Lithium Perchlorate-Assisted Substitution Reactions of Allylic Acetates and Allylic Alcohols

William H. Pearson* and Jeffrey M. Schkeryantz

Department of Chemistry, Willard H. Dow Laboratories, The University of Michigan, Ann Arbor, Michigan 48109

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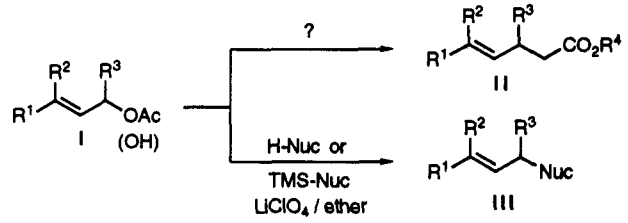
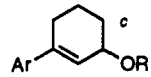
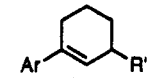
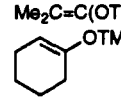
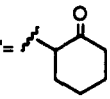
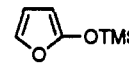
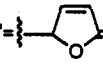
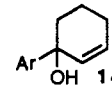
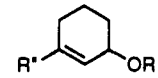
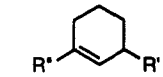
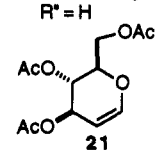
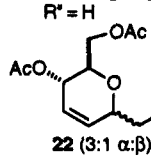
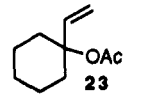
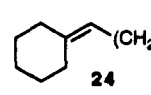
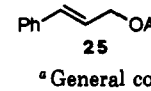
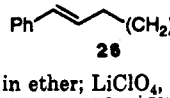
Summary: Substitution reactions of allylic acetates and allylic alcohols by a variety of nucleophiles proceed smoothly in the presence of lithium perchlorate in ether, providing a convenient alternative to transition metal catalyzed methods.

We recently required a method for a two-carbon chain extension of allylic alcohols or their derivatives (e.g., I → II). The transition metal catalyzed allylation of certain carbon nucleophiles is a widely used method.[1] However, such reactions failed to proceed efficiently in several cases that we required, which led us to seek alternative methods. We wish to report that the lithium perchlorate induced ionization of allylic acetates and allylic alcohols in the presence of a variety of nucleophiles provides an efficient and practical method for such chain extensions (e.g., I → III) and offers a convenient alternative to transition metal-based chemistry. Our studies find precedent in earlier work on the Lewis acid-promoted formation of carbocations and their use in carbon–carbon bond-forming reactions.[2,3] Lithium perchlorate has also been used recently by Grieco in [1,3] sigmatropic rearrangements of allyl vinyl ethers,[4,5] a process that is related to the present work.



Preliminary experiments show that exposure of allylic acetates and alcohols to various carbon nucleophiles in the presence of lithium perchlorate in ether led to substitution products in good yield, as shown in Table I. Electron-rich π-bonds such as those in ketene acetals, allyl- or propargyltrimethylsilane, enol ethers, and π-excessive heterocycles were excellent nucleophiles. In addition to carbon–

Table I. Substitution Reactions of Allylic Acetates and Alcohols

substrate[a]	nucleophile	time (temp, °C)	product	yield[b] (%)
				
1 R = $COCH_3$	CH_2=C(OTBS)OEt	1h (0)	2 R' = CH_2CO_2Et	92
3 R = H	CH_2=C(OTBS)OEt	1h (RT)	2 R' = CH_2CO_2Et	64[d]
1	CH_2=$CHCH_2TMS$	1h (RT)	4 R' = CH_2CH=CH_2	93
3	CH_2=$CHCH_2TMS$	1h (RT)	4 R' = CH_2CH=CH_2	81
1	Me_2C=C(OTBS)OMe	2h (RT)	5 R' = CMe_2CO_2Me	84
1		3h (RT)	6 R'= 	85[e]
1		1h (RT)	7 R'= 	79[e]
1	HC≡CCH_2TMS	1.5h (0)	8 R' = CH=C=CH_2	67
1	Indole	3h (0)	9 R' = indol-3-yl	85
1	3-methylindole	1h (RT)	10 R' = 3-methyl-indol-2-yl	81[f]
1	CH_2=$CHOCH_2OCH_3$	1h (RT)	11 R' = CH_2CHO	64
1	Me_3SiN_3	3h (RT)	12 R' = N_3	71
1	Me_3SiCN	1h (RT)	13 R' = CN	67
 14	CH_2=C(OTBS)OEt	1h (0)	2 R' = CH_2CO_2Et	90
14	CH_2=$CHCH_2TMS$	1h (0)	4 R' = CH_2CH=CH_2	92
				
15 R = $COCH_3$ R' = nBu	CH_2=C(OTBS)OEt	1h (RT)	16 R' = CH_2CO_2Et R' = nBu	85[g]
15 R = $COCH_3$ R' = nBu	CH_2=$CHCH_2TMS$	1.h (RT)	18 R' = CH_2CH=CH_2 R' = nBu	82
17 R = H R' = nBu	CH_2=$CHCH_2TMS$	1.5h (RT)	18 R' = CH_2CH=CH_2 R' = nBu	82
19 R = $COCH_3$ R' = H	CH_2=C(OTBS)OEt	2h (RT)	20 R' = CH_2CO_2Et R' = H	70
 21	CH_2=C(OTBS)OEt	1h (RT)	 22 (3:1 α:β)	61[h]
 23	CH_2=C(OTBS)OEt	2h (0)	 24	54[i,j]
 25	CH_2=C(OTBS)OEt	2h (0)	 26	48[j,k]

[a] General conditions: substrate, 0.25 M in ether; $LiClO_4$, 3.0 M in ether, 3 equiv of nucleophile, initial mixing at 0 °C. [b] Yield of isolated, purified products. [c] Ar = 3,4-(methylenedioxy)phenyl. [d] Accompanied by 30% of O-silylated starting material. [e] 1:1 mixture of diastereomers. [f] Contains 6% of indol-1-yl product. [g] A 6.5:1 mixture of 16 and the product of nucleophilic attack at the tertiary carbon of the allylic system. [h] For related reactions, see ref 3a–c. [i] Isolated after $LiAlH_4$/THF reduction of the crude ester. [j] A 2.5:1 mixture of 24 and 1-[(2-hydroxy)ethyl]-1-vinylcyclohexane, the product (after reduction) of nucleophilic attack at the tertiary carbon of the allylic system. [k] Plus 16% of 3-phenyl-3-vinyl-1-propanol, the product (after reduction) of nucleophilic attack at the benzylic position of the allylic system.

(1) For a review of transition metal mediated substitution reactions of allylic carboxylates by various enolates and enol derivatives, see: (a) Godleski, S. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, pp 585–661. Palladium-promoted reactions of allylic carboxylates with enol silanes and ketene acetals are specifically related to our work: (b) Tsuji, J.; Takahashi, K.; Minami, I.; Shimizu, I. *Tetrahedron Lett.* **1984**, *25*, 4783–4786. (c) Minami, I., Takahashi, K.; Shimizu, I.; Kimura, T.; Tsuji, J. *Tetrahedron* **1986**, *42*, 2971–2977. (d) Tsuji, J.; Ohashi, Y.; Minami, I. *Tetrahedron Lett.* **1987**, *28*, 2397–2398. (e) Carfagna, C.; Mariani, L.; Musco, A.; Sallese, G.; Santi, R. *J. Org. Chem.* **1991**, *56*, 3924–3927.

(2) (a) Reetz, M. T.; Hüttenhain, S.; Walz, P.; Löwe, U. *Tetrahedron Lett.* **1979**, 4971–4974. (b) Fleming, I. *Chem. Soc. Rev.* **1981**, *10*, 83. (c) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 96–108. (d) Mukaiyama, T.; Nagaoka, H.; Murakami, M.; Ohshima, M. *Chem. Lett.* **1985**, 977. (e) Mukaiyama, T.; Nagaoka, H.; Ohshima, M.; Murakami, M. *Chem. Lett.* **1986**, 1009–1012.

(3) Lewis acid catalyzed substitution reacton of glycosyl esters with silicon-capped nucleophiles: (a) Dawe, R. D.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1981**, 1180–1181. (b) Danishefsky, S. J.; Kerwin, J. F., Jr. *J. Org. Chem.* **1982**, *47*, 3803–3805. (c) Kozikowski, A. P.; Sorgi, K. L. *Tetrahedron Lett.* **1982**, *23*, 2281. Lewis acid catalyzed substitution reaction of allylic acetates assisted by a neighboring thioether: (d) Kudo, K.; Saigo, K.; Hashimoto, Y.; Houchigai, H.; Hasegawa, M. *Tetrahedron Lett.* **1991**, *32*, 4311–4312.

(4) Grieco, P. A.; Clark, J. D.; Jagoe, C. T. *J. Am. Chem. Soc.* **1991**, *113*, 5488–5489.

(5) Grieco, P. A. *Aldrichimica Acta* **1991**, *24*, 59–66.

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carbon bond formation, these nucleophiles led to the introduction of carbonyl, alkene, allene, and cyano functional groups, as well as heterocyclic rings. The formation of the allylic azide **12** illustrates the possibility of carbon–heteroatom bond formation.

Experimental evidence suggests that these reactions proceed by ionization to an allylic carbocation.[6] For example, regioisomeric allylic alcohols **3** and **14** gave the same product **2**, the result of attack of the nucleophile at the least substituted end of a common intermediate carbocation. Grieco has also obtained evidence for a carbocation intermediate in his work with allyl vinyl ethers.[4] Although most of the examples in Table I involve trialkyl allylic or aryldialkyl allylic substrates which may give particularly well-stabilized allylic carbocations, less substituted examples are also successful, e.g., **19**, **23**, and **25**.

The lithium perchlorate-promoted substitution reaction allows convenient access to γ,δ-unsaturated esters, ketones, and aldehydes, 1,5-dienes, 1,2,5-trienes, allylated heterocycles, allylic azides, and allylic nitriles. The mild conditions, simplicity, and efficiency of this method for carbon–carbon bond formation make it an attractive alternative to transition metal-catalyzed processes.[7] The ability to employ allylic alcohols directly (e.g., **3**, **14**, and **17**) is also significant, since it obviates the acetylation step. A full account of this work will outline the scope and stereochemistry of this process.

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(6) (a) Winstein, S.; Smith, S.; Darwish, D. *J. Am. Chem. Soc.* **1959**, *81*, 5511. (b) Pocker, Y.; Buchholz, R. F. *J. Am. Chem. Soc.* **1970**, *92*, 2075.

(7) The following procedure for the preparation of compound **2** is typical. Commercial lithium perchlorate (Aldrich Chemical Co.) was used without drying or further purification, since doing so led to no significant improvement in yields or reaction rates. To a solution of the acetate **1** (139 mg, 0.534 mmol) in ether (2 mL) was added 1-[(*tert*-butyldimethylsilyl)oxy]-1-ethoxyethene (324 mg, 1.60 mmol). The mixture was cooled to 0 °C and lithium perchlorate (636 mg, 6.00 mmol) was added. After the mixture was stirred for 1 h, water (10 mL) was added and the layers were separated. The water layer was extracted with ether (3 × 25 mL), and the combined organics were washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated. Chromatography (SiO_2, 5% EtOAc/hex) gave 140 mg (92%) of the ester **2** as a clear, colorless oil, R_f = 0.47 (25% EtOAc/hex): ^1H NMR ($CDCl_3$, 300 MHz) δ 6.88 (s, 1 H), 6.84 (d, J = 8.1 Hz, 1 H), 6.74 (d, J = 8.1 Hz, 1 H), 5.93 (s, 2 H), 5.84 (s, 1 H), 4.16 (q, J = 7.2 Hz, 2 H), 2.75 (m, 1 H), 2.35 (m, 4 H), 1.88 (m, 2 H), 1.69 (m, 1 H), 1.31 (m, 1 H), 1.27 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz, JMOD) δ 172.85 (–), 147.61 (–), 137.12 (–), 136.68 (–), 126.52 (+), 118.43 (+), 107.87 (+), 105.86 (+), 100.85 (–), 60.23 (–), 40.95 (–), 32.99 (+), 28.44 (–), 27.70 (–), 21.57 (–), 14.29 (+); IR (neat) 1731, 1606, 1504, 1487, 1444, 1371, 1278, 1244, 1219, 1176 cm^{-1}; MS (EI, 70 eV) m/z (rel int) 288 (M^+, 17.9), 214 (14.6), 201 (100.0), 135 (43.4) 115 (11.2), 79 (18.4); HRMS calcd for $C_{17}H_{20}O_4$ 248.1362, found 288.1369. Anal. Calcd for $C_{17}H_{20}C_4$: C, 70.81; H, 6.99. Found: C, 70.88; H, 6.91. Compound **2** has also been prepared on a larger scale from allylic alcohol **14**. Thus, **14** (6.44 g, 0.030 mmol), 1-[(*tert*-butyldimethylsilyl)oxy]-1-ethoxyethene (11.87 g, 0.060 mol), and lithium perchlorate (19.0 g, 0.179 mol) were combined for 1.5 h as reported above to yield 7.31 g (86%) of ester **2** after chromatography.

An Enantioselective Synthesis of the Spirotetronate Subunit of Kijanolide

James A. Marshall* and Shiping Xie

Department of Chemistry, The University of South Carolina, Columbia, South Carolina 29208

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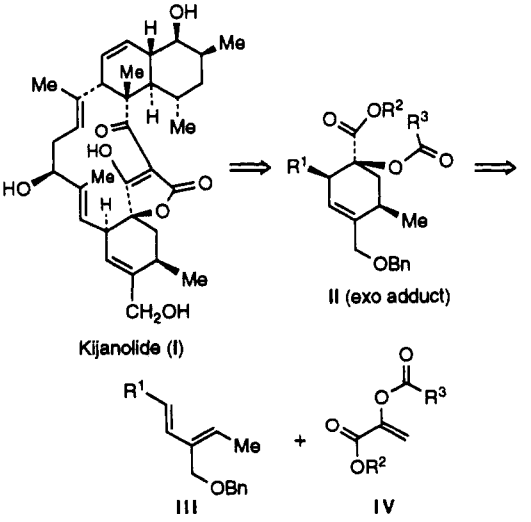
Summary: The Diels–Alder adduct **11** of α-bromoacrolein and triene **9** was converted to spirotetronate **21** through a sequence involving Pummerer rearrangement of the derived sulfoxide **16**, oxidation of the resulting aldehyde **17**, and Dieckmann cyclization of the diester **19** followed by in situ quench with MOMCl.

The spirotetronate subunit of kijanolide (**I**), the aglycon of the novel antitumor antibiotic kijanimicin,[1] has elicited significant synthetic activity in recent years.[2] Several routes to racemic equivalents of this subunit have been reported but to date no enantioselective synthesis has been achieved.[3] We have expended considerable effort on the design of α-acyloxy acrylic esters **IV** possessing chiral



(1) Mallams, A. K.; Puar, M. S.; Rossman, R. R.; McPhail, A. T.; Macfarlane, R. D.; Stephens, R. L. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1497.

(2) (a) Roush, W. R.; Brown, B. B. *Tetrahedron Lett.* **1989**, *30*, 7309. (b) Okumura, K.; Okazaki, K.; Takeda, K.; Yoshii, E. *Tetrahedron Lett.* **1989**, *30*, 2233. (c) Takeda, K.; Yano, S.; Sato, M.; Yoshii, E. *J. Org. Chem.* **1987**, *52*, 4135. (d) Takeda, K.; Shibata, Y.; Sagawa, Y.; Urahata, M.; Funaki, K.; Hori, K.; Sasahara, H.; Yoshii, E. *J. Org. Chem.* **1985**, *50*, 4673. (e) Schmidt, R. R.; Hirsenkorn, R. *Tetrahedron Lett.* **1984**, *25*, 4357. (f) Ireland, R. E.; Thompson, W. J. *J. Org. Chem.* **1979**, *44*, 3041.

(3) Though not yet reported, the sequence employed by Roush,[2a] which led to a racemic analogue of **21**, could easily be used to prepare the enantioenriched modification of that analogue. In fact, we have repeated the Roush sequence with enantioenriched dienophile to obtain a comparison compound (see ref 9).

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