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Practical Synthesis of Tetrasubstituted Thiophenes for Use in Compound Libraries

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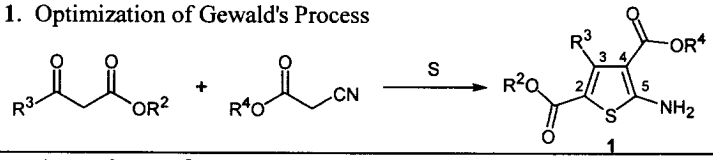
Abstract: Tetrasubstituted thiophenes, obtained by optimizing the multi-component reaction originally developed by Gewald, served as key templates for structural diversification and semi-automated library synthesis. Conditions were developed to carry out Gewald's reaction at room temperature and in high yield.

With the advent of automated combinatorial synthesis and an emphasis on the diversity of compound libraries, multi-component reactions are emerging as valuable processes for the preparation of new drug molecules. Multi-component reactions[1,2] such as the Ugi,[3] Passerini,[3d] Bignelli[4] and others[4c,d] are a highly efficient and cost effective method of generating complex compound libraries. We became interested in the underutilized reaction published by Gewald in the mid-1960's.[5] In this three component condensation reaction, a β-ketoester, cyanoacetate, and elemental sulfur condense in the presence of an organic base to yield a thiophene system that can be elaborated in four different directions. We recognized the potential of this core heterocycle as a template for parallel synthesis and produced a library of three thousand "drug-like" molecules. In the event, we also improved Gewald's process, enabling large scale synthesis of thiophenes.

Table 1. Optimization of Gewald's Process



Entry	R^4	R^3	R^2	Solvent	Base (equiv)	Time (h)	Temp (°C)	Yield (%)[a]
1	Me	Me	Et	*t*-BuOH	Et_2NH (1.0)	24	70	47
2	Me	Me	Et	*t*-BuOH	Et_2NH (0.25)	24	70	48
3	Me	Me	Et	*t*-BuOH	*i*-Pr_2NEt (0.25)	44	70	55
4	Me	Me	Et	*t*-BuOH	*i*-Pr_2NEt (1.0)	22	70	44
5	Me	Me	Et	pyridine	------	48	70	NR[b]
6	Me	Me	Et	pyridine	Et_2NH (1.0)	6	70	44
7	Me	Me	Et	pyridine	Et_2NH (1.0)	18	25	52
8	*t*-Bu	Me	Me	pyridine	Et_2NH (1.0)	48	25	69
9	*t*-Bu	Me	Bn	pyridine	Et_2NH (1.0)	48	25	71
10	*t*-Bu	CH_2OMe	Bn	pyridine	Et_2NH (1.0)	48	25	71

[a] Isolated yield [b] No reaction

The synthesis of **(1)** was reported to occur in 32%[5b] and 52%[5c] yield. Utilizing conditions reported by Bartlett,[5c] we were able to synthesize this thiophene in 47% yield after laborious purification on silica gel

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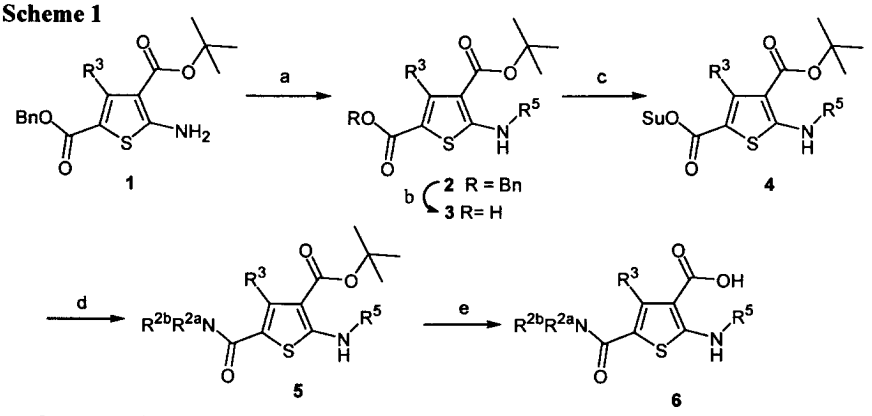
(Table 1, Entry 1). The requirement for large quantities of thiophene template **(1)** prompted us to probe Gewald reaction conditions. Initial attempts at modifying the amine base or the number of base equivalents did not affect the reaction yield (Entries 2 – 4). When the Doebner modification of Knoevenagel reaction, which uses pyridine as a solvent, was applied to the thiophene synthesis in the presence of diethylamine, 44% and 54% yields of product were obtained (Entries 6,7). Moreover, the condensation occurred at *room temperature* and product isolation was less tedious. The nature of the ester substituent on the cyanoacetate component had a profound effect on the course of the reaction. When *t*-butyl cyanoacetate was substituted for ethyl cyanoacetate, we observed a slower reaction rate but the overall yield increased substantially (Entries 8 - 10).[6] These subtle changes allowed the Gewald thiophene reaction to proceed at room temperature and produce the unique tetrasubstituted thiophene in a reproducible 70% yield on a 60 g scale.

Scheme 1



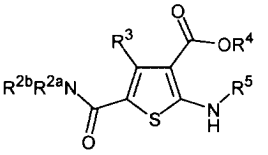
a) R^5COCl or $(R^5SO_2)_2O$ (60-85%) b) $Pd(OH)_2$, H_2, EtOH (85-95%) c) EDCI, HOBt, HOSu, Et_3N (70-83%)
d) amine $[HNR^{2a}R^{2b}]$, rt or 60°C e) TFA, DCM

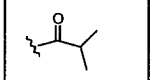
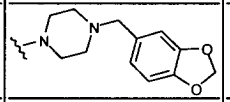
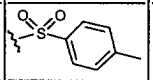
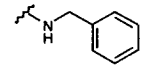
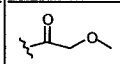
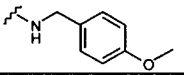
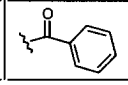
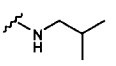
The diversification of **(1)** was approached by differentiating the ester groups (*tert*-butyl at C-4 and benzyl at C-2), acylation of the C-5 amino group, and using various β-ketoesters to add diversity at C-3. However, the C-3 position was not amenable to significant change. The thiophene synthesis did not occur with branched alkyl β-ketoesters, benzyl isobutyrylacetate, or benzyl benzoylacetate. Therefore, the library was limited to methyl and methoxymethyl at C-3.[7] Modifications of all substituents on the thiophene template were chosen to maximize library diversity and provide preliminary indications of a structure-activity relationship.

The thiophene template was elaborated through a simple and high yielding five-step procedure (Scheme 1). Acylation of the amino group at C-5 followed by deprotection of the C-2 ester produced carboxylic acid **(3)**. Amidation of **(3)** involved a large set of amines and was slated for robotic handling. This process required optimization of all reaction variables to ensure high purity and yield of product with simple aqueous work-up. Hence, several amide forming methods were investigated with the *N*-hydroxysuccinimide active ester method

providing the best results. The *N*-hydroxysuccinimide esters are not easily hydrolyzed by water and can be isolated, purified to >95% and stored for long periods of time. Furthermore, the byproducts are water soluble and purification is accomplished by a simple water wash. These conditions were then transferred to a HP-7686 Solution Phase Synthesizer[8] in order to increase compound throughput. This robot combines the liquid handling capability of a pipetting station with heating and mixing capabilities. In parallel fashion, the robotic workstation added DMF, Et_3N and the active ester to 80 septum sealed vials each containing a different amine. Primary amines reacted with the active ester (**4**) at room temperature while secondary and hindered primary amines required heating to 70°C. The amides (**5**) were isolated as single compounds in approximately 20 mg quantities following automated aqueous workup and concentration. Deprotection of the *t*-butyl ester with TFA was facile yielding the carboxylic acid (**6**) in 60 - 80% yield and >80% purity over two steps. To ensure the integrity of the library components, a representative sample (5%) covering a range of amine reactivities, was analyzed by ^{1}H-NMR and/or LC-MS.[9] Selected examples are depicted in Table 2.

Table 2. Selected Examples from the Thiophene Library



#	R^5	R^4	R^3	$NR^{2a}R^{2b}$	% purity[1]
5a		*t*-Bu	Me		81
5b		*t*-Bu	CH_2OCH_3		80
6a		H	Me		94
6b		H	CH_2OCH_3		87

[1] HPLC purity

In summary, multi-component reactions are convenient and elegant processes for generating diverse sets of compounds. Herein, we improved Gewald's reaction conditions to provide thiophenes as templates for semi-automated parallel synthesis. We are currently exploring other aspects of this work and will report our progress in the near future.

***General Procedure - Thiophene Forming Reaction*; 2-Benzyl 4-(*tert*-butyl) 5-amino-3-methyl-thiophene-2,4-dicarboxylate:** Diethylamine (7.61 g, 104.1 mmol) was added dropwise to a solution containing benzyl

acetoacetate (20.0 g, 104.1 mmol), t-butyl cyanoacetate (14.7 g, 104.1 mmol), sulfur (3.5 g, 109.3 mmol) and pyridine (120 mL). After 2 days, the black solution was concentrated under reduced pressure, dissolved in Et_2O and filtered through silica. The eluent was then concentrated. Chromatography (silica, 7:1 hexane/EtOAc) yielded 25.58 g (71%) of a orange oil which slowly crystallized upon standing. ^{1}H-NMR ($CDCl_3$) δ 1.58 (s, 9H), 2.70 (s, 3H), 5.27 (s, 2H), 7.38 (m, 5H), MS (ES): 347.5 (M^++1).

We are grateful to Marcus Colucci for analytical support.

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(6) We speculate that the more bulky esters may hinder aldol side reactions leading to oligomerization.

(7) For functionalization of a 4-methyl substituent on a similar thiophene nucleus see: (a) Furuya, S. *et al*, WO 95/28405A (Takeda Chemical Industries Ltd.), 1995. (b) Furuya, S. *et al*, US 5,744,479A (Takeda Chemical Industries Ltd.), 1998.

(8) For the use of the HP-7686 Solution Phase Synthesizer in the lead optimization for corticotropin-releasing factor$_1$ receptor antagonists see: Whitten, J.; Xie, Y.; Erickson, P.; Webb, T.; DeSouza, E.; Grigoriadis, D. McCarthy, J. *J. Med. Chem.* **1996**, *39*, 4354.

(9) **(5a):** ^{1}H-NMR ($CDCl_3$) δ 1.29 (d, 6H, J = 7.0 Hz), 1.59 (s, 9H), 2.31 (s, 3H), 2.43 (brs, 2H), 2.69 (m, 1H), 3.61 (brs, 2H), 5.30 (s, 2H), 5.95 (s, 2H), 6.74 (s, 2H), 6.85 (s, 1H), MS (ES): 530.4 (M^++1). **(5b):** ^{1}H-NMR ($CDCl_3$) δ 1.40 (s, 9H), 2.37 (s, 3H), 3.58 (s, 2H), 3.85 (s, 3H), 4.36 (d, 2H, J = 5.9 Hz), 5.75 (brs, 1H), 7.1 - 7.4 (m, 7H), 7.72 (d, 2H, J = 8.4 Hz), 8.03 (brs, 1H), MS (ES): 531.3 (M^++1). **(6a):** ^{1}H-NMR ($CDCl_3$) δ 2.67 (s, 3H), 3.48 (s, 3H), 3.77 (s, 3H), 4.08 (s, 2H), 4.47 (d, 2H, J = 6.5Hz), 6.84 (d, 2H, J = 8.8 Hz), 7.23 (d, 2H, J = 8.8 Hz), MS (ES): 393.1 (M^++1). **(6b):** ^{1}H-NMR ($CDCl_3$) δ 0.86 (d, 6H, J = 6.8 Hz), 1.78 (m, 1H), 3.11 (t, 2H, J = 6.2 Hz), 3.76 (s, 2H), 3.98 (s, 3H), 6.05 (brs, 1H), 7.56 (m, 3H), 7.98 (m, 2H), 8.24 (brs, 1H), MS (ES): 391.2 (M^++1).