Solid-phase Functionalization of Heterocycles by Direct Lithiation

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Abstract: Lithiation of polymer-bound 3-furanmethanol and 3thiophenemethanol followed by the addition of electrophiles and resin cleavage afforded 2,4-disubsituted furans and thiophenes respectively in good yield. The 2,4-substituted thiophene can also be further lithiated on solid-phase at C-5 to give 2,3,5-substituted thiophenes.

In recent years, combinatorial chemistry has emerged as an important tool for drug discovery and medicinal chemistry.¹ The consequent need to produce large numbers of compounds in good yield and purity has caused an explosion of interest² in Solid-Phase Organic Synthesis (SPOS). Expansion of the synthetic repertoire compatible with solid supports depends on the successful adaptation of a variety of classical and modern organic reactions previously performed in solution.

Polystyrene can be directly lithiated on the aromatic ring, as reported³ by Fyles and Leznoff more than two decades ago (the benzylic carbon, another potential site for deprotonation, is not lithiated⁴). This implies that a polystyrene-based matrix may be unsuitable for solid-phase reactions involving strongly basic organometallic reagents. Nevertheless, conditions⁵ for polystyrene lithiation are solvent-dependent and require elevated temperatures, suggesting that kinetically controlled reactions of resin-bound substrates can still be selectively accomplished. In recent examples, *n*-butyllithium was used in solid-phase nucleophilic additions,⁶ transmetalation,⁷ deprotonation,⁸ and lithium-halogen exchange,⁹ and *t*-butyllithium¹⁰ for formamidine deprotonation. Here, we report the first solid-phase investigation into *C*-lithiation of heteroaromatic compounds, a well-established and important synthetic procedure in solution.¹¹

Initially, we attached 3-furanmethanol and 3-thiophenemethanol to polystyrene-trityl resin (Novabiochem, loading capacity of 0.67 mmol/g). The loading of 3-thiophenemethanol was determined to be 0.4 mmol/g by resin cleavage and recovery of the alcohol. In the case of 3-furanmethanol, instability to the acidic cleavage conditions prevented direct determination of loading efficiency, and it was assumed to be similar to that of the thiophene. Direct lithiation of the resins 1 and 2 (Scheme 1) generated orange-colored beads. Quenching with electrophiles followed by resin cleavage gave the corresponding 2,4-disubstituted furan (3) or thiophene (4) derivatives in good yields (Table 1).¹²



Reagents and conditions: (i) furan or thiophene methanol, DMAP, DMF, 80 °C, 15 h (ii) *n*-BuLi, -30 °C, THF, 4 h; electrophile, THF, -30 °C to rt, 2h (iii) 5 % TFA, Et_3SiH, CH_2Cl_2

Scheme 1

| Resin, electrophile | Resin, electrophile Product | | Yield (%)* | | | | |
|--|-----------------------------|---|------------|--|--|--|--|
| 1, DMF | 3a | СНО | 68 | | | | |
| 1, CH,CONMe ₂ | 3b | COCH, | 51 | | | | |
| 2, DMF | 4a | СНО | 81 | | | | |
| 2, CH ₂ CONMe ₂ | 4b | COCH ₃ | 75 | | | | |
| 2 , MeI | 4c | Me | 66 | | | | |
| 2, CH ₂ =CHCH ₂ Br | 4d | CH ₂ CH=CH ₂ | 72 | | | | |
| 2, TMSBr | 4e | TMS | 82 | | | | |
| 2, p-MeC ₆ H ₄ CHO | 4f | CH(OH)C ₅ H ₄ -p-Me | 84 | | | | |
| 2, Thiophene-3-CHO | 4g | 3-CH(OH)thiophene | 78 | | | | |

Table 1. Synthesis of 2,4-substituted furans and thiophenes

| Isolated 7 | yields after | preparative 7 | TLC | purification, | based on | loading of | 0.4 mmol/g |
|------------|--------------|---------------|-----|---------------|----------|------------|------------|
|------------|--------------|---------------|-----|---------------|----------|------------|------------|

In solution, lithiation of the *t*-butyldimethylsilyl ether of 3-furan or thiophene methanol occurs¹³ at C-2. It is likely that the steric bulk of the trityl group in our examples outweighs the beta-directing effect,¹¹ cleanly promoting C-5 lithiation.¹⁴ The resulting 2,4-disubstitution pattern is difficult to obtain synthetically, and previous methods have often temporarily blocked C-2.^{13a,15}

We have also investigated the feasibility of sequential lithiations. Resin **2** was lithiated and reacted with an electrophile, followed by extensive washing (THF, MeOH). The dried resin was resubjected to lithiation, which now takes place adjacent to the alkoxymethyl group (**Scheme 2**). The preparation of **5** and **6** illustrates the potential of this method to build up 2,3,5-trisubstituted thiophenes from simple precursors.





In conclusion, *C*-lithiation represents a powerful method for the solidphase functionalization of furans and thiophenes. We are presently extending these studies to other carbocyclic and heterocyclic aromatic ring systems.

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