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Facile and Efficient One-Pot Synthesis of Highly Functionalized Thieno[2,3-*b*]thiopyran-4-ones from *β*-Keto *ε*-Xanthyl Phosphonates

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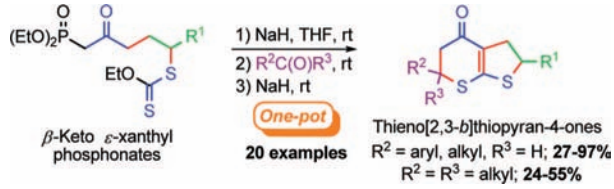
ABSTRACT

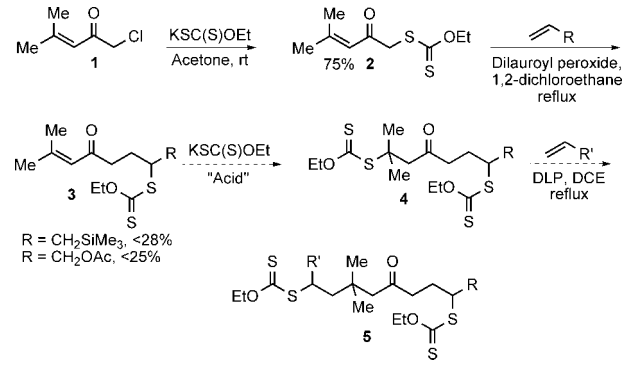


The one-pot synthesis of various functionalized thieno[2,3-*b*]thiopyran-4-ones from readily available *β*-keto *ε*-xanthyl phosphonates has been accomplished by combining a Horner−Wadsworth−Emmons olefination with a base-induced intramolecular domino cyclization/thio-Michael addition. The use of cyclic ketones in this transformation allowed a facile access to novel spiro-type thieno[2,3-*b*]thiopyran structures.

In our effort aimed at developing new synthetic tools for organic chemists based on the xanthate transfer radical chemistry,[1] we planned to synthesize a novel and useful buiding block **2** that would allow facile and sequential radical additions to olefins (Scheme 1).[2] New carbon−carbon bonds would therefore be created easily and rapidly. Our strategy was based on the possibility that compound **3** would undergo Michael addition of potassium *O*-ethylxanthate in acidic medium, based on previous results reported a few years ago.[3]

This new conjecture appeared to us as a logical continuation of our recent experience with a three-component, two-step coupling strategy utilizing a *β*-keto *γ*-xanthyl phosphonate and its ability to undergo both group transfer radical addition to olefins and a Horner−Wadsworth−Emmons (HWE) reaction with aldehydes and ketones.[4] Unfortunately, radical additions proceeded in low yields (less than 28%, the resulting isolated adducts being highly unpure), and several byproducts were formed in the course of the reaction. The presence of the α,*β*-unsaturated moiety in the substrate was clearly problematic. We therefore modified our strategy and contemplated taking advantage of the highly conjunctive *β*-keto *γ*-xanthyl phosphonate reagent **6** (Scheme 2).[4]

Scheme 1



(1) (a) Zard, S. Z. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 672. (b) Quiclet-Sire, B.; Zard, S. Z. *Phosphorus, Sulfur Silicon Relat. Elem.* **1999**, *153*, 137. (c) Quiclet-Sire, B.; Zard, S. Z. *Top. Curr. Chem.* **2006**, *264*, 201. (d) Quiclet-Sire, B.; Zard, S. Z. *Chem.−Eur. J.* **2006**, *12*, 6002. (e) Zard, S. Z. *Org. Biomol. Chem.* **2007**, *5*, 205.

(2) For the preparation of **1**, see: Mellegaard-Waetzig, S. R.; Wang, C.; Tunge, J. A. *Tetrahedron* **2006**, *62*, 7191.

(3) Binot, G.; Quiclet-Sire, B.; Saleh, T.; Zard, S. Z. *Synlett* **2003**, 382.

(4) Corbet, M.; de Greef, M.; Zard, S. Z. *Org. Lett.* **2008**, *10*, 253.

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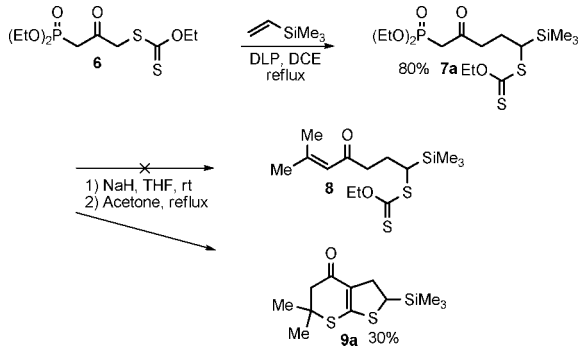
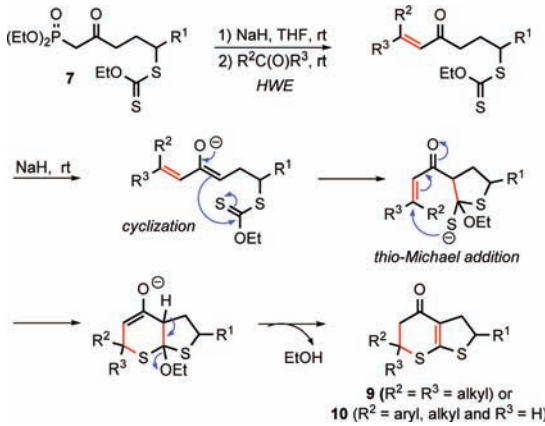
Scheme 2



Treatment of the xanthate adduct **7a** with sodium hydride (1 equiv) followed by excess acetone (10 equiv) at room temperature resulted in a slow reaction. When it was heated at reflux, the reaction took another pathway. We observed the formation of 2,3,5,6-tetrahydro-thieno[2,3-*b*]thiopyran-4-one **9a** in a 30% isolated yield. This unexpected compound results from a Horner−Wadsworth−Emmons olefination, which is immediately followed by an intramolecular domino cyclization/thio-Michael addition. Presumably, the second deprotonation at higher temperature and subsequent domino reaction are fast enough to prevent a total prior conversion of the phosphonate into the expected HWE product **8**. This type of transformation is akin to one we observed a few years ago with adducts of 2,4-difluorophenacyl xanthate which underwent a domino cyclization when treated with potassium carbonate in a mixture of *tert*-butanol and acetonitrile to afford thieno[2,3-*b*]benzothiopyran structures.[5]

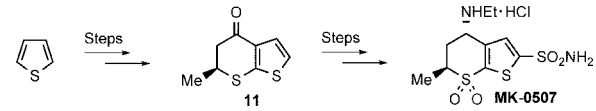
We rapidly found that this reaction was best achieved by treating adduct **7** with sodium hydride (1 equiv) at room temperature, followed by addition of the aldehyde (1.1 equiv) with subsequent deprotonation using further sodium hydride (1.5 equiv) in the same pot, providing functionalized 2,3,5,6-tetrahydro-thieno[2,3-*b*]thiopyran-4-ones. The mechanism of this one-pot transformation, which is complete in less than 30 min, is depicted in Scheme 3. Members of the 5,6-dihydro-

Scheme 3. Mechanism for the Formation of Tetrahydro-thieno[2,3-*b*]thiopyran-4-ones **9** and **10**



thieno[2,3-*b*]thiopyran class and especially sulfonamide derivatives have attracted much interest since they were reported to posess important antiglaucoma activity (Scheme 4).[6]

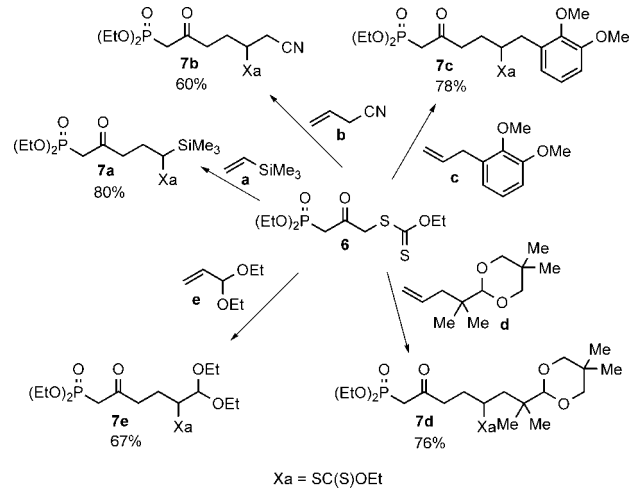
Scheme 4. Synthesis of Trusopt (MK-0507) via (*S*)-6-Methyl-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-4-one **11** by Merck Laboratories



In fact, Trusopt (dorzolamide hydrochloride, Merck & Co., Inc.) is probably one of the most popular topically active carbonic anhydrase inhibitors (CAI), which causes a decrease in the aqueous humor secretion and therefore reduction of the intraocular pressure (IOP).[6] Other 5,6-dihydro-thieno[2,3-*b*]thiopyran structures have also been described.[7] In most cases, the starting material is the 5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-4-one reported for the first time by Cagniant and Cagniant in 1966.[8] More recently, Liang et al. reported an efficient synthesis of novel tetracyclic thieno[2,3-*b*]thiopyran-fused imidazo[1,2-*a*]pyridine/pyrido[1,2-*a*]pyrimidines.[9] However, unfunctionalized or functionalized 2,3,5,6-tetrahydro-thieno[2,3-*b*]thiopyran-4-ones have not been described in the litterature. They could be seen as potential bioactive analogues of **11** and its derivatives.

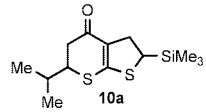
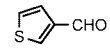
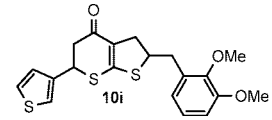
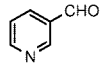
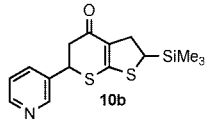
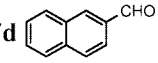
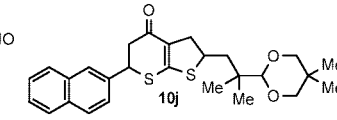
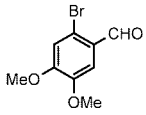
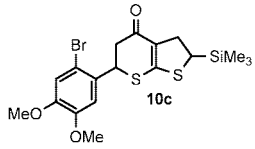
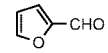
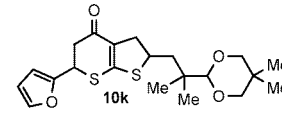
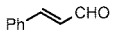
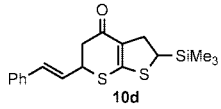
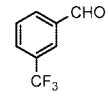
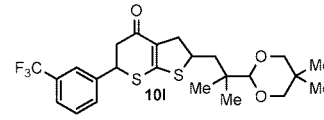
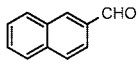
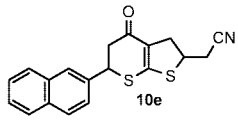
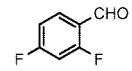
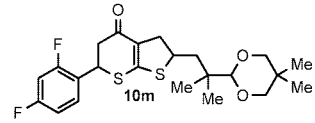
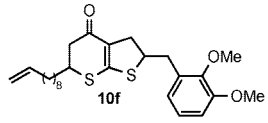
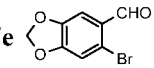
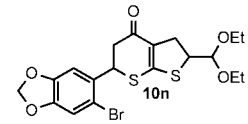
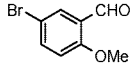
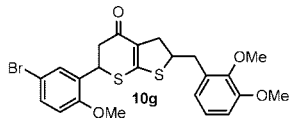
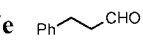
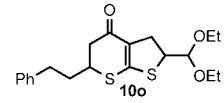
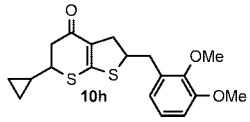
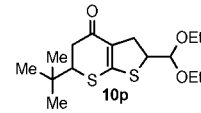
Our finding allows a facile access to a large variety of tetrahydro-thieno[2,3-*b*]thiopyran-4-ones substituted in the 2- and 6-positions in only two steps from known β-keto γ-xanthyl phosphonate **6**. Molecular diversity in the 2-position can be introduced by using various olefins in the xanthate transfer radical addition (Scheme 5). Xanthate **6** afforded moderate to

Scheme 5. Radical Addition of Xanthate **6** to Olefins **a**−**e**



good yields of adducts **7a**−**e** when treated with a substoichiometric amount of lauroyl peroxide (DLP) (15−35 mol %) and

Table 1. Synthesis of Functionalized 2,3,5,6-Tetrahydro-thieno[2,3-*b*]thiopyran-4-ones **10a**−**p** Using Aldehydes[a]

entry	7	aldehyde[b]	product **10a-p**	yield[c] (%)	entry	7	aldehyde[b]	product **10a-p**	yield[c] (%)
1	**7a**	*i*-PrCHO	 **10a**	85	9	**7c**		 **10i**	90
2	**7a**		 **10b**	83	10	**7d**		 **10j**	89
3	**7a**		 **10c**	97	11	**7d**		 **10k**	82
4	**7a**		 **10d**	84	12	**7d**		 **10l**	81
5	**7b**		 **10e**	27	13	**7d**		 **10m**	82
6	**7c**		 **10f**	72	14	**7e**		 **10n**	85
7	**7c**		 **10g**	80	15	**7e**		 **10o**	36
8	**7c**		 **10h**	71	16	**7e**	*t*-BuCHO	 **10p**	74

[a] Reactions were performed in one pot in THF. [b] All reagents were purchased from commercial sources, and liquid aldehydes were distilled prior to use. [c] Isolated yields.

the corresponding olefin **a**−**e** (2−3 equiv) in refluxing 1,2-dichloroethane (DCE). These radical reactions are easy to carry out and rather efficient.[10] The resulting adducts **7a**−**e** were submitted to the optimized reaction conditions (vide supra) employing various aldehydes. As a consequence, many highly functionalized heterocyclic systems (**10a**−**p**) were formed in moderate to excellent yields (Table 1).

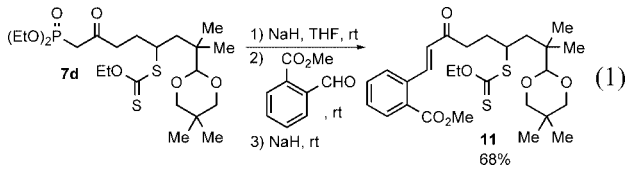
All compounds were obtained as inseparable one to one mixtures of diastereoisomers. When xanthate adduct **7b** was submitted to these reaction conditions (entry 5), HWE olefination did not proceed cleanly, and several byproducts were formed resulting in a poor overall yield (27%). Generally, transformations utilizing aliphatic aldehydes gave the desired compounds in lower yields (entries 6, 8, and 16) as compared to those obtained with aromatic carboxaldehydes (entries 2, 3, 7, 9, 10, 11, 12, 13, and 14). On the one hand, the use of cyclopropane carboxaldehyde in the reaction allowed facile introduction of a cyclopropyl group onto the thieno[2,3-*b*]thiopyran moiety (71%, entry 8) giving rise to potentially bioactive compound **10j**. Cyclopropanes are indeed of high

(5) Boivin, J.; Boutillier, P.; Zard, S. Z. *Tetrahedron Lett.* **1999**, *40*, 2529.

(6) (a) Ponticello, G. S.; Freedman, M. B.; Habecker, C. N.; Lyle, P. A.; Schwam, H.; Varga, S. L.; Christy, M. E.; Randall, W. C.; Baldwin, J. J. *J. Med. Chem.* **1987**, *30*, 591. (b) Ponticello, G. S.; Freedman, M. B.; Habecker, C. N.; Holloway, M. K.; Amato, J. S.; Conn, R. S.; Baldwin, J. J. *J. Org. Chem.* **1988**, *53*, 9. (c) Baldwin, J. J.; Ponticello, G. S.; Christy, M. E. U.S. Patent 4 797 413, 1989. (d) Baldwin, J. J.; Ponticello, G. S.; Anderson, P. S.; Christy, M. E.; Murcko, M. A.; Randall, W. C.; Schwam, H.; Sugrue, M. F.; Springer, J. P.; Gautheron, P.; Grove, J.; Mallorga, P.; Viader, M.-P.; McKeever, B. M.; Navia, M. A. *J. Med. Chem.* **1989**, *32*, 2510. (e) Jones, T. K.; Mohan, J. J.; Xavier, L. C.; Blacklock, T. J.; Mathre, D. J.; Sohar, P.; Turner Jones, E. T.; Reamer, R. A.; Roberts, F. E.; Grabowski, E. J. J. *J. Org. Chem.* **1991**, *56*, 763. (f) Blacklock, T. J.; Sohar, P.; Butcher, J. W.; Lamanec, T.; Grabowski, E. J. J. *J. Org. Chem.* **1993**, *58*, 1672. (g) Tempkin, O.; Blacklock, T. J.; Burke, J. A.; Anastasia, M. *Tetrahedron: Asymmetry* **1996**, *7*, 2721.

(7) (a) Cauquil-Caubère, I.; Kamenka, J.-M. *Eur. J. Med. Chem.* **1998**, *33*, 867. (b) Bates, D. K.; Li, K. *J. Org. Chem.* **2002**, *67*, 8662.

importance, especially in medicinal chemistry, because of their unique structural and electronic properties.[11] On the other hand, the presence of halogen containing aromatic carboxaldehydes (entries 3, 7, and 14) opens new perspectives for further functionalization employing cross coupling technologies. The low yield obtained for compound **10o** (36%, entry 15) can be rationalized by its surprising instability on silica gel. In contrast, analogous derivative **10p** appeared more stable (74%, entry 16). Reaction of β-keto ε-xanthyl phosphonate **7d** with methyl 2-formylbenzoate did not give the expected compound. A "gummy" material precipitated out at the second addition of sodium hydride, and it did not go back into solution. Hydrolysis afforded the simple HWE product **11** in 68% yield (eq 1).



(1)

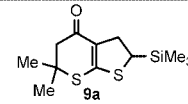
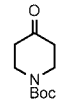
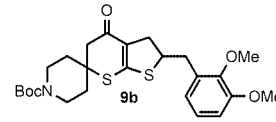
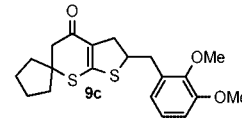
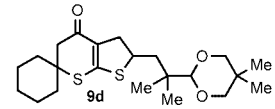
Attempts to heat the heterogeneous solution resulted in total decomposition of the products, and diluting the reaction mixture did not give any useful results.

It is worth noting that this fast, facile, and efficient overall process can be seen as a "coupling" reaction between an aldehyde and the 6-position of a 2-substituted 2,3,5,6-tetrahydro-thieno[2,3-*b*]thiopyran-4-one scaffold. In addition, reaction conditions satisfying the name of domino reaction for the transformation of β-keto ε-xanthyl phosphonates **7a**,**e** to functionalized thieno[2,3-*b*]thiopyran-4-one **10a**,**n** have proven to be efficient.[12] Indeed, in the case of xanthate **7e**, the use of sodium hydride (2.5 equiv) followed by addition of 6-bromopiperonal gave the expected thieno[2,3-*b*]thiopyran-4-one **10n** in a similar yield (85%) as compared to that of sequential addition of base (entry 14). However, for reaction of xanthate **7a** with *iso*-butyraldehyde under these conditions, the yield dropped down to 61% (against 85%, entry 1). This is probably due to the presence of acidic protons α to the aldehyde carbonyl.

We then turned our attention to the ability of the xanthate adducts **7c**−**d** to undergo the one-pot transformation with cyclic and symmetric ketones. This would therefore allow an easy access to interesting spiro-type thieno[2,3-*b*]thiopyran-4-ones **9b**−**d**. Although the isolated yields were rather moderate (24−55%), we were glad to see that all reactions proceeded smoothly using the same conditions as with aldehydes (Table 2).

Reaction times were however longer. A time of 3−4 h was needed for the HWE reaction to go to completion (entries 1−4). Some highly polar byproducts were formed along with the desired α,β-unsaturated ketone intermediate (TLC analysis). Xanthates in basic medium are, of course, not indefinitely stable. Heating the reaction mixture at 45 °C or at reflux resulted in the formation of some noticeable degradation products. In fact, the Horner−Wadsworth−Emmons olefination is the limiting step of this otherwise efficient process. Eventually, thieno[2,3-*b*]thiopyran-4-one **9a** (entry 1) could be obtained in 48% yield under these conditions.

Table 2. Synthesis of Functionalized Spiro 2,3,5,6-Tetrahydro-thieno[2,3-*b*]thiopyran-4-ones **9b**−**d** Using Ketones[a]

entry	7	ketone[b]	product **9a-c**	yield[c] (%)
1	**7a**			48
2	**7c**			46
3	**7c**			24
4	**7d**			55

[a] Reactions were performed in one pot in THF. [b] Cyclopentanone, cyclohexanone, and acetone were purchased from commercial sources and distilled prior to use. [c] Isolated yields.

In summary, we have developed a facile and highly efficient one-pot synthetic route toward functionalized 2,3,5,6-tetrahydro-thieno[2,3-*b*]thiopyran-4-ones from easily accessible β-keto ε-xanthyl phosphonates. This overall transformation uses simple reagents, and only small quantities of solvant are required. Moreover, it is time- and labor-saving and easy to perform. A broad molecular diversity around the thieno[2,3-*b*]thiopyran-4-one scaffold could be introduced in only two steps from simple β-keto γ-xanthyl phosphonate. The syntheses of novel and unprecedented spiro thieno[2,3-*b*]thiopyran-4-ones were also readily achieved. Ultimately, the overall process could become of pharmaceutical interest because of its "coupling-like" nature and the "druglike" structures obtained. Finally, it illustrates an interesting aspect of the radical and nonradical chemistry of xanthates.

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Supporting Information Available: Experimental procedures, full spectroscopic data, and copies of ^{1}H and ^{13}C NMR spectra for compounds **7c**−**e**, **9a**−**d**, **10a**−**p**, and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Cagniant, P.; Cagniant, D. *Bull. Soc. Chim. Fr.* **1966**, 2172.
(9) Liang, F.; Zhang, J.; Tan, J.; Liu, Q. *Adv. Synth. Catal.* **2006**, *348*, 1986.
(10) Addition reactions were performed by portionwise addition of DLP (5 mol %) every 90 min to a refluxing degassed 1 M solution of **6** (1 equiv) in DCE in the presence of the olefin (2−3 equiv) until **6** had entirely reacted. Products **7a** and **7b** were previously reported. See ref 4.
(11) Salaün, J. *Top. Curr. Chem.* **2000**, *207*, 1.
(12) (a) Tietze, L. F *Chem. Rev.* **1996**, *96*, 115. (b) For other reviews on the subject, see: Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134, and ref 1 therein.