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Tandem Alkylation−Michael Addition to Vinylogous Carbonates for the Stereoselective Construction of 2,3,3,6-Tetrasubstituted Tetrahydropyrans

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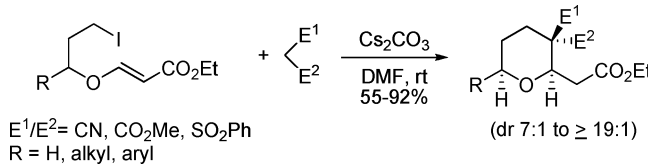
ABSTRACT



A stereoselective method for the synthesis of substituted tetrahydropyran derivatives employing a tandem S_N2−Michael addition sequence to vinylogous carbonates is developed. The method is extended to the synthesis of bicyclic ether motifs present in polyether ladder toxins.

The ubiquitous presence of tetrahydropyran (THP) moieties in important bioactive cyclic ethers has provided impetus to the research directed at new methods for the synthesis of THP derivatives. Over the years, vinylogous carbonates or β-(alkoxy)acrylates have come to the fore as excellent radical acceptors. Consequently, a plethora of methods have been developed for the construction of THP derivatives using alkyl and acyl radical cyclization to vinylogous carbonates under a variety of conditions.[1] Recently, we were able to demonstrate the utility of alkyl radical cyclization to vinylogous carbonates for the stereoselective synthesis of new oxa-cage compounds.[2] In contrast, vinylogous carbonates have been sparingly used for the synthesis of THPs under nonradical conditions; e.g., acid-promoted Prins cyclization to vinylogous carbonates has been used for the construction of the 2,4,6-trisubstituted THP derivatives.[3] Vinylogous carbonates have been shown to participate in intramolecular Setter reaction involving carbanion intermediates in a Michael fashion in the synthesis of tetrahydrofurans (THFs)[4] and very recently in the synthesis of THPs.[5] These reports not withstanding, in general, the utility of vinylogous carbonates as Michael acceptors under nonradical conditions for the synthesis of THPs is still largely underdeveloped.

(1) For some selected examples, see: (a) Lee, E.; Tae, J. S.; Lee, C.; Park, C. M. *Tetrahedron Lett.* **1993**, *34*, 4831. (b) Lee, E. *Pure Appl. Chem.* **2005**, *77*, 2073. (c) Kang, E. J.; Cho, E. J.; Ji, M. K.; Lee, Y. E.; Shin, D. M.; Choi, S. Y.; Chung, Y. K.; Kim, J. S; Kim, H. J.; Lee, S. G.; Lah, M. S.; Lee, E. *J. Org. Chem.* **2005**, *70*, 6321. (d) Song, H. Y.; Joo, J. M.; Kang, J. W.; Kim, D. S.; Jung, C. K.; Kwak, H. S.; Park, J. H.; Lee, E.; Hong, C. Y.; Jeong, S. W.; Jeon, K.; Park, J. H. *J. Org. Chem.* **2003**, *68*, 8080. (e) Hori, N.; Matsukura, H.; Matsuo, G.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 2811. (f) Evans, P. A.; Raina, S.; Ahsan, K. *Chem. Commun.* **2001**, 2504. (g) Evans, P. A.; Roseman, J. D. *J. Org. Chem.* **1996**, *61*, 2252. (h) Leeuwenburgh, M. A.; Litjens, R. E. J. N.; Codée, J. D. C.; Overkleeft, H. S.; Van der Marel, G. A.; Van Boom, J. H. *Org. Lett.* **2000**, *2*, 1275. (i) Sibi, M. P.; Patil, K.; Rheault, T. R. *Eur. J. Org. Chem.* **2004**, 372. (j) Chakraborty, T. K.; Samanta, R.; Ravikumar, K. *Tetrahedron Lett.* **2007**, *48*, 6389, and references therein.

(2) Gharpure, S. J.; Porwal, S. K. *Synlett* **2008**, 242.

(3) (a) Nussbaumer, C.; Frater, G. *Helv. Chim. Acta* **1987**, *70*, 396. (b) Kozmin, S. A. *Org. Lett.* **2001**, *3*, 755. (c) Hart, D. J.; Bennett, C. E. *Org. Lett.* **2003**, *5*, 1499. (d) Kwon, M. S.; Woo, S. K.; Na, S. W.; Lee, E. *Angew. Chem., Int. Ed.* **2008**, *47*, 1733.

(4) For some selected examples, see: (a) Ciganek, E. *Synthesis* **1995**, 1311. (b) Frank, S. A.; Mergott, D. J.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 2404. (c) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10298. (d) Kerr, M. S.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 8876, and references therein.

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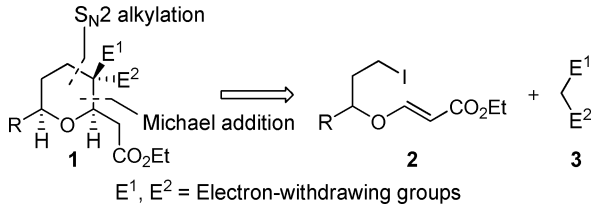
In the present day when the environmental concerns are very high, tandem reactions are highly desirable since they generate several bonds in a "single-pot" operation thereby minimizing the amount of waste that is generated.[6] Recently, we developed a stereoselective synthesis of 1,2,2-trisubstituted Indane derivatives employing a tandem S_N2−Michael addition sequence.[7] Herein, we now describe the tandem S_N2−alkylation−Michael addition to vinylogous carbonates for the stereoselective construction of THP derivatives.[8] This study further demonstrates that vinylogous carbonates can act as good Michael acceptors under nonradical conditions as well.

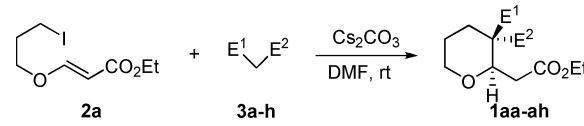
We envisaged that the THP derivative **1** could be synthesized from the iodide **2** and the active methylene compound **3** employing a tandem S_N2−Michael addition sequence (Scheme 1). In this transformation, the C3−C4

Scheme 1. Retrosynthesis for Tetrasubstituted Tetrahydropyrans



bond of the THP would be formed by an alkylation reaction, whereas the C2−C3 bond would be formed by the Michael addition of the active methylene moiety to vinylogous carbonate. To test the feasibility of the proposed THP synthesis, the iodide **2a** was treated with malononitrile (**3a**) in DMF in the presence of Cs_2CO_3 at room temperature, which gratifyingly led to the formation of 2,3,3-trisubstituted THP derivative **1aa** in excellent yield. To study the scope of the nucleophiles, the reaction was carried out with a variety of active methylene compounds. The results are summarized in Table 1. Dimethyl malonate (**3b**) was also

Table 1. Tandem Alkylation−Michael Addition for the Synthesis of THPs: Scope of the Nucleophiles



entry	E^1	E^2		product	time (h)	yield (%)	dr[a]
1	CN	CN	**3a**	**1aa**	3	85	−
2	CO_2Me	CO_2Me	**3b**	**1ab**	8	83	−
3	$PhSO_2$	$PhSO_2$	**3c**	**1ac**	12	0[b]	−
4	CN	$PhSO_2$	**3d**	**1ad**	4	68	≥19:1
5	CN	CO_2Et	**3e**	**1ae**	8	65	≥19:1
6	CO_2Me	$PhSO_2$	**3f**	**1af**	12	74	≥19:1
7	H	CH_2NO_2	**3g**	**1ag**	12	0[c]	n.a.
8	CO_2Me	Ph	**3h**	**1ah**	12	0[d]	n.a.

[a] Determined on crude reaction mixtures by ^1H NMR. [b] Only the alkylation product was obtained even at higher temperature (80 °C). [c] A complex mixture of products obtained.[10] [d] Only the alkylation product was obtained in 25% yield.

found to be a good nucleophile in this transformation leading to the formation of triester **1ab** in good yield (Table 1, entry 2). On the other hand, the reaction of the bis-sulfone **3c** furnished quantitatively only the alkylation product; the subsequent Michael addition to furnish **1ac** did not take place (Table 1, entry 3). Similarly, the reaction of methyl phenylacetate (**3h**) with the iodide **2a** furnished only the alkylated product in 25% yield (Table 1, entry 8). These examples suggested that the alkylation is indeed the first step in this tandem reaction sequence. Moreover, it is apparent that under the reaction conditions employed the retro-oxy-Michael reaction is sufficiently slow allowing for the isolation of the THPs.[9]

The iodide **2a** was then subjected to reaction with unsymmetrically substituted nucleophiles such as sulfone-nitrile **3d**, ethyl cyanoacetate (**3e**), and sulfone-ester **3f** which also gave the corresponding THP derivatives **1ad**−**af**, respectively, in good yield with excellent diastereoselectivity (Table 1, entries 4−6). On the other hand, reaction of the iodide **2a** with nitromethane (**3g**) led to the formation of a complex mixture (Table 1, entry 7). This is surprising given that Desmaele et al. have found nitromethane to be a good nucleophile in a tandem alkylation−Michael reaction sequence for the formation of cyclohexane derivatives.[8g] To establish the relative stereochemistry of the substituents at C-2 and C-3, the sulfone-ester **1af** was subjected to single-crystal X-ray diffraction studies, and it was found that the bulky $PhSO_2$ and CH_2CO_2Me groups occupy the equatorial positions whereas the less bulky CN and H occupy the axial orientation (see Supporting Information). This is presumably due to the fact that these bulky substituents want to occupy the equatorial position reducing the 1,3-diaxial interaction. The relative stereochemistry of the substituents in other cases was assigned by analogy.

After establishing the scope of the reaction with various nucleophiles, we turned our attention to using this reaction for the synthesis of 2,3,3,6-tetrasubstituted tetrahydropyran

(5) (a) McErlean, C. S. P.; Willis, A. C. *Synlett* **2009**, 233. For an example of attempted sulfonium ylide annulation of vinylogous carbonates leading to chromenes, see: Ye, L.-W.; Sun, X.-L.; Zhu, C.-Y.; Tang, Y. *J. Org. Chem.* **2007**, *72*, 1335. (b) Ye, L.-W.; Sun, X.-L.; Zhu, C.-Y.; Tang, Y. *Org. Lett.* **2006**, *8*, 3853.

(6) Reviews: (a) Bunce, R. A. *Tetrahedron* **1995**, *51*, 13103. (b) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134. (c) Nicolaou, K. C.; Montagnon, T.; Snyder, S. A. *Chem. Commun.* **2003**, 551.

(7) Gharpure, S. J.; Reddy, S. R. B.; Sanyal, U. *Synlett* **2007**, 1889.

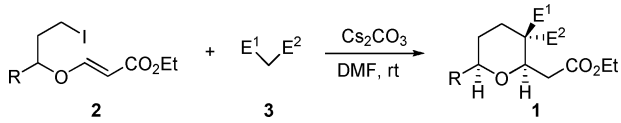
(8) For some selected examples of tandem alkylation−Michael reaction sequence for the synthesis of heterocycles and carbacycles, see: (a) Bunce, R. A.; Peeples, C. J.; Jones, P. B. *J. Org. Chem.* **1992**, *57*, 1727. (b) Bunce, R. A.; Kotturi, S. V.; Peeples, C. J.; Holt, E. M. *J. Heterocycl. Chem.* **2002**, *39*, 1049. (c) Bunce, R. A.; Allison, J. C. *Synth. Commun.* **1999**, *29*, 2175. (d) Goff, D. A. *Tetrahedron Lett.* **1998**, *39*, 1473. (e) Watanabe, H.; Onoda, T.; Kitahara, T. *Tetrahedron Lett.* **1999**, *40*, 2545. (f) Le Dreau, M. -A.; Desmaele, D.; Dumas, F.; dAngelo, J. *J. Org. Chem.* **1993**, *58*, 2933. (g) Desmaele, D.; Louvet, J. -M. *Tetrahedron Lett.* **1994**, *35*, 2549. (h) Srikrishna, A.; Reddy, T. J.; Kumar, P. P. *Synlett* **1997**, 663. (i) Prabhu, K. R.; Sivanand, P. S.; Chandrasekaran, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 4316. (j) Liu, H. -J.; Han, Y. *J. Chem. Soc., Chem. Commun.* **1991**, 1484.

(9) This is in contrast to the observation by Tang and coworkers (ref 5) who found that the Michael addition of sulphonium ylide to vinylogous carbonates derived from phenol derivatives lead to 2*H*-chromenes and 4*H*-chromenes via a retro-oxy-Michael reaction followed by S_N2' substitution rather than the cyclopropabenzofuran derivatives.

(10) The complete characterization of some of the products obtained is underway.

derivatives. Initially, the iodides **2b**−**i** were subjected to reactions with symmetrically substituted active methylene compounds such as malononitrile (**3a**) and dimethyl malonate (**3b**) to furnish, after tandem alkylation−Michael addition sequence, the corresponding 2,3,3,6-tetrasubstituted THPs **1ba**−**hb** (Table 2, entries 1−10). The reactions, in general,

Table 2. Tandem Alkylation−Michael Addition for the Synthesis of 2,3,3,6-Tetrasubstituted THPs: Substrate Scope



entry	R		E^1	E^2		product	time (h)	yield (%)[b]	dr[a]
1	Me	**2b**	CN	CN	**3a**	**1ba**	4	70	7:1
2	^{i}Pr	**2c**	CN	CN	**3a**	**1ca**	6	85	8:1
3	$PhCH_2CH_2$	**2d**	CN	CN	**3a**	**1da**	7	92	9:1
4	2-furyl	**2e**	CN	CN	**3a**	**1ea**	12	80	≥10:1
5	Cy	**2f**	CN	CN	**3a**	**1fa**	5	90	≥19:1
6	Ph	**2g**	CN	CN	**3a**	**1ga**	12	79	≥19:1
7	*p*-MeO-C_6H_4	**2h**	CN	CN	**3a**	**1ha**	4	74	≥19:1
8	*p*-Me-C_6H_4	**2i**	CN	CN	**3a**	**1ia**	7	84	≥19:1
9	Me	**2b**	CO_2Me	CO_2Me	**3b**	**1bb**	12	71	≥19:1
10	*p*-MeO-C_6H_4	**2h**	CO_2Me	CO_2Me	**3b**	**1hb**	12	81	≥19:1
11	Me	**2b**	CN	CO_2Et	**3e**	**1be**	4	62	≥19:1
12	Me	**2b**	CN	SO_2Ph	**3d**	**1bd**	7	66	≥19:1
13	Me	**2b**	CO_2Me	SO_2Ph	**3f**	**1bf**	12	55	≥19:1
14	^{i}Pr	**2c**	CN	SO_2Ph	**3d**	**1 cd**	12	74	≥10:1
15	Ph	**2g**	CN	SO_2Ph	**3d**	**1gd**	12	88	≥19:1
16	*p*-MeO-C_6H_4	**2h**	CN	SO_2Ph	**3d**	**1hd**	10	81	≥19:1

[a] Determined on crude reaction mixtures by ^{1}H NMR. [b] Isolated yields.

were found to be quite efficient and gave the THP derivatives with excellent diastereoselectivity in most cases (Table 2, entries 4−10). In a few cases, where the substituent at C-6 was relatively less bulky, moderate selectivities for the THP derivatives were observed (Table 2, entries 1−3). The *cis* stereochemistry of the major diastereomers was confirmed with the help of NOE experiments.

To expand the scope of this tandem alkylation−Michael addition reaction by incorporating one more stereocenter in the THP fragment, these iodides were subjected to the reaction with unsymmetrically substituted active methylene nucleophiles **3d**−**f** (Table 2, entries 11−16). In all the cases, the corresponding product was obtained in good yields with excellent diastereoselectivity. Interestingly, the comparison of the entry 1 vs 11−13, and entry 2 vs 14 reveals that there is an increase in the diastereoselectivity while using unsymmetrical nucleophiles than with symmetrical nucleophiles. To unambiguously ascertain the relative stereochemistry of the substituents in the case of unsymmetrical nucleophiles, the nitrile **1gd** was subjected to single-crystal X-ray diffraction studies (Figure 1). It revealed that the bulkier substituents at C-2, C-3, and C-6 on the THP ring occupy the equatorial position, presumably to avoid the 1,3-diaxial interactions. In the other cases (Table 2, entries 11−14 and 16), the stereochemistry shown is by analogy to this example.

We envisioned that the construction of the tertiary ether would be challenging and thereby highlight the synthetic utility of the developed tandem S_N2−Michael reaction. Even

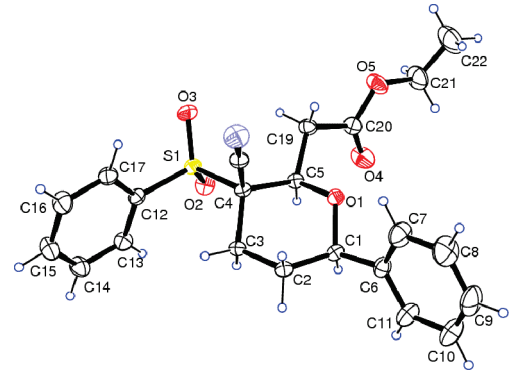
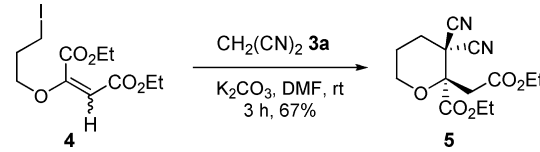


Figure 1. ORTEP diagram for the sulfone nitrile **1gd**.

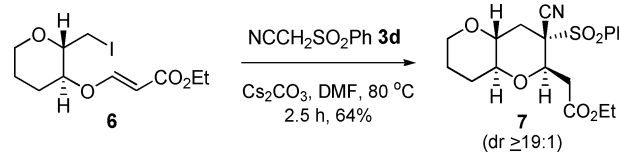
though the reaction of the iodide **4** with malononitrile (**3a**) using cesium carbonate as the base furnished the 2,2,3,3-tetrasubstituted THP derivative **5** in moderate yield, changing the base to potassium carbonate improved the yield of the THP derivative **5** which contained tertiary ether with a carbethoxy group substitution (Scheme 2). It is also interesting to note here that the reaction proceeds through alkylation followed by 6-*exo* Michael addition to "vinylogous carbonate" rather than 7-*endo* Michael addition to "α-alkoxyacrylate" motif..

Scheme 2. 2,2,3,3-Tetrasubstituted THP Derivative with Angular Substitution



In recent years, there is significant effort directed toward the synthesis of fused polycyclic ethers.[11] Many ladder like polyether toxins contain *trans*-fused tetrahydropyran motifs. To further the scope of our tandem S_N2−Michael protocol, we decided to employ it for the synthesis of fused bicyclic THP fragments on the iodide **6**, which was readily synthesized from tri-*O*-acetyl-(D)-glucal. We were delighted to see that the reaction of the iodide **6** with sulfone nitrile **3d** under reoptimized conditions led to the formation of bis-THP derivative **7** in good yield with excellent diastereoselectivity

Scheme 3. Synthesis of *trans*-Fused Bicyclic THPs



(Scheme 3) The relative orientations of various substitutions were confirmed with the help of single-crystal X-ray diffraction studies on the sulfone nitrile **7** (Figure 2). This reaction demonstrated that the method is useful for the assembly of *trans*-fused THP rings applicable to polyether ladder toxins.

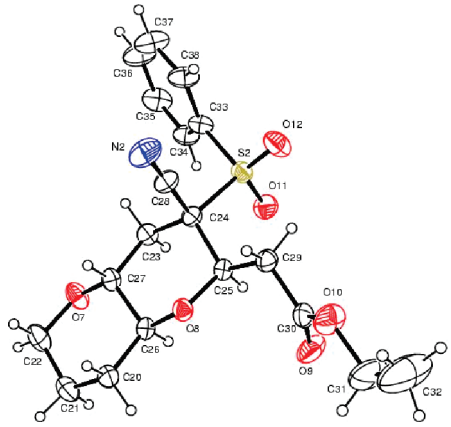


Figure 2. ORTEP diagram for the sulfone nitrile **7**.

In conclusion, we have developed a concise, stereoselective, and efficient approach toward the synthesis of 2,3,3,6-tetrasubstituted THP derivatives employing a tandem S_N2-Michael addition sequence. We have demonstrated that the diastereoselectivity of the reaction can be enhanced by using unsymmetrical active methylene compounds. It has been shown that tertiary ether can be introduced on the THP fragment. Finally, the method has been extended to the synthesis of fused bis-THP derivatives applicable in polycyclic ether fragments of ladder toxins.

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Supporting Information Available: Synthetic schemes for the iodide precursors **2**, **4**, and **6**, the spectral data for the compounds **1**, **2**, and **4**−**7**, and X-ray analysis of the sulfones **1af**, **1gd**, and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) For some recent reviews, see: (a) Sasaki, M.; Fuwa, H. *Nat. Prod. Rep.* **2008**, *25*, 401. (b) Valentine, J. C.; McDonald, F. E. *Synlett* **2006**, 1816. (c) Clark, J. S. *Chem. Commun.* **2006**, 3571. (d) Inoue, M. *Chem. Rev.* **2005**, *105*, 4379. (e) Nakata, T. *Chem. Rev.* **2005**, *105*, 4314. (f) Marmsater, F. P.; West, F. G. *Chem.*−*Eur. J.* **2002**, *8*, 4346.