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A green chemistry approach to gewald reaction

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ABSTRACT

The Gewald Reaction is a synthesis of 2-aminothiophenes via a multi-component condensation between sulfur, an α-methylene carbonyl compound and an α-cyanoester. Green chemistry encourages the design of synthetic processes that minimize the use and generation of hazardous substances. The application of microwave assisted organic synthesis to conduct Gewald reaction has been demonstrated by the microwave assisted transformation of ethylcyanoacetate, cyclohexanone, anisidines and sulphur into 2-Amino-3-o/p-anisidyl-carboxamido-4,5,6,7-tetrahydro-benzo (b) thiophenes. The transformation has been confirmed by conventional synthesis.

Key words: Gewald reaction, microwave assisted organic synthesis, thiophenes

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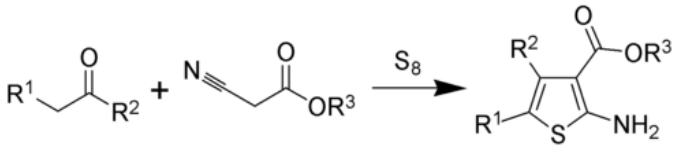
INTRODUCTION

Amongst the various methods of synthesis reported for thiophenes, the **Gewald reaction** (named after the German chemist Karl Gewald) is quite an interesting one. It is an organic reaction involving the condensation of a ketone or an aldehyde (when R^2 = H) with a α-cyanoester in the presence of elemental sulphur and base to give a poly-substituted 2-amino-thiophene.[1]



The reaction mechanism of the Gewald reaction has only recently been elucidated partially though.[2] Besides, Cope reaction[3] and Michael addition[4] are also helpful to understand the formation of the intermediate involved in the synthesis of thiophenes by this method.

Gewald reaction provides a very useful tool to create a library of compounds by choosing different ketone/aldehyde, α-cyanoester and substituent for the third position of the thiophene ring. The primary amino group attached to the lipophilic nucleus was of particular interest since it could be reacted with various classes of organic compounds and form a library of compounds. We decided to use cyclohexanone as the ketone, ethylcyanoacetate as the α-cyanoester and ortho or para anisidine for the third position of the thiophene ring. The primary amino group at the second position would enable derivatisation.

Gewald reaction has seldom been reported with green chemistry approaches. Therefore, we explored Microwave Assisted Organic Synthesis (MAOS) Approach. The MAOS approach has been successful only for the first pot of this three pot synthesis. Spectroscopic studies, melting point determinations and TLC have confirmed that identical end products have been obtained by both conventional and MAOS approach.

MATERIALS AND METHODS

Chemicals and solvents were of reagent grade. Melting points were recorded on a capillary melting point apparatus and are uncorrected. IR spectra were recorded using SHIMADZU FT-IR spectrometer. Mass spectra were recorded by Perkin-Elmer mass spectrometer. ^{1}H NMR spectra were recorded at 400 MHz using DMSO as solvent at room temperature. The synthesized compounds have been screened for anti-inflammatory and analgesic activities.

Synthesis of 2-Amino-3-o/p-anisidyl-carboxamido-4,5,6,7-tetrahydro-benzo (b) thiophenes by conventional method

Ortho or para ansidine (0.1 mol) was mixed with ethylcyanoacetate (0.1 mol) and heated for about eight hours at 170 – 180°C. The reaction mixture was then kept aside overnight, washed with ethanol and recrystallised from acetone-water mixture to get the corresponding N-cyanoacetyl anisidne. The latter was heated to mild boiling conditions for 10 hours with cyclohexanone (0.1 mol) and catalytic amounts of ammonium acetate and glacial acetic acid in benzene and cooled. The cold solution was then neutralized with an aqueous solution of sodium carbonate, dried over anhydrous sodium sulphate and excess benzene was distilled off to get a semisolid product. The latter was dissolved in ethanol and stirred with sulphur in the presence of diethylamine to get the desired title compound. The synthesized compounds have been characterized by C^{13} NMR, ^{1}H NMR, mass and IR spectra. They have been screened for anti-inflammatory, analgesic and anti-microbial activities.

Synthesis of 2-Amino-3-(o/p-anisidyl)-carboxamido-4,5-tetramethylene thiophenes by MAOS

Ortho or para ansidine (0.1 mol) was mixed with ethylcyanoacetate (0.1 mol) and subjected to microwave irradiation in a domestic microwave oven for 8 minutes. Further steps were same as those in the conventional method described above. The synthesized compounds have been characterized by ^{13}C NMR, ^{1}H NMR, mass and IR spectra.

2-Amino-3-(o-anisidyl)-carboxamido-4,5-tetramethylene thiophene synthesized by conventional method

Yield: 65%; m.p.: 215.2°C; MS: *m/e* = 303.2 (M+1); ^{1}H NMR (400 MHz, DMSO) δ: 1.8 (m, 4H, 2 x CH_2), 2.3 (t, 2H, CH_2), 2.6 (t, 2H, CH_2), 3.8 (s, 3H, Ar-OCH_3), 4.5 (s, 2H, NH_2), 7.5 (t, 2H, Ar-H), 7.8(dd, 2H, Ar-H), 10.7(s, 1H, CONH)(Fig.2). ^{13}C NMR(100 MHz, DMSO-d_6)δ : 159.3, 142.2, 135.7, 138.8, 135.7, 133.7, 131.8, 130.8, 128.9, 116.4, 114.8, 56.3, 43.2, 42.2, 35.7, 32.9. IR (KBr) cm^{-1}: 1080 (ester C=O), 1650 (CONH), 2830(OCH_3), 3290, 3360 (NH_2).

2-Amino-3-(o-anisidyl)-carboxamido-4,5-tetramethylene thiophene synthesised by MAOS method

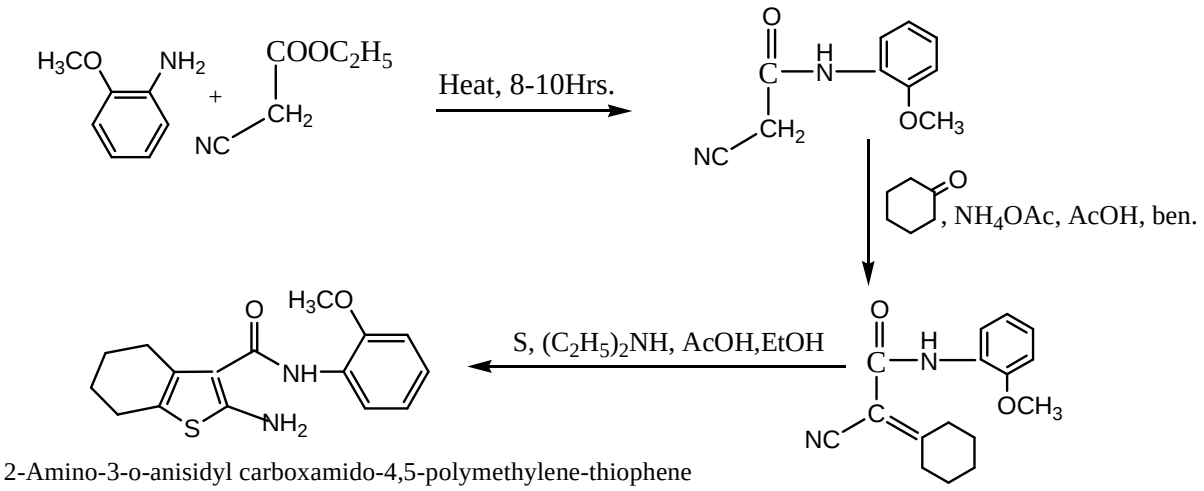
Yield: 69%; m.p.: 215.3°C; MS: *m/e* = 303.4 (M+1); ^{1}H NMR (400 MHz, DMSO) δ: 1.9 (m, 4H, 2 x CH_2), 2.4 (t, 2H, CH_2), 2.7 (t, 2H, CH_2), 3.8 (s, 3H, Ar-OCH_3), 4.6 (s, 2H, NH_2), 7.4 (t, 2H, Ar-H), 7.6(dd, 2H, Ar-H), 10.5(s, 1H, CONH).

2-Amino-3-(p-anisidyl)-carboxamido-4,5-tetramethylene thiophene synthesized by conventional method

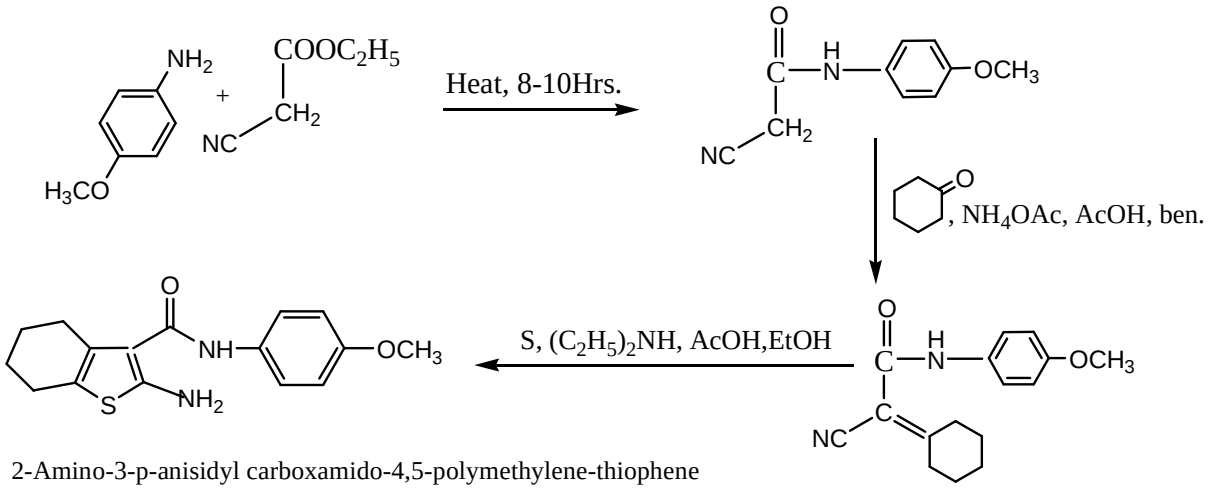
Yield: 70%; m.p.: 194.4°C; MS: *m/e* = 303.2 (M+1); ^{1}H NMR (400 MHz, DMSO) δ: 2.0 (m, 4H, 2 x CH_2), 2.7 (t, 2H, CH_2), 3.1 (t, 2H, CH_2), 3.8 (s, 3H, Ar-OCH_3), 5.0 (s, 2H, NH_2), 6.9 (t, 2H, Ar-H), 7.6(dd, 2H, Ar-H), 11.0(s, 1H, CONH); ^{13}C NMR(100 MHz, DMSO-d_6)δ : 167.5, 142.8, 139.1, 135.8, 132.7, 131.7, 131.5, 130.9, 127.2, 117.1, 116.2, 60.2, 44.2, 42.3, 37.8, 34.2; IR (KBr) cm^{-1}: 1100(ester C=O), 1630(CONH), 2850 (OCH_3), 3290, 3440 (NH_2).

2-Amino-3-(o-anisidyl)-carboxamido-4,5-tetramethylene thiophene synthesised by MAOS method

Yield: 73%; m.p.: 194.6°C; ^{1}H NMR (400 MHz, DMSO) δ: 1.9 (m, 4H, 2 x CH_2), 2.6 (t, 2H, CH_2), 2.9 (t, 2H, CH_2), 3.9 (s, 3H, Ar-OCH_3), 4.8 (s, 2H, NH_2), 7.2 (t, 2H, Ar-H), 7.6(dd, 2H, Ar-H), 10.8 (s, 1H, CONH).



2-Amino-3-o-anisidyl carboxamido-4,5-polymethylene-thiophene



2-Amino-3-p-anisidyl carboxamido-4,5-polymethylene-thiophene

Scheme 1: Synthesis of 2-Amino-3-(o/p-anisidyl)-carboxamido-4,5-tetramethylene thiophenes by conventional method. The MAOS method replaced the 8-10 hours of heating of 1st step by microwave irradiation for about 8-10 minutes

RESULTS AND DISCUSSION

2-Amino-3-o/p-anisidyl-carboxamido-4,5,6,7-tetrahydro-benzo (b) thiophenes have been synthesized by both conventional as well as MAOS methods. The efforts to synthesise 2-Amino-3-o/p-anisidyl-carboxamido-4,5,6,7-tetrahydro-benzo (b) thiophenes by MAOS was partially successful. Only the first step could be performed successfully by MAOS. The process time was reduced from eight-ten hours to about eight-ten minutes.

In both the synthetic approaches, the reactions were monitored by melting point, Rf values and Lassaigne's test for sulphur element. The products by both the methods had sharp and same melting points. They gave positive test for sulphur in the Lassaigne's test. Finally, the spectroscopic studies confirmed the products of both the approaches as one and the same. The ^{1}H NMR spectra have showed a peak within 4.5–5.0 δ which corresponds to the two hydrogens of a primary amine, a peak within 10.5–11.0 δ for the amide hydrogen and eight hydrogens could be accounted within the 1.8–3.1 δ proving the presence of methylenic hydrogens. The IR spectra reveal the presence of characteristic peaks for functional groups – ester carbonyl at 1080-1100, amide at 1630-1650, methoxy at 2830-2850 and a pair of peaks corresponding to the primary amine within 3250-3450 region. The ^{13}C NMR spectra have

confirmed the presence of 18 carbon atoms per molecule in both MAOS and conventional synthesis compounds. The mass and ^{1}H NMR spectra of MAOS products were in agreement with those of conventional synthesis products.

CONCLUSION

The green chemistry approach of performing Gewald reaction by Microwave Assisted Organic Synthesis resulted in partial success. However, it resulted in significant improvement of process time.

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