Pergamon

Tetrahedron Letters, Vol. 35, No. 28, pp. 4951-4954, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)00994-5

On the Utility of α-Heteroatom Substituted Orthoesters in the Johnson Claisen Rearrangement‡

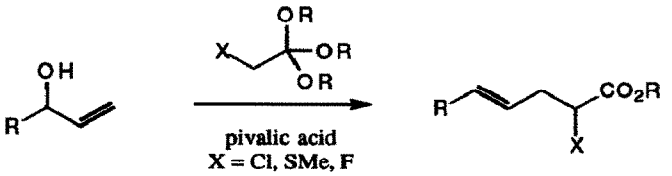
Todd R. Elworthy, David J. Morgans, Jr., Wylie S. Palmer, David B. Repke, David B. Smith*, and Ann Marie Waltos

Institute of Organic Chemistry, Syntex Discovery Research
3401 Hillview Avenue, Palo Alto, CA 94304

Abstract: α-Heteroatom substituted orthoesters were prepared and found to undergo the Johnson Claisen rearrangement with a variety of allylic alcohols giving γ,δ -unsaturated α-heteroatom substituted esters in fair to excellent yields. The diastereoselectivity of the process was examined.

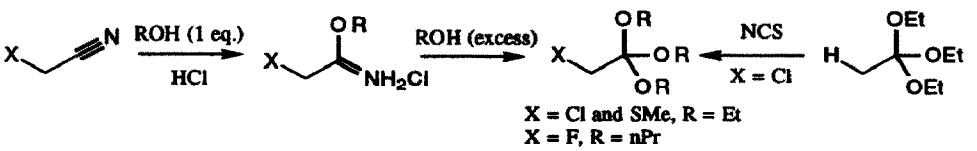
The Claisen rearrangement[1], along with numerous variants reported to date[2], has proven to be a useful tool to the practicing organic chemist. Herein we report a novel variant of the Johnson[3] procedure which utilizes α-heteroatom substituted orthoesters and thus provides unsaturated α-heteroatom substituted esters as the products (Scheme 1).[4]

Scheme 1

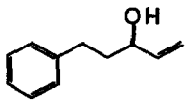
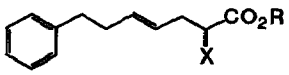
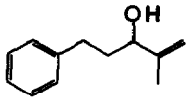
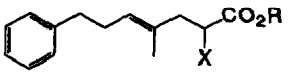
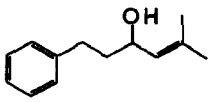
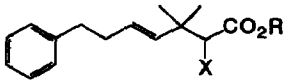
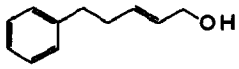
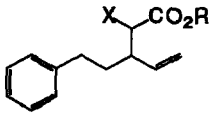
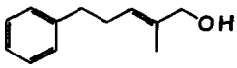
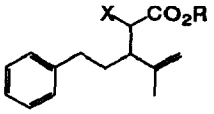
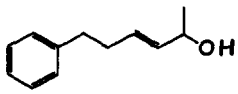
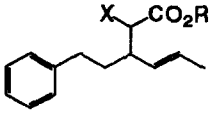
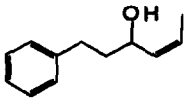
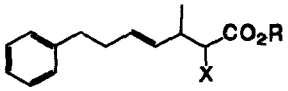
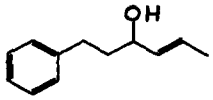
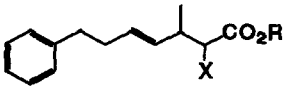


The orthoesters used in this study were prepared in analogy to the literature procedures (Scheme 2). Simple NCS chlorination of triethylorthoacetate provided large quantities of 2-chloro-1,1,1-triethoxyethane.[5] Alternatively, this compound could be prepared via alcoholysis of the imidate hydrochloride derived from chloroacetonitrile and ethanol (the Pinner reaction). This latter procedure was useful for the preparation of the 2-thiomethyl derivative as well.[6] The 2-fluoro substituted orthoester, a previously unknown reagent, could also be prepared using the Pinner method. After some experimentation, handling considerations prompted us to employ the tri-n-propyl derivative of the fluoro orthoester.[7]

Scheme 2



Table[12]

Entry	Substrate	Product	Yield(ratio) X = Cl (R = Et)	X = SMe (R = Et)	X = F (R = nPr)
1			45%	75%	60%
2			63%	85%	29%
3			56%	44%	19%
4			77% (1:1)	65% (1:1)	55% (1:1)
5			71% (1:1)	---	---
6			37% (1:1)	---	---
7			92% (1:1)	---	---
8			79% (1:1)	---	---

With a supply of the orthoesters in hand, we turned our attention to performing the Johnson rearrangement with a series of alkenols[8] (Table). These substrates were chosen in order to explore the chemistry using a wide variety of substitution patterns. Reactions using these substrates could readily be followed to completion using TLC with UV activity as a marker.

Generally, reactions were performed with xylenes as co-solvent in the presence of a catalytic amount of pivalic acid. An excess (1.1-3.0 eq.) of the orthoester was required to achieve complete reaction. Prolonged heating (4-12 h) using an oil bath at temperatures of 140-160 °C afforded the highest yields, and the products could be isolated using flash chromatography on silica gel.[9]

The data presented in the Table clearly shows the utility of this procedure with the three orthoesters examined. Most notable is the ability to introduce fluorine via this procedure (entries 1-4), as α-fluoro carbonyl systems have attracted the interest of medicinal chemists for some time.[10] As can be seen in entry 3, the more highly substituted substrate gave lower yields with all orthoesters examined. This may be due to steric congestion in the transition state for this substrate. Entries 4-8 were designed to probe the potential to transfer asymmetry using this simple procedure. We discovered that these substrates gave a nearly 50:50 mixture of diastereomers under the conditions described. This suggests that elimination of alcohol from the initially formed mixed orthoester intermediate proceeds with virtually no stereoselectivity.[11a,b]

In summary, we have demonstrated a useful method for the preparation of unsaturated α-heteroatom substituted esters. Under the current protocol, the reaction proceeds with no diastereoselectivity, and this may limit the utility of the procedure for the synthesis of stereodefined and nonracemic targets. This method could easily be extended to the synthesis of other unsaturated α-heteroatom substituted systems.[4]

Typical Procedure: Ethyl (*E*)-2-chloro-3-methyl-7-phenylhept-4-enoate (Table entry 8): Into a 25 mL round bottom flask containing a stirbar was placed (*E*)-6-phenyl-4-hydroxy-hex-2-ene (301 mg, 1.7 mmol) and 2-chloro-1,1,1-triethoxyethane (400 mg, 2.0 mmol, 1.15 eq.). Xylenes (10 mL) were added and stirring was begun under a nitrogen atmosphere. After dissolution of the substrates, pivalic acid (43 mg, 0.42 mmol, 0.25 eq.) was added and the reaction vessel was placed into an oil bath heated to 145 °C. After 6 h, the solution was cooled to 60 °C and the volatiles were removed under reduced pressure. Diethyl ether (25 mL) was added and the excess orthoester was decomposed over 2 h by stirring with 1M $NaHSO_4$ (5 mL). After partitioning the layers, the organic phase was dried over $MgSO_4$. Filtration was followed by solvent removal and flash chromatography (silica gel, 230-400 mesh, 3% ethyl acetate in hexanes) to afford the product as a colorless oil (378 mg, 79%). ^1H NMR (300 MHz) indicated a 1:1 mixture of diastereomers (partial data); δ 4.13 (d, J = 7.17 Hz, 1H, $CH_3CHCClHCOOEt$, diastereomer A), 4.06 (d, J = 7.48 Hz, 1H, $CH_3CHCClHCOOEt$, diastereomer B). Analysis calculated for $C_{16}H_{21}ClO_2$: C, 68.44; H, 7.54; Cl, 12.63. Found: C, 68.53; H, 7.55; Cl, 12.54.

References and Notes

‡ Contribution #895 from the Institute of Organic Chemistry.

1. Claisen, L. *Chem. Ber.* **1912**, *45*, 3157.

2. Reviews: a) Blechert, S. *Synthesis* **1989**, 71. b) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423. c) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 2. d) Bennett, G. B. *Synthesis* **1977**, 589. e) Ziegler, F. E. *Acc. Chem. Res.* **1977**, *10*, 227.

3. Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741.

4. For leading references related to rearrangements affording α-heteroatom substituted systems, see: a) Welch, J. T.; Araki, K. *Tet. Lett.* **1993**, *34*, 2251. b) Yamamoto, H.; Hattori, K. *J. Org. Chem.* **1993**, *58*, 5301. c) Hatakeyama, S.; Sugawara, M.; Kawamura, M.; Takano, S. *J. Chem. Soc. Chem. Comm.* **1992**, 1229. d) Panek, J. S.; Clark, T. D. *J. Org. Chem.* **1992**, *57*, 4323. e) Davidson, A. H.; Eggleton, N.; Wallace, I. H. *J. Chem. Soc. Chem. Comm.* **1991**, 378. f) Posner, G. H.; Crouch, R. D.; Kinter, C. M.; Carry, J-C. *J. Org. Chem.* **1991**, *56*, 6981. g) Ritter, K. *Tet. Lett.* **1990**, *31*, 869. h) Ito, Y.; Higuchi, N.; Murakami, M.*Tet. Lett.* **1988**, *29*, 5151. i) Boeckman, R. K.; Potenza, J. C.; Enholm, E. J. *J. Org. Chem.* **1987**, *52*, 469. j) Yuan, W.; Berman, R. J.; Gelb, M. H. *J. Am. Chem. Soc.* **1987**, *109*, 8071. k) Kamber, M.; Just, G. *Can. J. Chem.* **1985**, *63*, 823. l) Ishino, Y.; Nishiguchi, I.; Kim, M.; Hirashima, T. *Synthesis*, **1982**, 740. m) Ager, D. J.; Cookson, R. C. *Tet. Lett.* **1982**, *23*, 3419. n) Lythgoe, B.; Manwaring, R.; Milner, J. R.; Moran, T. A.; Nambuding, M. E. N.; Tideswell, J. *J. Chem. Soc. Perk. Trans. 1* **1978**, 387. o) Lythgoe, B.; Milner, J. R.; Tideswell, J. *Tet. Lett.* **1975**, 2593.

5. Mylari, B. L.; Scott, P. J.; Zembrowski, W. J. *Synth. Commun.* **1989**, *19*, 2921.

6. Ueno, H.; Maruyama, A.; Miyake, M.; Nakao, E. Nakao, K.; Umezu, K; Nitta, I. *J. Med. Chem.* **1991**, *34*, 2468.

7. 2-Fluoro-1,1,1-tri-n-propyloxyethane was prepared in two steps and 27% overall yield from fluoroacetonitrile and gave the following data: boiling point (1 atm) 198-200 °C; ^{1}H NMR (300 MHz) δ 4.42 (d, J = 47.1 Hz, 2H, $FC\underline{H}_2C(OCH_2CH_2CH_3)_3$), 3.53 (t, J = 6.8 Hz, 6H, $FCH_2C(OC\underline{H}_2CH_2CH_3)_3$), 1.62 (m, 6H, $FCH_2C(OCH_2C\underline{H}_2CH_3)_3$), 0.94 (t, J = 7.4 Hz, 9H, $FCH_2C(OCH_2CH_2C\underline{H}_3)_3$); ^{19}F NMR (282 MHz) δ -236.1 (t, J = 47.1 Hz). Analysis calculated for $C_{11}H_{23}FO_3$: C, 59.43; H, 10.43. Found: C, 59.25; H, 10.27.

8. The alkenol substrates[12b] employed in this study are known compounds and were prepared starting from the commercially available (Aldrich) 3-phenylpropanal. Substrates for Table entries 1-3 were prepared using the appropriate Grignard reagent, see for example: Trost, B. M.; Kulawiec, R. J. *J. Am. Chem. Soc.* **1993**, *115*, 2027. To prepare substrates for Table entries 4 and 5, a Wittig olefination/Luche reduction sequence was employed. For the substrate in Table entry 6 the Wittig olefination product leading to alkenol entry 4 was intercepted with methyl magnesium bromide. Substrates for Table entries 7 and 8 were prepared via stereoselective reduction of the adduct derived from 1-lithio-1-propyne and 3-phenylpropanal (cis, entry 7: Sondengam, B. L.; Charles, G.; Akam, T. M. *Tetrahedron Lett.* **1980**, *21*, 1069; trans, entry 8: Denmark, S. E.; Jones, T. K. *J. Org. Chem.* **1982**, *47*, 4595).

9. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

10. For some leading references see: a) Fritz-Langhals, E.; Schutz, G. *Tetrahedron Lett.* **1993**, *34*, 293. b) Purrington, S. T.; Woodard, D. L. *J. Org. Chem.* **1990**, *55*, 3423. c) Camps, F.; Messeguer, A.; Sanchez, F-J. *Tetrahedron* **1988**, *44*, 5161. d) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123.

11. a) This assumes that each ketene acetal intermediate would lead to one of the two products with high stereoselectivity. This is known to be the case for the corresponding alkyl substituted systems (the Ireland Claisen rearrangement: Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 5897). For a related case involving the stereoselective rearrangement of a fluoro substituted ketene acetal, see: Welch, J. T.; Samartino, J. S. *J. Org. Chem.* **1985**, *50*, 3663. b) Another possible explanation for the observed lack of selectivity is that equilibration occurs under the conditions of the reaction. For one of the products in Table entry 4 (X = F, R = nPr), we were able to purify one diastereomer from the mixture. Resubjection of this diastereomer to the conditions of the reaction gave no epimerization.

12. a) Isolated yields of purified products based on alkenols. b) All compounds were characterized by ^{1}H and ^{13}C NMR, IR, MS, UV and analysis or HRMS.

(*Received in USA* 25 *March* 1994; *revised* 12 *May* 1994; *accepted* 18 *May* 1994)