

# Gewald synthesis of 2-aminothiophenes on a soluble polymer-support

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A variety of polysubstituted thiophenes have been prepared via a solvent-free one-pot microwave assisted Gewald reaction using poly (ethylene glycol) as a soluble polymer support.

**Keywords:** thiophene synthesis, Gewald reaction, soluble polymer-support, solvent-free

The Gewald syntheses of polysubstituted thiophenes has attracted increasing interest due to their extensive potential in medicinal chemistry<sup>1–5</sup> since the original publication in 1961 by Gewald and co-workers.<sup>6</sup> However, most of the published Gewald syntheses of thiophenes require long reaction times for the condensation step and the purification of products for further modification is difficult.<sup>7–10</sup> Recently, Hoener and co-workers reported the Gewald syntheses of thiophenes using an insoluble polymer as support. However, there were some drawbacks such as difficulty of monitoring the reaction progress and configuration of polymer-bound products.<sup>11</sup> Herein, we report a solvent-free one-pot microwave assisted Gewald synthesis on a soluble polymer-support as an improved route.

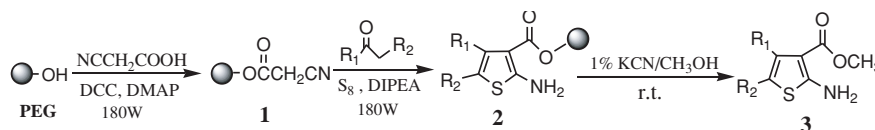
We chose to perform our reactions using poly(ethylene glycol) 3400 (PEG<sub>3400</sub>) as a soluble polymer support, which coupled the advantages of homogeneous solution chemistry (high reactivity, lack of diffusion phenomena and ease of analysis) with those of solid-phase methods (use of excessive reagents, easy isolation and purification of products). As shown in Scheme 1 PEG-bound cyanoacetic ester **1** was prepared by treatment of PEG<sub>3400</sub> with cyanoacetic acid under DCC/DMAP

coupling conditions. Then, **1** was treated with aldehydes or ketones, elemental sulfur and diisopropylethylamine (DIPEA) in a one-pot Gewald procedure for only 20 min to give the PEG-bound thiophene **2**. The coupling and Gewald reactions were all carried out in a microwave oven with a mechanical stirrer at power of 180W under solvent-free conditions. Treatment of **2** with potassium cyanide in methanol gave the thiophenes **3** in good yields. The polymer-supported products were purified by precipitating, filtering and washing away the excessive materials with cold Et<sub>2</sub>O. Thus, the process is not only an efficient route to Gewald condensations (short reaction time, convenience of analysis, easy purification of products and good yield), but is also environmentally friendly.

To establish the scope of this reaction, a variety of ketones and aldehydes were investigated. The results are presented in Table 1.

## Experimental

*General procedure for the preparation of compounds 3:* Cyanoacetic acid (0.51g, 6 mmol), DCC (1.24g, 6 mmol), and DMAP (0.12g, 1 mmol) were added to dried PEG (2.00 g, 1.16 mmol). The reaction



Scheme 1

Table 1 Products from Gewald reaction and yields

Entry	Ketone/thiophene	Aldehyde	Yield/% <sup>a,b</sup>	Entry	Ketone/thiophene	Aldehyde	Yield/% <sup>a,b</sup>
1			90	6			89
2			87	7			32
3			84	8			27
4			91	9			48
5			93	10		No product	—

<sup>a</sup>Yields were of isolated products. <sup>b</sup>products were characterised by their physical constants, IR, <sup>1</sup>H NMR, elemental analysis and comparison with references

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mixture was irradiated in a flask for 5 min in the microwave oven with stirring. After cooling to r.t., the resulting mixture was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (3 ml) and precipitated by addition of cold Et<sub>2</sub>O. **1** was afforded by filtering, washing with cold Et<sub>2</sub>O and drying under vacuum. Aldehyde or ketone (6 mmol), elemental sulfur (0.19g, 6 mmol) and DIPEA (0.17ml, 1 mmol) were added to the dried **1**. The mixture was irradiated and stirred for 20 min in the microwave oven. **2** was obtained by using the procedure described above for **1.2** was treated with 1% KCN in CH<sub>3</sub>OH at r.t. overnight. After removing CH<sub>3</sub>OH, the residue was redissolved in CH<sub>2</sub>Cl<sub>2</sub> (3 ml), precipitated and filtered as described above. The combined filtrate was evaporated and purified by column chromatography on silica gel (EtOAc–petroleum, 1:4) to afford the desired thiophenes **3**.

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