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Synthesis of tetrasubstituted thiophenes on solid-support using the Gewald reaction

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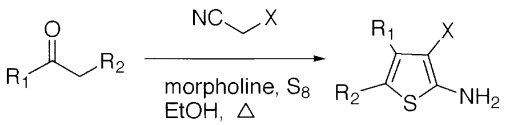
Abstract—The Gewald reaction was performed on solid support. This reaction combines a ketone or aldehyde, an activated nitrile, and sulfur in the presence of a suitable amine base to make tri- and tetrasubstituted thiophenes. After optimizing conditions for maximum yield and purity, the scope of the reaction was investigated. Finally, this method is highlighted in the synthesis of two biologically relevant compounds. © 2001 Elsevier Science Ltd. All rights reserved.

Tri- and tetrasubstituted thiophenes **2** prepared via the Gewald reaction[1] (Scheme 1) provide important scaffolds for medicinal applications. The core structure formed in the multicomponent condensation between a ketone or aldehyde **1**, an activated nitrile, and sulfur is found in inhibitors of the phosphatase PTP1B,[2] serotonin receptor subtype 5-HT_{1A},[3] human leukocyte elastase,[4] and adenosine receptor A_3.[5] In addition, this thiophene scaffold is prevalent in screening libraries available from commercial sources and is therefore a likely candidate for analog synthesis.[6] Recently, the utility of this scaffold as a starting point for further parallel synthesis has been described.[7]

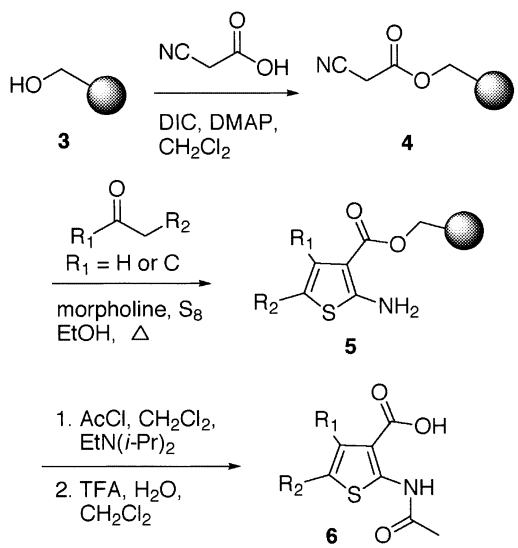
The generation of such a highly functionalized core structure and its prevalence in medicinal chemistry prompted us to investigate this reaction on solid support. Performing the Gewald reaction on solid support would eliminate a necessary purification step and make this reaction more amenable for high throughput library synthesis. Reactions with activated nitriles such as ethyl cyanoacetate (X = CO_2Et, Scheme 1) result in



Scheme 1. Gewald synthesis of tetrasubstituted thiophenes.

3-carboxy substituted 2-aminothiophenes that present two additional functionalities for further elaboration. This being our choice of nitrile, an ester linkage through the acid labile phenoxybenzylalcohol resin linker (Wang)[8] was a logical choice for resin attachment. In addition, it was found that ethyl esters of some Gewald products proved difficult to hydrolyze via traditional saponification, making an acid-mediated cleavage using the Wang linker beneficial.

Acylation of Argogel® Wang resin **3** with cyanoacetic acid under standard DIC/DMAP coupling conditions gave the resin-bound cyanoacetic ester **4** (Scheme 2).



Scheme 2. Solid-phase route to thiophenes.

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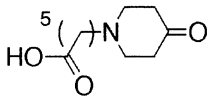
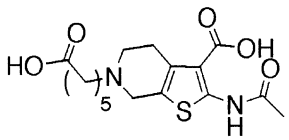
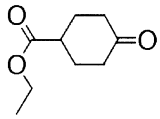
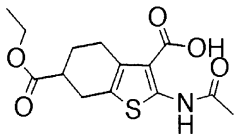
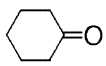
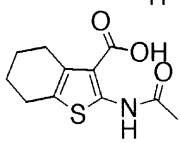
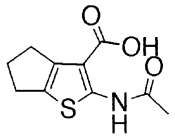
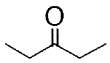
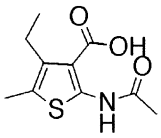
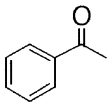
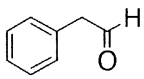
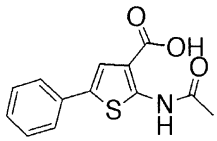
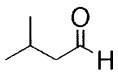
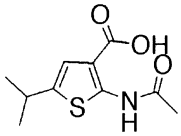
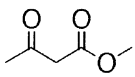
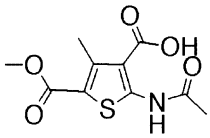
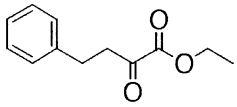
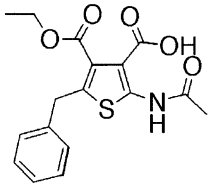
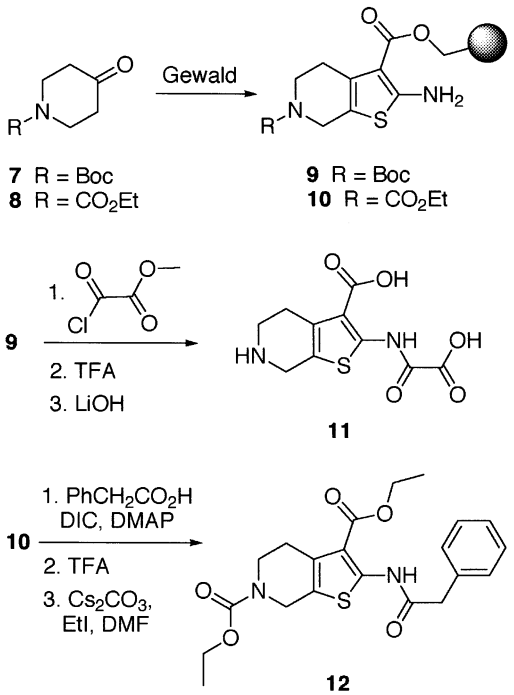
Table 1. Products from solid-phase synthesis, yields and purities

Entry	ketone/ aldehyde	Product	% Crude Yield	HPLC Purity
1			92%	95%
2			93%	96%
3			84%	97%
4			100%	75%
5			27%	63%
6		No Reaction	0%	-
7			44%	80%
8			44%	100%
9			46%	64%
10			34%	87%

The PEG based support was chosen due to its favorable swelling properties in ethanol, the reaction solvent. The Gewald reaction was performed in a 10 mL reaction vessel on a Quest™ 210 synthesizer. The resin was suspended in ethanol containing the ketone or aldehyde, morpholine, and solid sulfur (0.75 M in each component) and heated at reflux for 18 h to form the resin-bound thiophene **5**. After cooling to room temperature, the resin was washed extensively with alternating methanol, DMF, and methylene chloride. Direct isolation of the aminothiophene **5** was inefficient due to decomposition of the product during TFA cleavage. Acylation of the amine using acetyl chloride resulted in products **6** stable to the cleavage conditions.

A highly concentrated reaction solution was necessary to obtain respectable yields of the thiophene product. Time course experiments showed an 8 h reaction time to be optimal with shorter times resulting in isolated starting material, cyanoacetic acid, once the resin was cleaved with TFA. Performing the reaction at a higher temperature in refluxing butanol (from 78 to 118°C) or the use of pyridine, a reported alternative solvent,[9] at room temperature provided no improvement in yield.

To establish the scope of this reaction on solid support a variety of ketones and aldehydes were investigated (Table 1). Following the condensation all compounds were acylated with acetyl chloride prior to cleavage from the resin with TFA. Product homogeneity was analyzed by LC–MS[10] and structure confirmation was obtained by NMR. Cyclic ketones performed best in this reaction (entries 1–4), resulting in both high yields (84–92%, measured as crude weights based on loading) and purity (75–95%, estimated by HPLC[11]). These results compare favorably to yields observed in the literature for cyclopentanone (82%) and cyclohexanone (59%) using ethyl cyanoacetate.[1b] One example of a cyclic ketone (entry 5), resulted in a lower yield (27%) and purity (63%), also in agreement with previous results. Benzophenone (entry 6), gave no measurable product. Successful condensation of aryl ketones have been reported in a two-step process by isolating the Knoevenagel–Cope condensation product between the ketone and nitrile prior to thiolation and ring closure.[1b] Aldehydes (entries 7 and 8), performed well giving products of sufficient purities (80–100%) with lower recoverable yields (~45%). This also seems to be the case for β- and α-keto esters (entries 9 and 10), which are reasonable substrates (64 and 87% purity) with lower recovered yields (46 and 34%). Not shown are 1,3- and 1,4-cyclohexadione, which gave a complex mixture of products.



Scheme 3.

To demonstrate the utility of this reaction we performed the synthesis of a known PTP1B (protein tyrosine phosphatase 1B) inhibitor **11** and an adenosine receptor A_3 inhibitor **12** using this new route (Scheme 3). For the phosphatase inhibitor **11**,[2] Boc-4-piperidone **7** was used in the Gewald reaction to give thiophene **9**. Acylation with methyl oxalylchloride followed by TFA-mediated cleavage and Boc deprotection gave the methyl ester (100% crude yield and 97% purity). This crude material was then treated with 3 equiv. of LiOH in THF/H_2O for 1 h to give **11**. The diacid was precipitated in a 10% acetic acid/water solution and filtered to give **11** in 81% yield (based on resin loading).

Compound **12** is known to inhibit the adenosine receptor A_3 with an IC_{50} of 0.6 μM.[3] The solid-phase Gewald reaction was performed with 4-piperidone ethylcarbamate **7** to give aminothiophene **10** which was coupled with phenylacetic acid using DIC/DMAP. Reaction was slow and required an additional treatment with fresh reagents over 6 h to complete. Cleavage from the resin with TFA gave the acid in 72% crude yield and 78% purity. The acid was then alkylated with ethyliodide in DMF using Cs_2CO_3. Silica gel chromatography was performed to give **12** in 20% overall yield.

Highly functionalized, biologically active scaffolds are ideal tools for medicinal chemists. By performing the Gewald reaction on solid-support, appropriately protected and functionalized ketones or aldehydes like those found in Table 1 could be starting points for larger libraries. The 3-carboxylthiophene could be further elaborated post cleavage, as shown in the synthesis of thiophene **12**, or with other solution-phase schemes, such as amide-bond couplings. These and other alternatives are being investigated.

Representative procedure

Synthesis of compound 11. Cyanoacetic acid (1.25 g 14.7 mmol) was activated with diisopropylcarbodiimide (3.9 ml, 25.0 mmol) and dimethylaminopyridine (45 mg, 0.37 mmol) in dichloromethane (130 ml) for 20 min, added to Argo-Gel Wang Resin (10 g, 0.37 mmol/g loading) and agitated with nitrogen for 3 h. The reaction was drained and rinsed three times each with MeOH, dichloromethane (DCM), DMF, and again with DCM and dried under vacuum.

The resin (300 mg, 0.11 mmol) was distributed into a Quest™ 210 10 ml reaction vessel. Boc-4-piperidone (598 mg, 3.0 mmol), elemental sulfur (96 mg, 3.0 mmol), and morpholine (262 μl, 3.0 mmol) were added to the reaction vessel in 4 ml of EtOH, and the mixture was agitated and refluxed for 8 h. The vessel was then drained and the resin washed as described above.

Methyl chlorooxoacetate (111 μl, 1.0 mmol) and diisopropylethylamine (175 μl, 1.0 mmol) were added to the

reaction vessel in 4 ml of DCM to acylate the free amine. The reaction was agitated for 1 h, drained, and rinsed as described above.

Products were cleaved from the resin for 1 h in a mixture of 92.5% TFA, 5% dichloromethane, and 2.5% water to afford the methyl ester following filtration and evaporation. Lithium hydroxide monohydrate (13 mg, 0.30 mmol) was added to the ester in 4 mL of 50/50 THF/H_2O. The reaction was agitated for 1 h and evaporated. The product was redissolved in 0.5 mL of H_2O and precipitated by addition of 0.05 mL of AcOH and filtered to give 22 mg of **11** (81% overall yield).

Acknowledgements

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10. LC–MS was performed using a 50×4.6 mm column packed with 5 micron C-18 starting at 0% CH_3CN/H_2O and ramping to 90% CH_3CN/H_2O over 5 min with a 2 ml/min flow rate.
11. HPLC was performed using a 100×4.6 mm column packed with 5 micron C-18 starting at 5% CH_3CN/H_2O and ramping to 100% CH_3CN/H_2O over 15 min with a 1.2 ml/min flow rate.