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Tetrahedron Letters 49 (2008) 2425–2428
Tetrahedron Letters

Facile synthesis of 3-substituted thieno[3,2-*b*]furan derivatives

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Received 3 December 2007; revised 7 February 2008; accepted 11 February 2008
Available online 14 February 2008

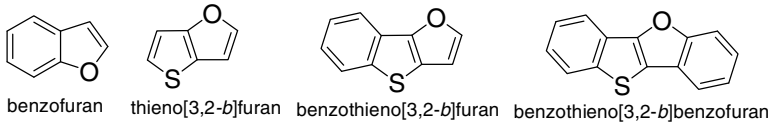
Abstract

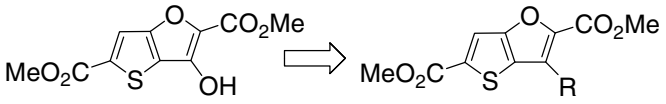
A facile synthesis of dimethyl 3-hydroxythieno[3,2-*b*]furan-2,5-dicarboxylate is reported from the available methyl thioglycolate and dimethyl acetylenedicarboxylate starting materials. This compound represents an efficient precursor for the synthesis of 3-substituted thieno[3,2-*b*]furan derivatives.

Keywords: Furan; Thienofuran; Dieckmann cyclization; Heterocyclic chemistry

Furan derivatives constitute an important class of heteroaromatic compounds which exhibit a large variety of applications involving both the fields of natural products, pharmaceuticals and organic materials.[1–7] Among fused furan heterocycles, benzofuran[8] derivatives have been largely developed whereas for thieno[3,2-*b*]furan series very little examples are known. Thieno[3,2-*b*]furan and 5-methylsulfanylthieno[3,2-*b*]furan, respectively, synthesized by Paulmier et al.[9] and McNab and co-workers[10] are presented as unstable compounds. Svoboda et al. have synthesized benzothieno[3,2-*b*]furan and indicated a low stability in acidic media.[11] The authors have shown that this heterocycle reacts as dienophile in Diels–Alder reaction with electron-rich dienes to lead to benzothieno[3,2-*b*]benzofuran derivatives.[12,13] Some examples of more stable thieno[3,2-*b*]-furan derivatives have been obtained by grafting electron-withdrawing groups on the 2 and 3 positions of furan cycle.[14–19]

The main approach to synthesize the thieno[3,2-*b*]furan unit is based on the construction of the furan ring by cyclocondensation reaction under basic condition starting from 2-formyl or 2-cyano-3-methoxycarbonylmethyloxy-thiophene.[9,14–18] As an extension of this method, we report here on a facile synthesis of dimethyl 3-hydroxythieno[3,2-*b*]-





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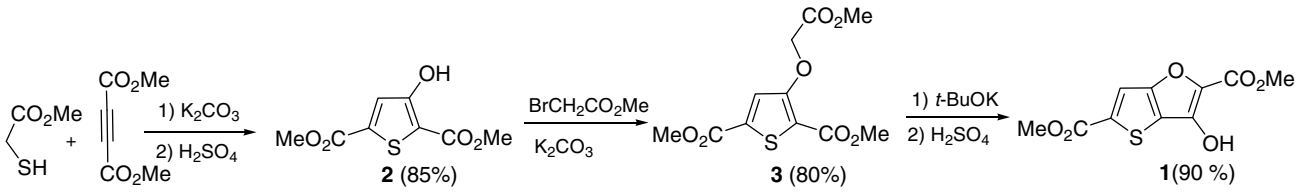
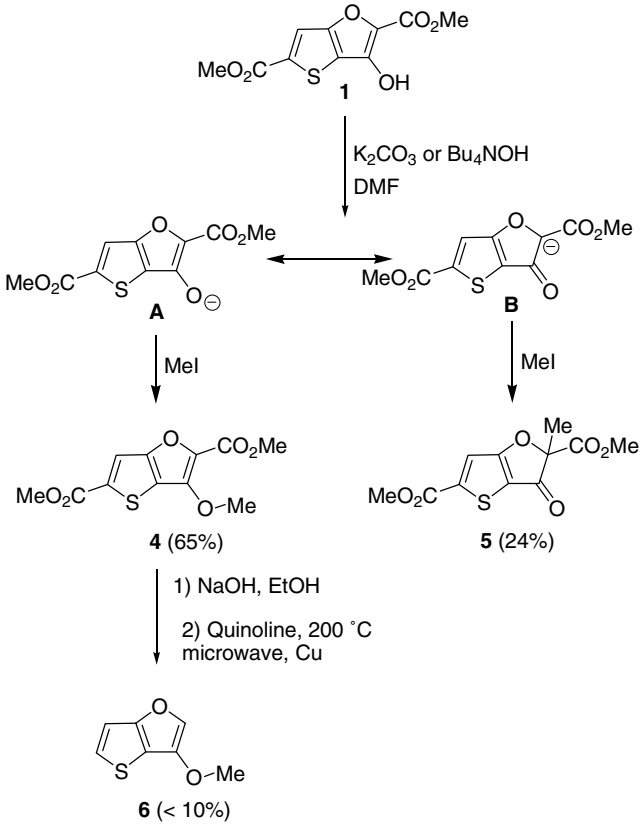
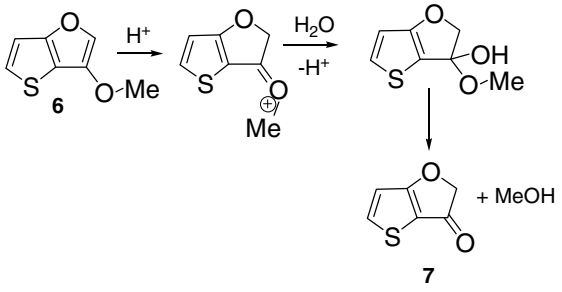
doi:10.1016/j.tetlet.2008.02.058



Scheme 1.



Scheme 2.



Scheme 3.

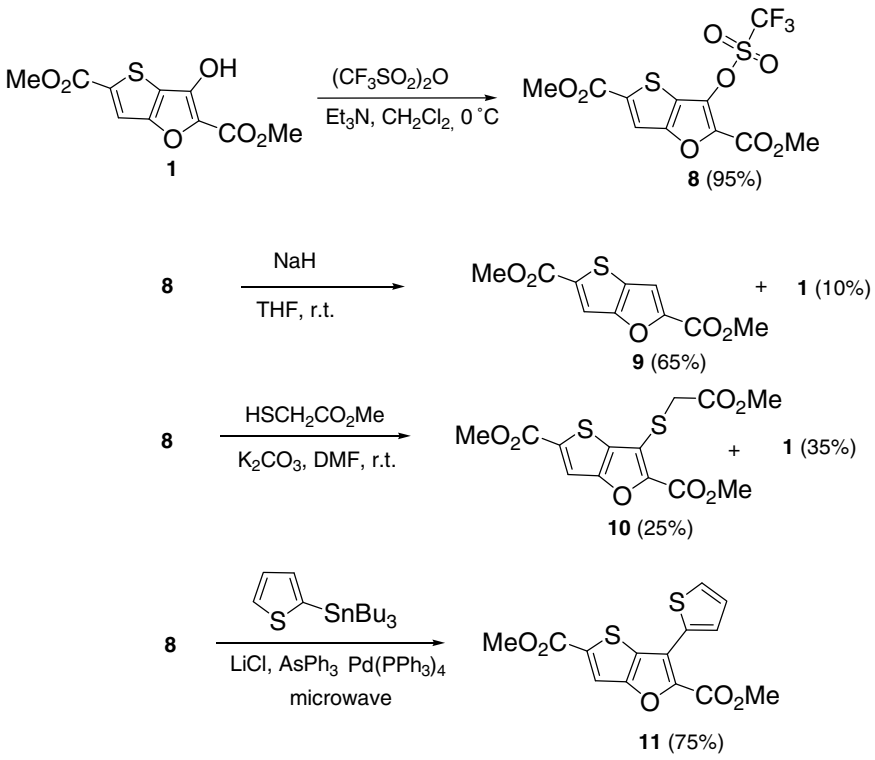
furan-2,5-dicarboxylate **1** which represents an efficient precursor for the development of 3-substituted thieno-[3,2-*b*]furan derivatives.

The synthesis of compound **1** is based on two intramolecular cyclizations of Dieckmann as shown in Scheme 1. The Michael reaction between the thiolate of methyl thioglycolate and the dimethyl acetylenedicarboxylate, followed in situ by the first intramolecular cyclization, afforded dimethyl 2,5-dicarboxylate-3-hydroxythiophene **2** in 85% yield. Treatment of **2** by a slight excess of methyl bromoacetate in the presence of K_2CO_3 as the base in DMF gave compound **3** in 80% yield. The second cyclization reaction was performed by the action of *t*-BuOK in THF on **3** for obtaining **1** in 90% yield.[20] For each step, the compounds were easily isolated by precipitation after the addition of acidified water (H_2SO_4, 0.5 M).

The nucleophilic substitution of the anion of **1**, generated by the addition of K_2CO_3 in DMF, with a slight excess of MeI led to a mixture of compounds **4** and **5** in 65% and 24% yields, respectively (Scheme 2). The anion of **1** can be regarded as an ambident enolate anion present in two mesomeric forms A and B. The O-alkylation of A gave **4** whereas the C-alkylation of B afforded **5**. The carboxylic acid resulting from the saponification of compound **4** was decarboxylated at 200 °C in quinoline under microwave irradiation in the presence of powder of copper to lead to 3-methoxythieno[3,2-*b*]furan **6** in very low yield (inferior to 10%). Compound **6** presents a low stability in solution in CH_2Cl_2 or $CHCl_3$ but also in benzene or ethyl acetate under illumination with day light.

The ^1H NMR spectrum of **6** in $CDCl_3$ shows an evolution corresponding to the formation of ketone **7** and of methanol (Scheme 3 and Fig. S1 in Supplementary data). For compound **6**, the aromatic protons of thiophene give two doublets at 6.95 and 7.17 ppm while the proton of the furan ring presents a broad singlet at 7.17 ppm. After 2 h in solution, the singlet at 3.82 ppm corresponding to the methoxy group of **6** disappears while two new singlets appear at 5.00 ppm and 3.50 ppm relative to CH_2 in α of carbonyl group of **7** and methanol, respectively. The chemical shifts of the protons of thiophene ring are very different in compound **7** with two doublets at 7.88 and 6.30 ppm. Such evolution, already observed for 3-methoxyfuran and 3-methoxybenzofuran, is catalyzed by a low concentration of H^+.[21]

In an effort to develop new thieno[3,2-*b*]furan derivatives from the readily accessible compound **1**, the hydroxyl group has been *quasi* quantitatively transformed into triflate **8** by the action of triflic anhydride in the presence of Et_3N (Scheme 4) in anhydrous methylene chloride at 0 °C.[20] The treatment of **8** with sodium hydride in tetrahydrofuran gave compound **9** in 65% yield together with the hydroxy derivative **1** in 10% yield. With a bulkier anion such as the thiolate of methyl thioglycolate, the aromatic



Scheme 4.

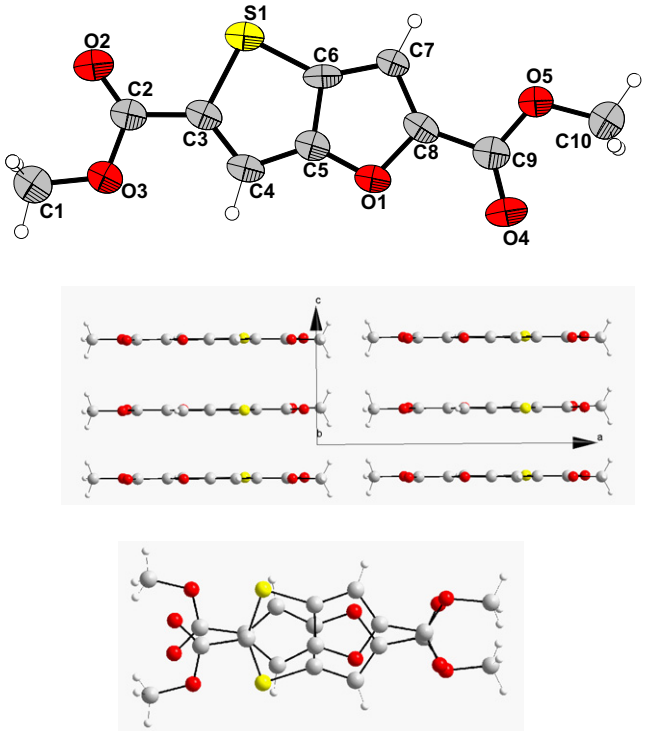


Fig. 1. X-ray structure of compound **9**.

nucleophilic substitution was less efficient and led to compound **10**[20] in 25% yield only while the major product **1** was obtained in 35% yield. Triflates are known to present similar reactivity to bromides in Pd-mediated reactions.[22] We have tested the reaction of compound **8** in a Stille coupling with tributylstannylthiophene under microwave irradiation by using the general procedure recently described by Lopez et al.[23] Irradiation for 5 min at 80 °C of a mixture of **8** in toluene with a slight excess of stannic derivative (1.3 equiv), and $Pd(PPh_3)_4$ (10 mol %) as the catalyst in the presence of LiCl and $AsPh_3$ led to compound **11**[20] in 75% yield.

Single crystal of **9**, obtained by slow evaporation from a chloroform/ethanol solution, was analyzed by X-ray diffraction[24] and constitutes the second example of structure for thienofuran derivatives indexed in the Cambridge database.[19] As shown in Figure 1 (left), the molecule is fully planar with the two ester groups in the prolongation of the thienofuran unit. The fusion of the thiophene and furan rings induces an important deformation of the cycles when compared with their non-fused forms. Thus bond length C3–C4 (1.34 Å) of thiophene is very short compared to central bond C5–C6 (1.38 Å) and conversely the bond length C7–C8 (1.39 Å) of furan is relatively large. The molecules stack along the *c* axis by presenting an overlap of thienofuran units which does not allow S–S contacts. The intermolecular distances between the planes of thienofuran moieties of 3.37 Å are compatible with the existence of π interactions.

In summary we have presented a facile synthesis of dimethyl 3-hydroxythieno[3,2-*b*]furan-2,5-dicarboxylate. Such a derivative constitutes an interesting precursor for the development of thienofuran derivatives. Hence, by

the utilization of the triflate group, the synthesis of 3-substituted thieno[3,2-*b*]furans was also achieved.

Acknowledgment

The authors thank the SCAS of the University of Angers for analytical characterization.

Supplementary data

Evolution of the ^{1}H NMR spectrum of **6** in $CDCl_3$. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.02.058.

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20. All new compounds exhibited spectral properties consistent with the assigned structures.
    Selected examples:
    Compound **1**: White solid, mp 220 °C, dec ^{1}H NMR (500 MHz, $CDCl_3$) 3.93 (s, 3H), 4.00 (s, 3H), 7.67 (s, 1H), 8.2 (br s, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$) 52.2, 52.7, 89.3, 116.8, 117.6, 119.6, 130.5, 138.7, 156.1, 162.4; MS (EI) 256 [$M^{+\cdot}$].
    Compound **8**: White solid, dec from 210 °C. ^{1}H NMR (500 MHz, $CDCl_3$) 3.95 (s, 3H), 4.01 (s, 3H), 7.06 (s, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$) 52.8, 52.9, 116.6, 117.2 (q, $^1J_{C-F} = 321$ Hz), 120.5, 136.7, 138.8, 139,3, 155.5, 157.2, 161,7; MS (EI) 388 [$M^{+\cdot}$].
    Compound **9**: White solid, mp 112 °C, ^{1}H NMR (500 MHz, $CDCl_3$) 3.93 (s, 3H) and 3.97 (s, 3H), 7.52 (s, 1H), 7.77 (s, 1H); MS (EI) 240 [$M^{+\cdot}$].
    Compound **10**: White solid, mp 131–132 °C. ^{1}H NMR (500 MHz, $CDCl_3$) 3.75 (s, 3H), 3.93 (2s, 5H), 3.98 (s, 3H), 7.73 (s, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$) 34.7, 52.4, 52.7, 53.0, 116.5, 124.8, 129.5, 137.8, 143.5, 156.4, 159.0, 162.2, 168.8; MS (EI) 344 [$M^{+\cdot}$].
    Compound **11**: White solid, mp 157 °C. ^{1}H NMR (500 MHz, $CDCl_3$) 3.95 (s, 3H), 4.02 (s, 3H), 7.20 (dd, 1H, $^3J = 5.2$ Hz, $^3J = 3.7$ Hz); 7.53 (d, $^3J = 5.2$ Hz), 7.78 (s, 1H), 7.89 (d, 1H, $^3J = 3.7$ Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$) 52.5, 52.8, 116.6, 127.7, 128.4, 128.6, 129.0, 130.4, 130.9, 138.0, 141.5, 155.7, 159.6, 162.5; MS (EI) 322 [$M^{+\cdot}$].
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24. *Crystallographic data for* **9**: Crystal size ($0.29 \times 0.14 \times 0.02$ mm^3), $C_{10}H_8O_5S$, $M_r = 240.22$, orthorhombic, space group *P bcm*, $a = 13.5456(8)$ Å, $b = 11.5419(9)$ Å, $c = 6.6921(4)$ Å, $\alpha = \beta = \gamma = 90°$, $V = 1046(26)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.525$ g/cm^3, 12,836 reflections collected in the 3–27° θ range, 1253 independent reflections from which 534 with $I > 2\sigma(I)$ converged to $R = 0.0523$ and wR_2 (all data) = 0.1413 with 98 parameters, GOF = 0.892.
    Crystallographic data excluding structure factors have been deposited with the Cambridge Crystallographic Data under reference CCDC: 669379.