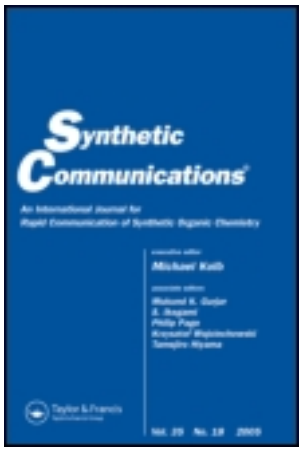

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CALCINED Mg-Al HYDROTALCITE AS A HETEROGENEOUS BASE CATALYST FOR GEWALD AMINOTHIOPHENE SYNTHESIS

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ABSTRACT

Calcined Mg-Al hydrotalcite (Mg/Al = 4) has been conveniently employed as a heterogeneous base catalyst in the synthesis of 2-amino-3-cyanothiophenes adopting a one pot Gewald aminothiophene methodology.

The Gewald reaction constitutes a very useful and versatile method for the synthesis of 2-aminothiophene with an electron withdrawing substituent in the 3-position and alkyl and/or aryl groups in the 4- and 5-positions.[1] Aminothiophenes found their way as very important diazo components for azo dyes which give exotic colours with high tinctorial strength. The development of Gewald reaction for the synthesis of 2-amino-3-cyano, 2-amino-3-carbethoxy and 2-amino-3-carbonyl substituted thiophenes has been made

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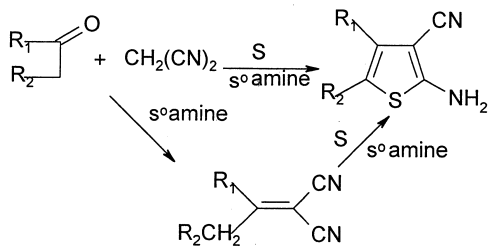
possible the synthesis of an enormous number of thieno-fused heterocycles of great medicinal interest such as thienopyrimidines and thienodiazepines.

In one version of Gewald reaction aliphatic aldehydes, ketones or β-dicarbonyl compounds react with active nitriles and sulfur in presence of amines. Amines such as diethyl amine and morpholine have been employed as catalysts. Both one step and two step routes have been adopted with numerous ketones and aldehydes or their Knoevanagel – Cope condensation products (Scheme 1). In particular, cyclic and heterocyclic saturated ketones have been used extensively.



A

Scheme 1.

Herein we report our preliminary results on the application of calcined Mg-Al htdrotalcite as a heterogeneous catalyst in the Gewald aminothiophene synthesis. Hydrotalcites are interesting class of materials, which can be utilized as precursors for mixed metal oxides with pronounced basic properties. They can be efficiently used as basic heterogeneous catalysts in many organic transformations such as aldol and Knoevenagel condensations,[2] epoxidation,[3] cyanoethylation[4] and Meerwein–Ponndorf–Verley reduction.[5] Mg-Al hydrotalcites having $Mg:Al = 4:1$ was synthesized using the procedure reported by Miyata et al.[6] Typical XRD, IR, TGA and DTA patterns have substantiated the formation of hydrotalcites.

We have chosen methyl ethyl ketone and three cyclic ketones viz. cyclopentanone, cyclohexanone and cylcoheptanone for condensation with malononitrile in presence of sulfur to yield 2-amino-3-cyano-thiophenes (Scheme 2).

Results of Gewald reaction of cyclic ketones with malononitrile and sulfur are summarized in Table 1. The lower yield of the product in the case of cycloheptanone is attributed to the increasing nonbonded repulsive interaction between methylene protons in the middle and large sized rings fused to a planar five membered ring.[7]

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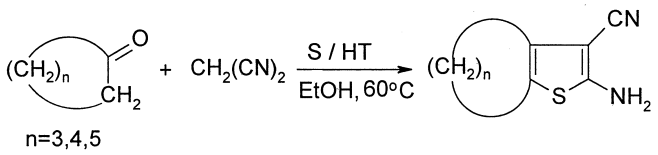


Scheme 2.

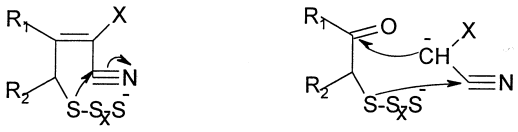
Table 1. Gewald Aminothiophene Synthesis over Calcined Mg-Al (Mg/Al = 4) Hydrotalcite Catalyst[a]

Substrate	Reaction time (h)	Yield (%)
Cyclopentanone	12	85
Cyclohexanone	8	91
Cycloheptanone	14	56
Ethyl Methyl Ketone	8	61
Cyclohexanone[b]	12	88
Cyclohexanone[c]	14	86
Cyclohexanone[d]	9	90

[a]Reaction conditions: cyclic ketone (0.002 moles), malononitrile (0.002 moles), sulfur (0.003 moles) and ethanol (7 ml), catalyst calcined in air at 450°C for 6 h (50 mg). [b–c]Second and third recycling. [d]Used catalyst reactivated in air at 450°C.

In the first step of the reaction, ketone reacts with malononitrile to form α,β-unsaturated nitrile by Knoevanagel – Cope condensation. In the second step, sulfur reacts with the intermediate compound formed in the first step to complete the cyclization (Scheme 3). To investigate the catalytic influence in detail, we separately carried out the reaction of cyclohexanone and malononitrile with hydrotalcite (first step). The condensed product formed was isolated and made to react with sulfur in presence of the catalyst under same experimental conditions (second step). We found that the first step of the reaction is completed in 3 h and no condensation takes place in the absence of catalyst. The second step of the reaction proceeded smoothly in presence of catalyst whereas, in the absence of catalyst reaction was very slow and never attained completion. From the rate of reaction of both the steps, it can be concluded that the reaction proceeds essentially through the intermediate A.

The reusability of the catalyst was examined by using the filtered catalyst for subsequent reactions. The catalyst was found to be reusable without appreciable loss in activity.



Scheme 3.

In conclusion, we have demonstrated that calcined Mg-Al hydrotalcite catalysts can be successfully employed to replace secondary amines in Gewald synthesis of aminothiophenes. Hope this will open new vistas in the field of recyclable heterogeneous base catalysis in heterocyclic synthesis.

EXPERIMENTAL

Preparation of Mg-Al Hydrotalcite Catalyst

To an aqueous solution containing $Mg(NO_3)_2 \cdot 6H_2O$ and $Al(NO_3)_3 \cdot 9H_2O$ mixed at the required ratio, an aqueous solution of NaOH and Na_2CO_3 was added dropwise with stirring, until the pH reached 10. The slurry was stirred at 313 K for 13 h, filtered and washed with deionised water to the neutral pH and dried at 373 K for 24 h. Finally the catalyst was calcined at 723 K in air for 12 h.

Characterization of Catalysts

The physico-chemical characterization of the catalysts has been done by XRD, thermogravimetry and BET surface area measurements. The ICPES method was adopted to estimate the ratio of M^{II} and M^{III} ions in calcined hydrotalcite.

Reaction Procedure

All the reactions were carried out batch wise in a 100 ml R.B. flask fitted with a reflux condenser with constant stirring. One equivalents of cyclic ketone (0.002 moles), malononitrile (0.002 moles) and 1.1 equivalents of sulfur (0.003 moles) and 7 ml ethanol as solvent were taken in a round bottom flask. 50 mg of freshly activated hydrotalcite catalyst was added to this suspension and temperature slowly raised to 60°C. Reaction was mon-

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itored by T.L.C. (eluent 10% ethylacetate in petroleum ether). After the reaction, the catalyst was filtered off, filtrate extracted with ethylacetate and finally purified by column chromatography. Physico-chemical characterization of the products were performed using NMR, MS, IR, elemental analysis and melting point determination. In the case of methyl ethyl ketone, the ketone itself was used as solvent instead of ethanol.

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