach is a most beneficial process for direct induction of sulfur atom into the organic molecules [2b]. The thiocyanate group in organic molecules is willingly transformed into other sulfur bearing functionalities [2c]. These functionalities are mainly helpful for the construction of sulfur containing heterocyclics such as thiozoles and thiazines [3]. In addition, the thiocyanate group shows a significant functionality in several anticancer agents [4]. So far, limited number of protocols have been reported for this process such as N-thiocyanatosuccinimide [5a], Ferric(III) chloride [5b], DDQ [5c], $Mn(OAc)_3$ [6a], Ceric ammonium nitrate [6b], montK10 clay [6c], oxone (oxidant) [7a], bromine/potassium thiocyanate [7b] and iodine/methanol [7c]. However, use of solvents, presence of oxidizing agents, expensive starting materials, toxicity of thiocyanate source reagents, and relatively long reaction times strongly indicate the demand to develop convenient methods with absence of solvent, high yields and shorter reactions. In order to overcome these disadvantages, we used a microwave assisted solid supported reaction for thiocyanation of aniline and indoles.

In continuation of our investigation on the solvent-free synthesis of organic compounds [8], we would like to report

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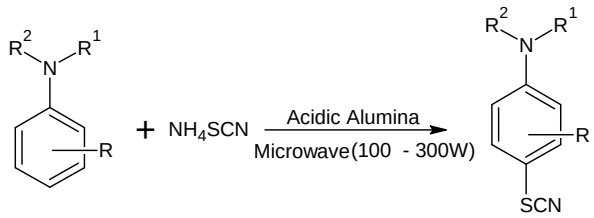


Scheme 1

here an efficient, solvent-free and microwave-promoted solid supported procedure for regioselective thiocyanation of substituted anilines and indoles. Using anilines and indoles as substrates, the reaction gave unique *para* thiocyno substituted anilines (Scheme 1) and 3-thio-cyano substituted indoles (Scheme 2), respectively.

EXPERIMENTAL

Chemicals and Apparatus

All the chemicals used in the present study are of analytical grade and were obtained from local suppliers. Melting points were recorded on Kumar capillary melting point apparatus and are uncorrected. The IR Spectra were recorded from KBr discs on Shimadzu IR Affinity-1 spectrophotometer. The NMR spectra were recorded on Joel JNM EX-90 FT NMR (90 MHz) spectrophotometer using TMS as an internal standard. The determination of the products purity and reaction monitoring were accomplished by TLC on silica gel plates.

General Procedure for the Preparation of 4-Aminophenyl Thiocyanate 2a

In a typical experimental procedure, a mixture of aniline **1a** (1 mmol), ammonium thiocyanate (1.2 mmol) and alumina (Al_2O_3, acidic, 2.0 g ms) were grinded with mortar and pistle and then irradiated under a microwave (Panasonic inverter, 200 W, 3 min). After completion of the reaction, the reaction mixture was diluted with water and then extracted with dichloromethane. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The obtained crude product was purified by column chromatography on silica gel, yielded **2a** in 90% (Table 1, entry 1). The above procedure was repeated without the alumina, yielded **2a** in 60% (Table 1, entry 1).

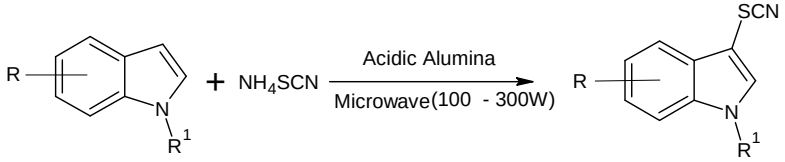
General Procedure for the Preparation of 1H-Indol-3-yl Thiocyanate 4a

In a typical experimental procedure, a mixture of indole **3a** (1 mmol), ammonium thiocyanate (1.2 mmol) and alumina (Al_2O_3, acidic, 2.0 g ms) were grinded with mortar and pistle and then irradiated under a microwave (Panasonic inverter, 200 W, 5 min). After completion of the reaction, the reaction mixture was diluted with water and then extracted with dichloromethane. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The obtained crude product was purified by column chromatography on silica gel, yielded **4a** in 85% (Table 1, entry 12), whereas same procedure was repeated without alumina, yielded **4a** in 57% (Table 1, entry 12).

Selected Spectral Data of the Products

4-Aminophenyl thiocyanate 2a (Table 1, entry 1). m.p.: 51-53 °C, IR (cm^{-1}): 3414, 2935, 2064, 1616, 1589, 1297, 1174, 685; ^{1}H NMR ($CDCl_3$) δ (ppm): 7.3-6.2 (4H, m, C_6H_4), 3.2 (2H, brs, NH_2); ^{13}C NMR ($CDCl_3$) δ (ppm): 145.6, 129.1, 124.8, 118.8, 115.3.

4-Amino-2-methylphenyl thiocyanate 2c (Table 1, entry 3). m.p.: 82-84 °C, IR (cm^{-1}): 3341, 2939, 2152, 1621, 1581,



Scheme 2

R = H, -CH_3, -$CH(CH_3)_2$, Cl, -OCH_3, -COOH, Br, -CN

R^1& R^2 = H, -CH_3

Table 1. Regioselective Thiocyanation of Substituted Anilines and Indoles on a Solid Surface of Al_2O_3 under Microwave Irradiation

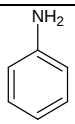
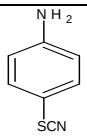
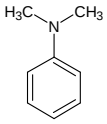
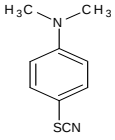
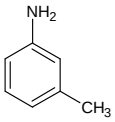
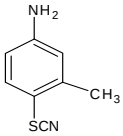
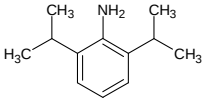
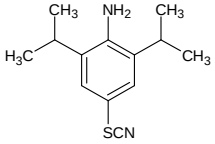
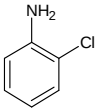
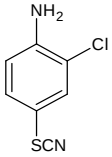
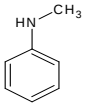
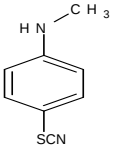
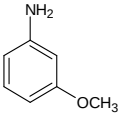
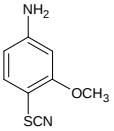
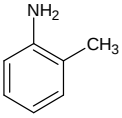
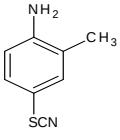
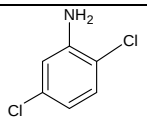
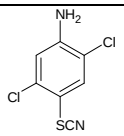
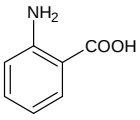
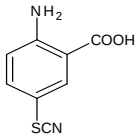
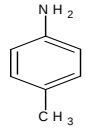
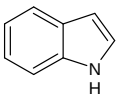
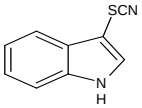
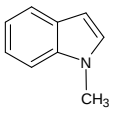
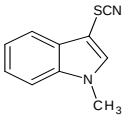
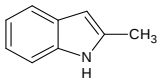
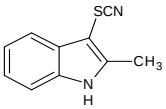
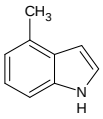
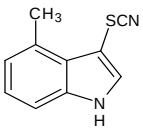
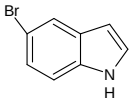
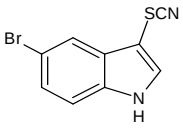
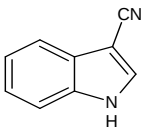
Entry	Substrate		Product		Absence of Al_2O_3		Presence of Al_2O_3	
					Time (m)	Yield (%)[a]	Time (m)	Yield (%)[a]
1		**1a**		**2a**	6	60	3 (25[c]) [10]	90 (88[d]) [10]
2		**1b**		**2b**	6	53	2.5 (20[c]) [10]	90 (94[d]) [10]
3		**1c**		**2c**	4.5	60	2.5 (20[c]) [6a]	85 (81[d]) [6a]
4		**1d**		**2d**	7	55	4	86
5		**1e**		**2e**	6	60	4 (20[c]) [6a]	85 (87[d]) [6a]
6		**1f**		**2f**	5	55	2.5 (20[c]) [6a]	86 (84[d]) [6a]
7		**1g**		**2g**	7	60	4.5 (15[c]) [11]	85 (94[d]) [11]
8		**1h**		**2h**	6.5	55	3 (120[c]) [6a]	84 (85[d]) [6a]

Table 1. Continued

9		**1i**		**2i**	5.5	65	3 (210^{c}) [5b]	80 (85^{d}) [5b]
10		**1j**		**2j**	7	60	3.5 (15-20^{c}) [12]	82 (73^{d}) [12]
11		**1k**	N.R[b]	-	-	-	-	-
12		**3a**		**4a**	9	57	5 (120^{c}) [6a]	85 (83^{d}) [6a]
13		**3b**		**4b**	9	55	6 (120^{c}) [6a]	85 (85^{d}) [6a]
14		**3c**		**4c**	7	35	4.5 (30^{c}) [13]	64 (85^{d}) [13]
15		**3d**		**4d**	8	45	4 (120^{c}) [6a]	80 (85^{d}) [6a]
16		**3e**		**4e**	7	60	3.5 (120^{c}) [6a]	90 (92^{d}) [6a]
17		**3f**	N.R[b]	-	-	-	-	-

[a]Isolated products. [b]N.R = No reaction observed. [c]Reported reaction times. [d]Reported yields.

1252, 1154, 610; ^{1}H NMR ($CDCl_3$) δ (ppm): 7.0-6.6 (3H, m, C_6H_3), 4.2 (2H, brs, NH_2), 2.9 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm): 151.5, 140.2, 127.2, 126.8, 121.8, 115.6, 109.9, 21.3.

4-Amino-2-methoxyphenyl thiocyanate 2g (Table 1, entry 7). m.p.: 99-100 °C, IR (cm^{-1}): 3344, 2966, 2150, 1625, 1584, 1298, 615; ^{1}H NMR ($CDCl_3$) δ (ppm): 7.2-6.7 (3H, m, C_6H_3), 4.1 (2H, brs, NH_2), 3.4 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm): 149.8, 143.8, 130.3, 126.8, 122.5, 118.9, 115.1, 52.1.

1H-Indol-3-yl thiocyanate 4a (Table 1, entry 12). m.p.: 103-105 °C, IR (cm^{-1}): 3333, 3001, 2145, 1548, 1519, 1274, 641; ^{1}H NMR ($CDCl_3$) δ (ppm):11.4 (1H, brs, NH), 7.68-6.51 (5H, m, C_8H_5N); ^{13}C NMR ($CDCl_3$) δ (ppm): 139.4, 131.6, 125.1, 124.0, 122.5, 117.0, 113.1, 100.7.

2-Methyl-1H-indol-3-yl thiocyanate 4c (Table 1, entry 14). m.p.: 100-101 °C, IR (cm^{-1}): 3341, 3010, 2140, 1580, 1519, 1281, 632; ^{1}H NMR ($CDCl_3$) δ (ppm): 11.1(1H, brs, NH), 7.9-7.2 (4H, m, C_8H_5N), 2.4 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm): 142.4, 139.5, 129.1, 124.0, 121.8, 118.2, 113.4, 105.6, 91.4, 15.4.

4-Methyl-1H-indol-3-yl thiocyanate 4d (Table 1, entry 15). m.p.: 127-128 °C, 3324, 3012, 2146, 1519, 1106, 654; ^{1}H NMR (CDCl3) δ (ppm): 11.2 (1H, brs, NH), 7.4-6.9 (4H, m, C_8H_5N), 2.8 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm): 140.1, 139.5, 129.1, 125.0, 124.5, 119.1, 113.2, 110.8, 92.4, 17.9.

RESULTS AND DISCUSSION

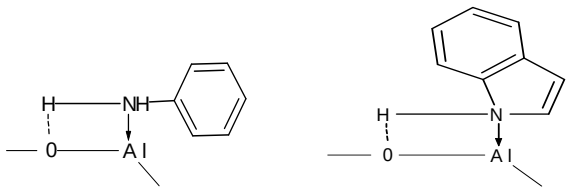
Our preliminary studies were focused on the reaction conditions for the synthesis of thiocyano anilines and indoles. A variety of anilines or indoles, ammonium thiocyanate and acidic alumina were mixed and placed in a microwave oven for the time specified in the Table 1. The reaction was monitored by TLC and complete disappearance of the starting material was observed during this period. Elution of the mixture with dichloromethane followed by evaporation of solvent furnished the crude product, which was purified by column chromatography. The obtained products were characterized by comparing their melting points, IR and NMR spectroscopic data with those reported in literature.

The occurrence of thiocyanation in anilines and indoles was examined by IR and NMR studies. The formation of SCN group in the product was confirmed by IR peaks obtained between 2064-2150 cm^{-1} (-SCN) and 632-748 cm^{-1} (-C-S-). ^{13}C NMR chemical shift ranging between δ116-113 ppm indicated that the thiocyano group is present in the products obtained by the microwave assisted solid supported reaction.

We examined the role of acidic alumina for conversion of anilines or indoles to corresponding thiocyano products. Therefore, we carried out reaction in presence and absence of acidic alumina under solvent-free microwave irradiation. Here we observed in absence of acidic alumina, the reaction required longer times and gave low yields, compared to the presence of acidic alumina reactions. The results are listed in Table 1. These findings showed acidic alumina enhanced the rate of the reaction and yield of products.

In the reactions performed on the solid surface of alumina under microwave conditions, the yields of mono-thiocyanated desired products were excellent. The comparison of yields between *para* and *meta* substituted anilines or methyl-substituted and unsubstituted amino groups in anilines did not show any significant change. In case of indoles, 2-methylindole **3c** reacts with ammonium thiocyanate to give yield with 64% of **4c** (Table 1, entry 14). As expected, a steric factor was pronounced to lower yield in this case. *Para*-methyl aniline **1k** and 3-cyanoindole **3f** did not react with ammonium thiocyanate (Table 1, entry 11 and 17), which conforms the -SCN group attacks regioselective to anilines and indoles.

On the basis of the mechanism proposed by A.-N. Ko, *et al*. for the alumina supported selective N-alkylation of anilines [9], we suggest that the possible mechanism for thiocyanation of anilines and indoles occurred by the formation of following intermediates (I) and (II), respectively. However, to establish the mechanism for this thiocyanation needs further investigation.



(I) (II)

CONCLUSIONS

Acidic alumina effectively promotes the regioselective

thiocyanation of anilines and indoles under solvent-free conditions. The notable advantages of this procedure are: (a) reasonably good yields; (b) shorter reaction times; (c) mild reaction conditions; (d) no need of oxidizing agents; (e) in tune with green synthesis avoiding toxic reagents and solvents. We believe our procedure will play an important role in the preparation of sulfur containing heterocyclic derivatives.

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