Green and efficient technique for the three component synthesis of 2-aminothiophenes using ball-milling method through Gewald reaction.

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Abstract

In this paper**,** a simple, green, and efficient approach was used to the synthesis of various 2-aminothiophenes derivatives with excellent yields (97%) in a short reaction time under ball milling technique without any solvent and any catalyst through Gewald reaction. A direct condensation of an equimolar amount of an ethyl acetoacetat/2-butanone, malononitrile/ethyl cynoacetate, and elemental sulfur under ball milling offered 2-aminothiophenes derivatives in 30 min at 750 rpm**.**

Keywords: Ball milling, Solvent-free, Catalyst-Free, 2-aminothiophene derivatives, Gewald reaction.

INTRODUCTION

Highly substituted thiophene derivatives have attracted considerable attention due to their importance in pharmaceutical and industrial fields.[1-8] The substituted 2-aminpthiophenes are reported to possess various biological activities such as adenosine receptor A3 inhibitors [9], phosphatase PTP1B inhibitors [10] and serotonin receptor subtype 5-HT1A inhibitors.[11]

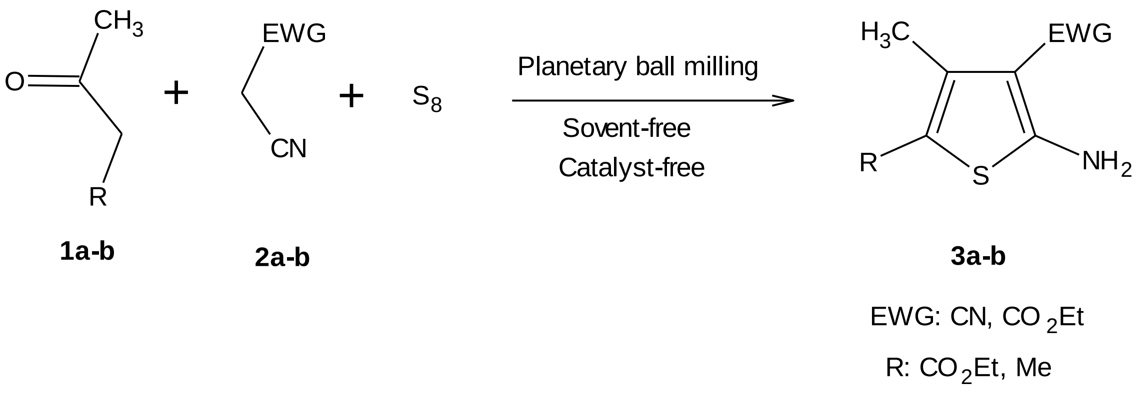
Several methods were reported in the literature for the synthesis of these heterocycles.[12−18] Nevertheless, the application of these methods with organic solvents and different catalysts leads to low yields of 2-aminpthiophenes with long reaction durations. Scholars have also increasingly focused on reduction of any source of pollution. Thus, efficient, clean, and flexible synthesis methods must be developed.

The use of the ball milling technique in organic synthesis has gained increasing attention over the last decades [19,120]. Ball milling is used to synthesize various types of organic compounds for the preparation of phosphorus ylides [21], reductive benzylation of malononitrile [22], functionalization of Knoevenagel condensations [23], functionalization of fullerenes [24], coordination polymers [25], synthesis of nitrones [26], protection of diols/diamines [27], Suzoku-type reaction [28], synthesis of functionalized indan-1,3-diones [29], aldol reaction [30,31], Heck-type reactions [32,33], symmetrical and unsymmetrical thioureas [34], pyrano pyrimidine-dione synthesis [35], functionalized 2- amino-3-cyano-4H-pyrans [36], and synthesis of thioxo- and oxo-pyrimidine-5-carbonitriles [37].

The present research paper investigates a high-yielding one-pot three-component synthesis of 2-aminpthiophene derivatives using ball-milling technique under solvent- and catalyst-free conditions.

RESULTS AND DISCUSSION

As a continuation of our research interest on the applications of ball milling in organic synthesis [37, 38], we report in this paper an eco-friendly, effective, and high-yield synthesis of 2-aminothiophene derivatives *via* a Gewald three component reaction. In this technique, ethyl acetoacetate/2-butanone, malonitrile/ethyl cynoacetate and elemental sulfur are directly placed in a simple planetary ball mill under solvent- and catalyst-free conditions (Scheme 1).



Scheme 1. 2-aminothiophene derivatives synthesis using planetary ball milling technique

To optimize the conditions for the synthesis of 2-aminothiophenes, we placed ethyl acetoacetate (0.02 mol), malonitrile (0.02 mol), and elemental sulfur (0.02 mol) (with a total mass of 4.56 g) in a tempered vial. We subsequently added 22.80 g of balls (ratio of the ball weight to the reagent weight is equal to 5) [37]. The progress of the reaction was monitored every 10 min of the milling cycle via thin-layer chromatography (TLC). 2-aminothiophene (3a) yield was low at low rotation speed of 250 rpm, whereas 2-aminothiophene (3a) yield was high after a short reaction time at 750 rpm (Table 1). Similar conditions were applied to different reactions, and all the synthesized products were obtained in the same time (30 min).

Table. 1 Comparison of the effect of different rotation speeds conditions for the condensation of ethyl acetoacetate (**1a**), malonitrile (**2a**) and elemental sulfur.

Entry	Speed (rpm)	Time (min)	Yield(%)
1	250	180	10
2	350	180	15
3	450	180	30
4	550	120	45
5	650	60	90
6	750	30	97

The spectral data correspond to different synthesized products. Products **3a–d** (Table 2) show a characteristic single peak in the ^{1}H-NMR spectra at approximately 4.60–6.60 ppm (br s, 2H). This peak corresponds to the protons of the amine group. Another signale peak at approximately 2.16-2.60 ppm corresponds to the vinylic methyl group.

Table. 2 Synthesis of 2-aminothiophene derivatives using ball milling solvent-free catalyst-free.

Entry	R	EWG	Product	Yield(%)
1	OEt	CN	3a	97
2	CH_3	CN	3b	93
3	OEt	CO_2Et	3c	96
4	CH_3	CO_2Et	3d	91

CONCLUSION

We described a simple, operational, and green one-pot synthesis of 2-aminothiophens (Table 2) *via* a Gewald three component reaction using the ball milling technique. This economical and eco-friendly method can be used to synthesize all products in a short period of time and with high yields**.**

EXPERIMENTAL PART

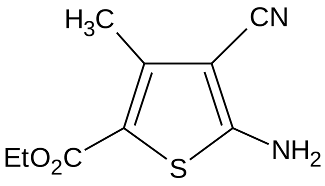
1. Materials and Techniques

The ball mill used in this study was a Planetary Micro Mill PULVERISETTE 7 classic line with 10 cm^3 stainless steel vials. Melting points were determined using the Stuart Melting point apparatus SMP10. The IR spectra were obtained using an FT-IR-Tensor 27 spectrometer in KBr pellets. The ^{1}H and ^{13}C NMR spectra were determined using a BRUKER 300 NMR spectrometer in $CDCL_3$ with TMS as the internal standard. Chemical shifts are expressed as δ ppm units. The progress of all reactions was monitored via TLC on silica gel 60 (Merck) by using a chloroform–ethanol system.

2. General Procedure for the Synthesis of Pyridine Compound 3a

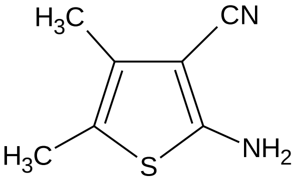
A mixture of ethyl acetoacetate (0.02 mol), malonitrile (0.02 mol), and elemental sulfur (0.02 mol) with a total mass equal to 4.56 g was placed in tempered vials with 22.80 g of tempered balls (ratio of the ball weight to the reagent weight is equal to 5). The vials were closed and then placed in a Planetary Micro Mill PULVERISETTE 7 classic line. Crude compound **3a** was obtained after 30 min of milling time and purified via recrystallization in ethyl acetate.

Ethyl 2-amino-3-cyano-5-methylthiophene-3-carboxylate (**3a**): mp 150-151 ^{0}C; IR (KBr): υ 3440, 3335, 3243, 2965, 2886, 2164, 1608, 1570, 1506, 1377, 1030 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): δ: 1.6(t, J = 6.6Hz, 3H), 2.2(s, 3H), 2.5(q, J = 6.6 Hz, 2H) 6.0(br s, 2H), ^{13}C NMR (CDCl$_3$, 100 MHz): δ 22.3, 23.4, 23.9, 60.2, 115.0, 121.9, 130.0, 153.5, 160.0.



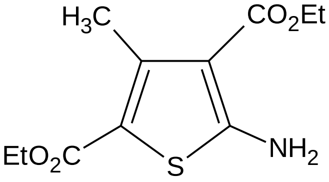
3a

2-Amino-4,5-dimethylthiophene-3-carbonitrile (**3b**): mp 141-142 ^{0}C; IR (KBr): υ 3438, 3345, 3223, 2923, 2867, 2164, 1612, 1572, 1496, 1398, 1092 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ: 2.07(s, 3H); 2.16 (s, 3H), 4.60 (br s, 2H): ^{13}C NMR (100 MHz, CDCl$_3$): δ: 12.3, 12.7, 90.6, 115.9, 117.2, 129.6, 159.1.



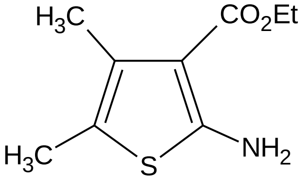
3b

Diethyl 2-amino-3-methyltiophene-3,4-dicarboxylate (**3c**): mp. 108-109 °C**;** IR (KBr): 3408, 3294, 1682, 1660, 1587, 1529, 1232 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ:1.33 (t, *J* = 7.1 Hz, 3H), 1.37 (t, *J* = 7.1 Hz, 3H), 2.70 (s, 3H); 4.26 (q, *J* = 7.1 Hz, 2H); 4.31 (q, *J* = 7.1Hz, 2H); 6.60 (br s, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ: 14.5, 14.6, 16.3, 60.2, 60.6, 108.6, 108.7, 148.2, 163.1, 166.3, 166.4.



3c

Ethyl 2-amino-4,5-dimethylthiophene-3-carboxylate (**3d**): mp 91-92 ^{0}C; IR (KBr): υ 3433, 3336, 3218, 2918, 2855, 2190, 1716, 1609, 1520, 1305, 1047 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): δ: 1.2(t, 3H, J = 7.0 Hz), 2.0(s, 3H), 2.3(s, 3H), 4.5(q, 2H, J = 7.0 Hz), 6.5(br s, 2H) ^{13}C NMR (CDCl$_3$, 100 MHz): δ: 21.8, 22.4, 23.5, 25.0, 99.0, 116.9, 121.3, 132.5, 160.0.



3d

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