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De novo synthesis of thiophenes on a polymeric support

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Abstract—The Hinsberg thiophene synthesis was expanded to support bound thioglycolic acid derived synthons, which reacted with arils to give thiophenes in high purity.

Thiophenes are of great importance both as pharmacophoric entities[1] and to material sciences[2] due to their unique electronic properties. We intended to utilize the Hinsberg thiophene synthesis[3] method to facilitate access to highly substituted thiophenes via parallel synthesis. The latter involves the reaction of a 'dimethyl sulfide motif' flanked by two carbanion stabilizing groups, such as thiodiglycolic diesters with 1,2-dicarbonyl-components. In solution phase, the mechanism of the Hinsberg synthesis is often thought to proceed via a multi-step process initiated by a Stobbe condensation,[4] though in some cases, evidence for alternative mechanisms have been reported.[5]

The complexity of the mechanism is likely the cause of complex reaction mixtures and low product yields observed in many applications of the Hinsberg method. We thought that linking thiodiglycolic acid or suitable carbanion analogs to bulky polymeric support may facilitate the removal of many side products from the reaction mixture. Thus, an ester linkage to a bulky chlorotrityl support is likely to resist premature, solvolytic cleavage of the product and may prevent possible lactone formation, as suggested by the Stobbe condensation mediated mechanism.[4]

At first, a selection of suitable carbanion analogs was synthesized on a polymeric support. Thus various acids, such as **2a**–**d** were bound to a chlorotrityl chloride resin (**1**) using standard procedures.[6] Compound **2b** was synthesized according to the procedure of Bhaskar Reddy et al.,[7] **2c** was obtained by aminolysis of thiodiglycolic anhydride.[8] Compound **3a** was esterified using isopropyl chloroformate-activation followed by an isopropanol quench[9] to give **4**. Resin **3d** was converted to the support-bound thioglycolic acid (**5**) by thiol exchange.[10] The latter could then be derivatized with the appropriate alkylating agents to give resins **3b**,**e** (Scheme 1).[11] The support bound latent 'di-carbanion'-analogs could then be reacted with various 1,2-dicarbonyl components.[12] In this scope and limitation study we screened, solvents, reaction temperature and bases (Table 1). Both NMP and THF were equally useful as solvents. The complexation of the enolate and the 1,2-diketo-component by the counter ion of the base had dramatic impact on the reaction. Thus, Schwesinger base P1[13] promoted only little conversion and bound tightly to the solid phase. In fact, it could not be washed off without concomitant cleavage of the product. In turn, KO*t*Bu appeared to be the base of choice, as it promoted clean formation of thiophenes with minimal premature cleavage of the product and without occurrence of massive filter-clotting precipitations.

At low temperature, ester **4** reacted with **7a** to substantial amounts of monoester **8b** suggesting that the thiophene formation proceeds at least in part via two consecutive Knoevenagel reactions. At higher temperatures ester **8b** was not obtained after prolonged reaction times, probably due to hydrolysis caused by the water liberated during the dehydration step (Scheme 2, Table 1).

The conditions of entry 10 in Table 1 were then used to obtain various thiophenes (Scheme 3, Table 2).[14] The 'Knoevenagel-route' was evidenced by the formation

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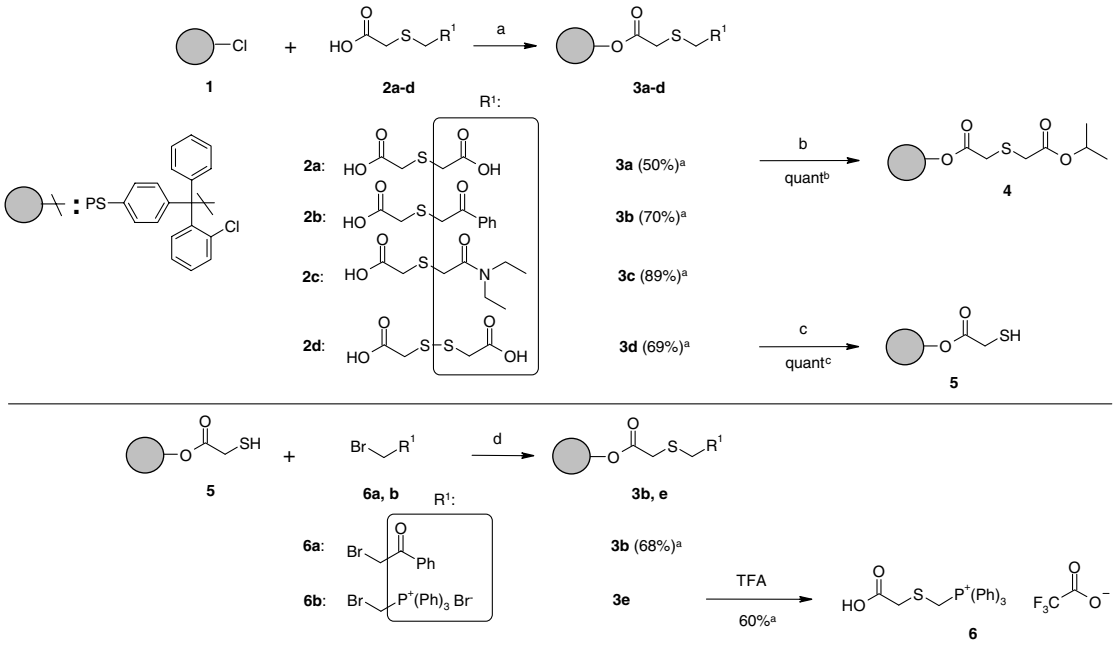
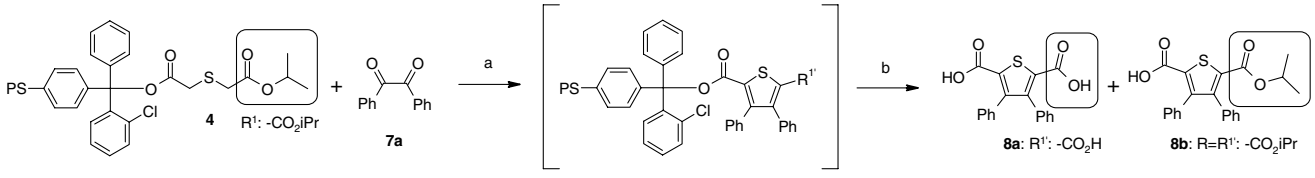


Scheme 1. Reagents and conditions: (a) acid (3 equiv), DIPEA (3 equiv), DMAP (0.03 equiv), DMF, 12 h, rt, 50–70%; (b) isopropyl chloroformate, DIPEA, *i*PrOH; (c) DMF/propane-1,3-dithiol 4:1 (v/v) (20 equiv thiol) 16 h, rt, quant; (d) halide (2 equiv), *N*-methylmorpholine (9 equiv), DMF, 18 h, rt, quant.; [(a)]Isolated yields from **1**, [(b)]Isolated yields from **3a**, [(c)]Isolated yields from **3d** after TFA-cleavage.[11]

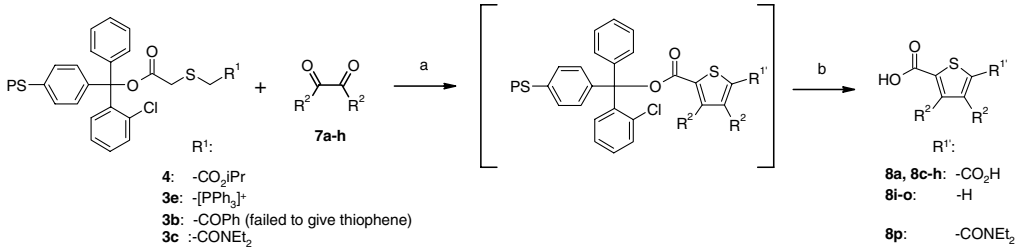
Table 1.

Entry	Base	Temperature (°C)	Time (h)	Thiophenes[a] (%)		Yield[b] (%)
				8a	**8b**	
1	LiHMDS	rt	16	22	48	n.d.
2	LiHMDS	60	4	63	—	n.d.
3	NaHMDS	rt	16	46	25	n.d.
4	NaHMDS	60	4	53	—	n.d.
5	NaOMe	60	16	49	—	n.d.
8	KO*t*Bu	rt	16	63	26	n.d.
9	KO*t*Bu	60	4	29	25	n.d.
10	KO*t*Bu	60	16	95	—	>95

[a] Determined by the integration based on area percent of the HPLC/MS-trace of the crude reaction at 220 nm.
[b] Isolated yield.

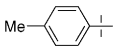
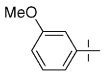
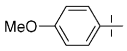
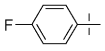
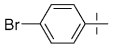
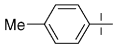
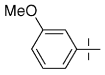
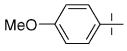
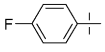
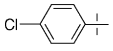
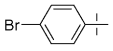


Scheme 2. Reagents and conditions: (a) conditions of Table 1:10 equiv of base, 5 equiv of **7a**; (b) 10% TFA, CH_2Cl_2.



Scheme 3. Reagents and conditions: (a) KO*t*Bu, see Ref. 14; (b) 10% TFA, CH_2Cl_2 see Ref. 10.

Table 2. The reaction in the box proceed via a Wittig olefination step[16]

Entry	R^2	No	R^1	Product	$R^{1'}$	Purity of crude product[a] (%)	Yield[b] (%)
1		**7b**	$-CO_2iPr$	**8c**	$-CO_2H$	80	73
2		**7c**	$-CO_2iPr$	**8d**	$-CO_2H$	83	>95
3		**7d**	$-CO_2iPr$	**8e**	$-CO_2H$	91	>95
4		**7e**	$-CO_2iPr$	**8f**	$-CO_2H$	71	29[e]
5		**7g**	$-CO_2iPr$	**8g**	$-CO_2H$	98	31
6		**7h**	$-CO_2iPr$	**8h**	$-CO_2H$	91[c]	53[e]
7		**7i**	$-CO_2iPr$	—	$-CO_2H$	—[d]	n.d.
8		**7j**	$-CO_2iPr$	—	$-CO_2H$	—[d]	n.d.
9		**7a**	$-[PPh_3]^+$	**8i**	H	80	34[e]
10		**7b**	$-[PPh_3]^+$	**8j**	H	68	28[e]
11		**7c**	$-[PPh_3]^+$	**8k**	H	84	>95
12		**7d**	$-[PPh_3]^+$	**8l**	H	56	34[e]
13		**7e**	$-[PPh_3]^+$	**8m**	H	73	>95
14		**7f**	$-[PPh_3]^+$	**8n**	H	71[f]	44[e]
15		**7g**	$-[PPh_3]^+$	**8o**	H	60[f]	24[e]
16		**7a**	$-CO_2iPr$	**8a**	$-CO_2H$	95	>95
17		**7a**		—	n.d.	0[f]	n.d.
18		**7a**	$-CONEt_2$	**8p**	$-CONEt_2$	71[f]	90[e]

[a] UV purity at 220 nm.
[b] Isolated yields.
[c] Two rotamers, stable at rt.
[d] Complex mixture.
[e] Isolated yield after MS-triggered HPLC.
[f] Rest is starting material.

of **8p** from **3c** (Table 2, entry 18). Thus, the initial attack of **7a–g** upon the less hindered ester enolate next to R^1 (Schemes 2 and 3) formed an α-hydroxy carbonyl compound. The latter could not attack the carbonyl group of the hindered trityl-support ester completing a Stobbe reaction.[4] In turn, the α-hydroxy carbonyl compound could either eliminate the starting material or perform a second Knoevenagel reaction leading, after dehydration, to a thiophene. The latter path could only be likely, if the α-hydroxy carbonyl intermediate was more basic than the adjacent thioglycolic ester enolate. Consequently, 1,2-diketo-building blocks bearing CH-acidic protons methyl pyruvate and 2-ketoaldehydes did not generate thiophenes. Glyoxal acetals were not sufficiently soluble to interact well with the synthesis support. 1,2-Diketones bearing hetrocyclic substituents (Table 2, entries 7 and 8) were probably consumed by the basic reaction medium prior to the reaction with

the support.[15] Intriguingly, resin **3b** also did not react with **7a** (Table 2, entry 17), while resin **3c** bearing a much less acidic enolate, reacted with **7a** to afford **8p** (Table 2, entry 18).

However, our procedure was expandable to support-bound carbanions stabilized by additional EWGs other than esters or amides (Table 2). In the case of the support-bound phosphonium salt **3e** a Wittig olefination is likely to initiate the thiophene formation.[16] Intriguingly, the presence of the nucleophile DMAP, which may have allowed the equilibration of a proposed olefinic intermediate did not influence the outcome of the reactions (Table 2, entries 9–15).

We have reported the first Hinsberg-based synthesis of thiophenes on solid phase. Thiophene-2-carboxylic acids and thiophene-2,5-dicarboxylic acids bearing aromatic residues at C3 and C4 were obtained in high yields and exceptional purity. The steric bulk of the resin linker promoted the thiophene formations to proceed via two consecutive Knoevenagel reactions and not via a Stobbe mechanism. The reason why support-bound [(2-oxo-2-phenylethyl)thio]acetic acid did not react is not clear.

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Supplementary data

Supplementary data consisting of the HPLC-traces of crude thiophenes, NMR and HRMS data of compounds **8a**,**c**–**p** is available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.03.111.

References and notes

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8. {[2-(Diethylamino)-2-oxoethyl]thio}acetic acid (**2c**): To thiodiglycolic anhydride (3.96 g, 30 mmol) dissolved in THF (15 mL) was added *slowly* under ice-cooling diethylamine (6.18 mL, 4.39 g, 60 mmol). The reaction mixture was stirred at rt for 2 h and then diluted with CH_2Cl_2 (150 mL). The reaction mixture was extracted with aq HCl (2 M). The aq phase (pH ~ 1) was back-extracted with CH_2Cl_2 (150 mL). The combined organic phases were evaporated to dryness to afford **2c** an oil which crystallizes upon initiation with a glass rod (5.34 g, 86%). ^{1}H NMR (400 MHz, DMSO) δ 12.63 (1H, br s), 3.51 (2H, s), 3.36 (2H, s), 3.27 (4H, q, $J = 7.1$ Hz), 1.13 (3H, t, $J = 7.1$ Hz), 1.02 (3H, t, $J = 7.1$ Hz); 12.63 (1H, br s), 3.51 (2H, s), 3.36 (2H, s), 3.27 (4H, q, $J = 7.1$ Hz), 1.13 (3H, t, $J = 7.1$ Hz), 1.02 (3H, t, $J = 7.1$ Hz); HRMS *m*/*z* Calcd for $C_8H_{15}NO_3S$: 206.0846 $(M+H)^+$ Found: 206.0856.
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11. For instance TFA-cleavage of {[(Carboxymethyl)thio]-methyl}(triphenyl)phosphonium trifluoroacetate (**6**): Resin **3e** (90 mg) was subjected to three consecutive treatments with 10% TFA in CH_2Cl_2 for 5 min each. The product solutions were combined and evaporated in vacuo. Yield: 36.4 mg (60% from **1**); ^{1}H NMR (400 MHz, DMSO) δ 12.85 (1H, br s), 7.77–7.96 (15H, m), 4.98 (2H, d, $J_{H-P} = 10.6$ Hz), 3.26 (2H, d, $J = 1.1$ Hz); HRMS *m*/*z* Calcd for $C_{21}H_{20}O_2PS$: 367.0916 $(M)^+$ Found: 367.0915.
12. The reactions on solid phase were performed in a Bohdan Miniblock® using 5 mL PP-fritt reactors equipped with a heating block and an orbital shaker. (Mettler-Toledo Bohdan, 562 Bunker Court, Vernon Hills, IL 60610 USA).
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14. *General procedure for synthesizing thiophenes:* To each reactor charged with 100 mg (0.06 mmol) of resins **3b**, **3c**, **3e** or **4** suspended in dry THF (1 mL) were added diketone (0.7 mmol) and 1 M KO*t*Bu solution in THF (1.4 mL). The suspensions were shaken at 60 °C for 15 h. Then, the reagents were filtered off and the resins were washed twice with the following sequence of solvents: MeOH (2×), THF (2×), H_2Cl_2 (2×). The products were cleaved off with TFA,[11] dried down in vacuo, and subjected to analytical HPLC for purity determination. (gradient: 10–90% MeCN–aq 0.1% TFA, 10 min) Products of inferior purity were subjected to preparative mass triggerd HPLC using the same gradient (Table 2).
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