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Convenient 'one-pot' synthesis of 3,4-substituted tetrahydrothiophenes through tandem Michael–Henry and Michael–Michael reactions

Achille Barco,[a] Nikla Baricordi,[a] Simonetta Benetti,[a,*] Carmela De Risi[b] and Gian Piero Pollini[b,*]

[a]*Dipartimento di Chimica, Via L. Borsari 46, I-44100 Ferrara, Italy*
[b]*Dipartimento di Scienze Farmaceutiche, Via Fossato di Mortara 19, I-44100 Ferrara, Italy*

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Abstract—In situ generated nitro alkenes underwent tandem Michael–Henry and Michael–Michael sequences leading to the 'one-pot' formation of 3,4-substituted tetrahydrothiophenes using the commercially available 1,4-dithiane-2,5-diol (the dimer of mercaptoacetaldehyde) or its 4-mercapto-2-butenoates derivatives as suitable bifunctional partners, respectively.

The widespread occurrence of five-membered oxa-, aza- and thia-ring system motifs in biologically significant natural products, drugs and drug candidates has stimulated great interest in the development of new synthetic approaches.[1]

In particular, thiolane derivatives continue to be of great interest due to their wide range of biological activities, including an essential coenzyme (biotin)[2] and a cholecystokinin type-B receptor antagonist (tetronothiodin)[3] (Fig. 1), potential inhibitors of HIV[4] and glucosidase inhibitors[5,6] (Fig. 2).

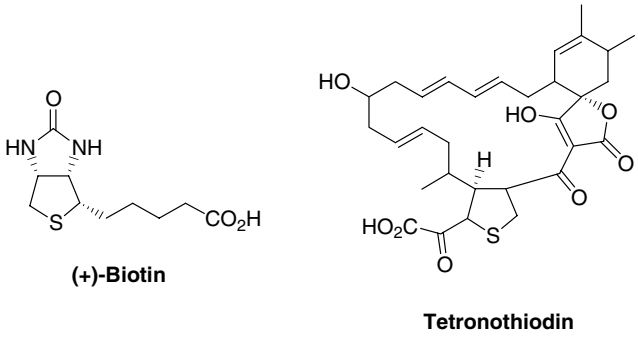

Figure 1.

A number of methods have been developed to synthesize substituted tetrahydrothiophenes, typically involving simple carbon–carbon or carbon–sulfur bond formation. Thus, the key step of an approach to the thiophane ring system involving nitroaldolization has been described earlier by Grob and von Sprecher[7] in 1952 along their efforts in the field of the synthesis of biotin. More recently, Ponce Molina and Overman[8] developed a new method for the stereocontrolled synthesis of a variety of substituted tetrahydrothiophenes by acid-promoted condensation of mercapto allylic alcohols and aldehydes and ketones. The ring forming step of both approaches was based on carbon–carbon bond formation. On the other hand, carbon–sulfur bond formation was the key step of the stereoselective synthesis of homochiral substituted tetrahydrothiophenes by electrophile-promoted thioetherification reported by Jana et al.[9]

Moreover, the 1,3-dipolar cycloadditions of a sulfur-containing 1,3-dipole to α,β-unsaturated acyl derivatives dipolarophiles resulting in the formation of *trans*-3,4-disubstituted tetrahydrothiophenes, involved two carbon–carbon bond-forming reactions.[10]

Keywords: Tandem reactions; Michael reactions; Henry reactions; Tetrahydrothiophenes.
* Corresponding authors. Tel.: +39 0532 291174; fax: +39 0532 240709 (S.B.); tel.: +39 0532 291286; fax: +39 0532 291296 (G.P.P.); e-mail addresses: bns@unife.it; pol@unife.it

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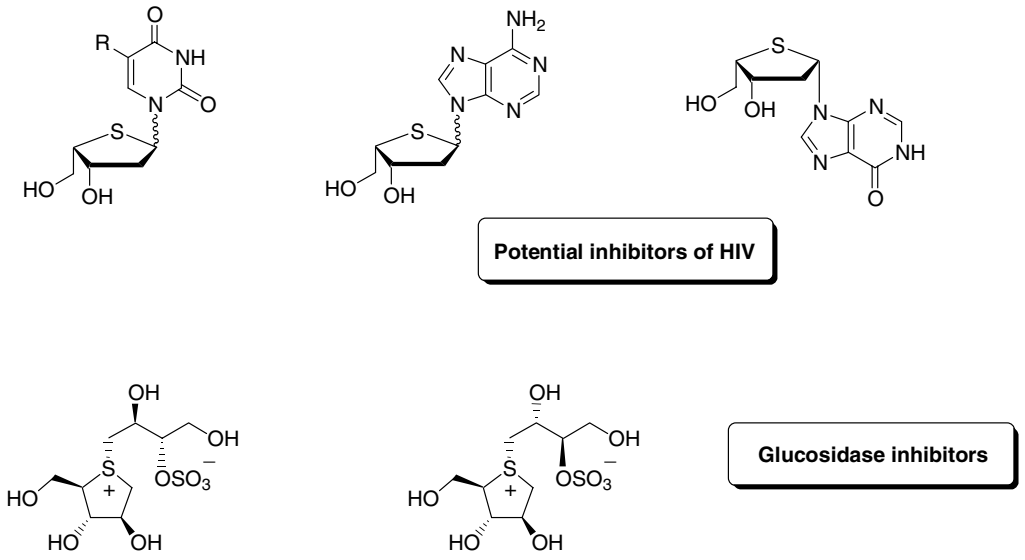
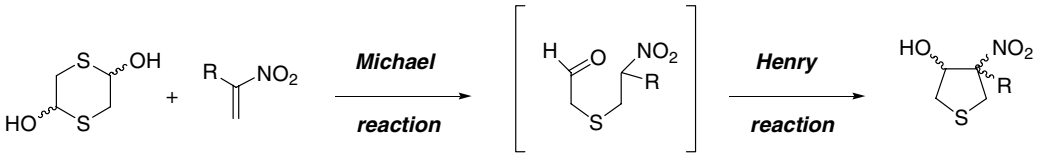


Figure 2.



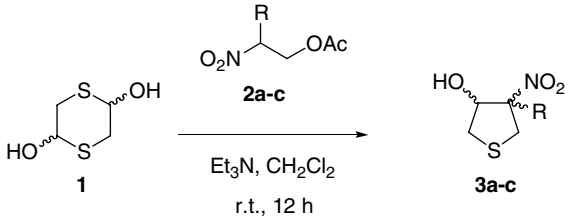
Scheme 1.

Previous investigations in our laboratories have shown that five-membered nitrogen heterocycles can be prepared by tandem Michael addition between nitroethylene and a nitrogen nucleophile, bearing at the β-position an aldehyde group, followed by an intramolecular Henry nitroaldol reaction of the derived nitroalkane adduct.[11,12]

Given our own interest in tandem annulation chemistry of unsaturated nitro derivatives, we envisaged a simple approach to 3,4-disubstituted tetrahydrothiophenes based on a 'one-pot' tandem Michael–Henry reaction.[13,14]

Our strategy entailed on the use of the commercially available 1,4-dithiane-2,5-diol (the dimer of mercaptoacetaldehyde) as a suitable bifunctional reagent possessing a sulfur nucleophile able to undergo Michael intermolecular addition to in situ generated nitroalkenes producing an intermediate nitroalkane adduct, which bears a suitably placed aldehyde group required for the subsequent intramolecular Henry nitroaldol reaction (Scheme 1).

To test the feasibility of our protocol, 2-nitroethyl acetate **2a**, used as a stable precursor for nitroethylene, was mixed with dimer **1** in dichloromethane containing triethylamine giving rise to the expected formation of 3-nitro-4-hydroxythiophane **3a** as a mixture of stereoisomers in a 65% yield (Scheme 2, Table 1).



Scheme 2.

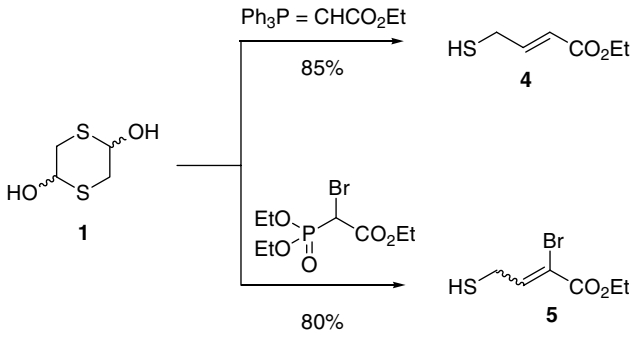
Table 1. Synthesis of tetrahydrothiophene derivatives **3a–c**

Nitro acetate	R	Compound **3** (% yield)[a]
2a	H	65
2b	CH_2OH	70
2c	$(CH_2)_2OCH_2OCH_3$	80

[a] Isolated yield after purification by column chromatography.

The same results were observed when **2b** and **2c** were used as counterparts in the reaction with 1,4-dithiane-2,5-diol **1** as shown in Table 1.[15]

A similar intramolecular sequence based on hetero-Michael/nitroaldolisation using thiophenol, nitroolefines and formaldehyde has been reported previously.[16]



Scheme 3.

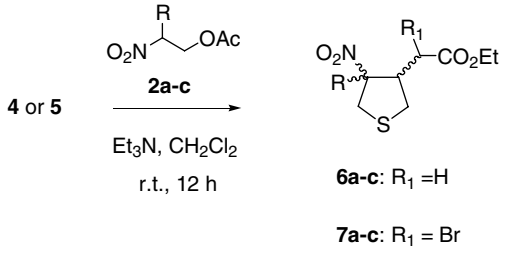
Furthermore, the mild protocol developed by Bunce and Pierce[17] to perform the Wittig reaction of **1** with both stabilized phosphoranes or phosphonates allowed us to obtain the interesting 4-mercapto-2-butenoates **4** and **5** (Scheme 3).

These compounds could be used as convenient partners of unsaturated nitro derivatives for a tandem Michael reaction producing a variety of nitro substituted tetrahydrothiophenes,[18] possessing functionalities easily amenable for further transformations (Scheme 4).

Thus, reaction of both **4** and **5** with nitro derivatives **2a–c**, suitable precursors for the in situ generation of the corresponding nitro alkenes, produced in good yields the substituted tetrahydrothiophenes **6a–c** and **7a–c**, respectively, as diastereomeric mixtures (Table 2).[19]

In summary, we have developed a convenient methodology for the preparation of 3,4-disubstituted tetrahydrothiophenes featuring the use of both carbon–sulfur and carbon–carbon bond-forming reactions to obtain in a 'one-pot' fashion the cyclic thioether products through a tandem Michael–Henry or Michael–Michael reaction. Efficiency, simplicity, mild reaction conditions and satisfactory yields of products make our approach a useful process for the synthesis of this important class of compounds.

Further applications of this methodology in synthesis are currently under way, and our results will be reported in due course.



Scheme 4.

Table 2. Synthesis of tetrahydrothiophene derivatives **6a–c** and **7a–c**

Nitro acetate	R	Compound **6** (% yield)[a]	Compound **7** (% yield)[a]
2a	H	70	60
2b	CH_2OH	55	50
2c	$(CH_2)_2OCH_2OCH_3$	65	65

[a] Isolated yield after purification by column chromatography.

Acknowledgements

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15. *Typical procedure for the preparation of* **3a**: A solution of 2-nitroethyl acetate (200 mg, 1.5 mmol) in CH_2Cl_2 (2 mL) was added to a stirred suspension of 1,4-dithiane-2,5-diol (114 mg, 0.75 mmol) in CH_2Cl_2 (2 mL) containing triethylamine (0.23 mL, 1.65 mmol). The reaction mixture was stirred at room temperature for 12 h, then the solvent was evaporated. The residual oil was purified by flash chromatography (EtOAc/cyclohexane 1:4) to give 3-nitro-4-hydroxythiophane **3a** (72 mg, 65%) as an oil. IR (film): 1550, 3480 cm^{-1}; ^1H NMR for the major isomer (300 MHz, DMSO-d_6): δ 2.72–2.89 (m, 1H), 3.05–3.12 (dd, 1H, $J = 11.2$, 6.2 Hz), 3.18–3.22 (m, 1H), 3.38 (dd, 1H, $J = 10.3$, 3.7 Hz), 5.05 (m, 1H), 5.18–5.22 (m, 1H).
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19. *Typical procedure for the preparation of* **6a**: A solution of ethyl 4-mercaptobut-2-enoate **4** (100 mg, 0.68 mmol) in CH_2Cl_2 (2 mL) and triethylamine (0.1 mL, 0.68 mmol) was successively added to a solution of 2-nitroethyl acetate (90 mg, 0.68 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was stirred at room temperature for 12 h, then the solvent was evaporated. The residual oil was purified by flash chromatography (EtOAc/cyclohexane 1:4) to give **6a** (105 mg, 70%) as an oil. IR (film): 1550, 1735 cm^{-1}; ^1H NMR for the major isomer (300 MHz, $CDCl_3$): δ 1.28 (t, 3H, $J = 7.1$ Hz), 2.52–2.59 (m, 2H), 2.74 (dd, 1H, $J = 11.2$, 6.2 Hz), 3.18–3.27 (m, 1H), 3.28–3.35 (m, 1H), 3.38 (dd, 1H, $J = 10.3$, 3.7 Hz), 3.54 (dd, 1H, $J = 12.2$, 5.8 Hz), 4.25–4.15 (q, 2H, $J = 7.1$ Hz), 4.92 (dd, 1H, $J = 12.5$, 6.1 Hz).