

A Novel Anionic Condensation, Fragmentation, and Elimination Reaction of Bicyclo[2.2.1]heptenone Ring Systems

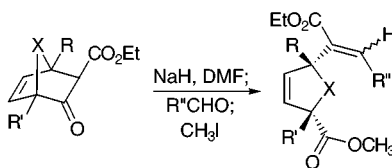
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Received March 18, 1999

ABSTRACT



We have identified an unprecedented anionic condensation, fragmentation, and elimination sequence from the coupling of bicyclo[2.2.1]heptenones with aldehydes. This reaction leads to the stereoselective formation of disubstituted five-membered rings which are present in a wide array of bioactive molecules.

Substituted furans are a key architectural feature in a wide array of biologically active molecules. Our interest in the 2,5-disubstituted furan-containing marine natural products gymnodimine^{1,2} and eleutherobin^{3,4} has directed our attention to the synthesis of these structural units. As envisioned, our

approach to the synthesis of substituted furans included (a) an aldol condensation between an oxabicyclo[2.2.1]heptenone⁵ and an aldehyde, (b) a subsequent fragmentation reaction,⁶ and (c) an elimination reaction to the corresponding olefin (Scheme 1). As described in this Letter, in the course of these

(1) (a) Seki, T.; Satake, M.; Mackenzie, L.; Kaspar, H. F.; Yasumoto, T. *Tetrahedron Lett.* **1995**, *36*, 7093–7096. (b) Stewart, M.; Blunt, J. W.; Munro, M. H. G.; Robinson, W. T.; Hannah, D. J. *Tetrahedron Lett.* **1997**, *38*, 4889–4890.

(2) For synthetic efforts to gymnodimine, see: Ishihara, J.; Miyakawa, J.; Tsujimoto, T.; Murai, A. *Synlett.* **1997**, 1417–1419.

(3) Lindel, T.; Jensen, P. R.; Fenical, W.; Long, B. H.; Casazza, A. M.; Carboni, J.; Fairchild, C. R. *J. Am. Chem. Soc.* **1997**, *119*, 8744–8745.

(4) Two total syntheses of eleutherobin have appeared. See: (a) Nicolau, K. C.; van Delft, F.; Ohshima, T.; Vourloumis, D.; Xu, J. H., S.; Pfefferkorn, J.; Kim, S.; Li, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2520–2524. (b) Chen, X.-T.; Zhou, B.; Bhattacharya, S. K.; Gutteridge, C. E.; Pettus, T. R. R.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 789–792.

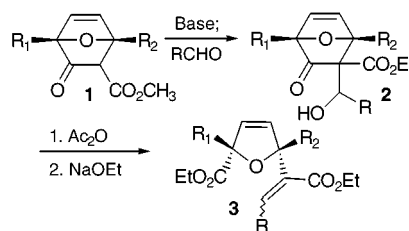
(5) Available from a furan Diels–Alder reaction. For a relevant review, see: Kappe, C. O.; Murphree, S. S.; Padwa, A. *Tetrahedron* **1997**, *53*, 14179–14233.

(6) For other uses of oxabicyclo[2.2.1] fragmentation reactions in the synthesis of substituted furans, see ref 5.

(7) Acid-mediated Aldol–Groβ fragmentations have been described. See: (a) Kabalka, G. W.; Tejedor, D.; Li, N.-S.; Malladi, R. R.; Trotman, S. J. *Org. Chem.* **1998**, *63*, 6438–6439. (b) Yamamoto, T.; Suemune, H.; Sakai, K. *Tetrahedron* **1991**, *47*, 8523–8528.

(8) The trisubstituted olefin geometry was determined through the identification of the appropriate NOESY cross-peaks (see the Supporting Information for more details).

Scheme 1. Sequential Diels–Alder, Condensation, and Fragmentation Approach to 2,5-Disubstituted Furans

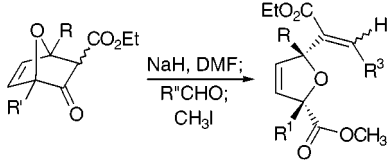


investigations we have uncovered an unprecedented anion-mediated condensation, fragmentation, and elimination reaction during which all of the goals outlined above were accomplished in a single flask.⁷

To investigate the sequence depicted in Scheme 1, we initially examined the condensation of oxabicyclo[2.2.1]heptenone

heptenone **4** with benzaldehyde (Table 1, entry 1). Surpris-

Table 1. Single Flask Condensation, Fragmentation, and Elimination to 2,5-Disubstituted Dihydrofurans

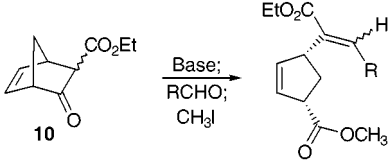


Entry	Ketone	R	R ¹	R ²	Furan	Yield	E:Z
1	4	OCH ₃	CH ₃	Ph	5	83%	0:1
2	4	OCH ₃	CH ₃	<i>i</i> Pr	6	78%	0:1
3	7	H	H	Ph	8	56%	3:1
4	7	H	H	<i>i</i> Pr	9	45%	1:2

ingly, rather than the simple condensation product, we isolated disubstituted furan **5** exclusively as its *Z*-alkene isomer in 83% yield after esterification. To our delight, we had achieved the condensation, fragmentation, and elimination in a single flask.

With the notion that this reaction might lead to the efficient synthesis of a number of substituted furans, we set out to determine the scope. As is depicted in Tables 1 and 2, other

Table 2. Single Flask Condensation, Fragmentation, and Elimination to 1,4-Disubstituted Cyclopentenes



entry	R	Base	Cyclopentene	Yield	E:Z
1	Ph	KO ^t Bu	11	91%	1:0
2	<i>i</i> Pr	KO ^t Bu	12	91%	3:1
3	<i>i</i> Pr	NaH	12	94%	3:1

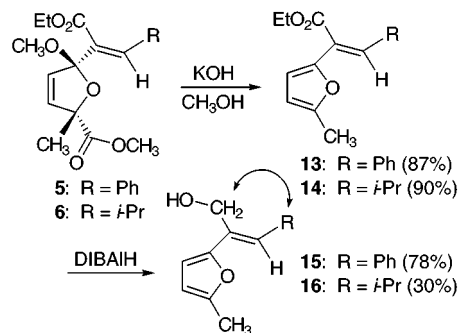
aldehydes and bicyclo[2.2.1] ring systems successfully underwent the reaction. For example, the condensation of isobutyraldehyde with **4** gave furan **6** exclusively as the *Z*-alkene isomer in 78% yield (Table 1, entry 2). The reaction is not specific to **4** as unsubstituted oxabicyclo[2.2.1]- β -keto ester **7** also underwent the condensation, fragmentation, and elimination reaction sequence. The unoptimized coupling of **7** with benzaldehyde and isobutyraldehyde gave furans **8** and **9**, respectively (Table 1, entries 3 and 4). Interestingly, while **4** gave exclusively the *Z*-alkene isomer with both benzaldehyde and isobutyraldehyde, **7** gave a 3:1 *E:Z* alkene mixture when condensed with benzaldehyde and a 1:2 *E:Z* mixture when condensed with isobutyraldehyde.⁸

We have also examined the reaction between bicyclo[2.2.1]heptenone **10** and aldehydes (Table 2). As with the synthesis of the furans mentioned previously, the condensa-

tion, fragmentation, and elimination reaction of **10** with benzaldehyde and isobutyraldehyde proceeded smoothly to give cyclopentenes **11** and **12**, respectively. However, in contrast to **4** and **7**, the condensation of **10** with benzaldehyde and isobutyraldehyde gave predominantly or exclusively the *E*-alkene isomer.⁸

In contrast to **8**, **9**, **11**, and **12**, the NOESY spectra of substituted furans **5** and **6** were devoid of information. However, we were able to determine the olefin geometry in **5** and **6** after derivatization of the furan (Scheme 2). That

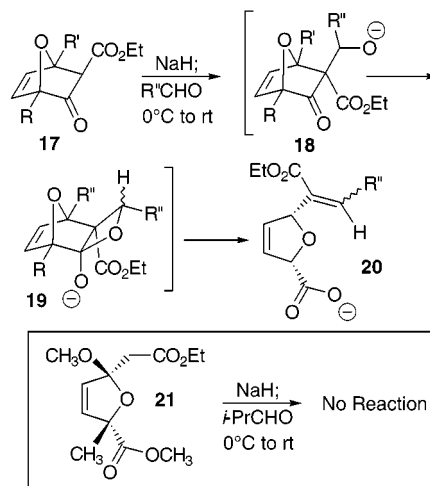
Scheme 2. Determination of the Olefin Geometry in Furans **5** and **6**



is, treatment of **5** and **6** with methanolic KOH resulted in hydrolysis, decarboxylation, and aromatization to give **13** and **14**, respectively. DIBAL reduction gave allyl alcohols **15** and **16**.⁹ As depicted, NOESY cross-peaks were observed between the isopropyl/phenyl hydrogens and the methylene hydrogens of the hydroxy methyl group, thereby establishing the trisubstituted olefin geometry.

While any detailed mechanistic discussion requires further experimentation, a reasonable working hypothesis is depicted in Scheme 3. It is highly likely that aldol condensation to

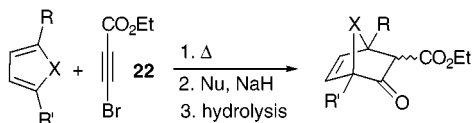
Scheme 3. Possible Mechanism for the Condensation, Fragmentation, and Elimination Reaction of Bicyclo[2.2.1]heptenes



give **18** precedes fragmentation as attempted aldol coupling between furan **21**¹⁰ and isobutyraldehyde resulted in the recovery of **21**. Lactol formation provides oxetane **19**.⁷ Oxetane fragmentation then leads to furan **20**. The nature of the substrate dependence on the *E,Z*-olefin selectivity is not readily apparent and is thus the focus of our current efforts.¹¹

The bicyclo[2.2.1] ring systems used in this study are readily accessible using a Diels–Alder cycloaddition reaction between bromopropynoate **22** and the appropriate diene (Scheme 4).^{12–14} A subsequent two-step hydrolysis of the

Scheme 4. Diels–Alder Approach to Bicyclo[2.2.1]heptenes



resulting bromoacrylate derivative gave β -keto esters **4**, **7**, and **10**.

To conclude, we have identified a novel anion-mediated condensation, fragmentation, and elimination reaction of

bicyclo[2.2.1]heptene ring systems. Our current efforts are focusing on the nature of the selectivity in this reaction as well as its use in the synthesis of furan-containing natural products.

Acknowledgment. We gratefully acknowledge the National Institutes of Health (GM56677) for partial support of this work. Support from the Department of Chemistry at The University of Arizona as well as The University of Arizona Foundation is also acknowledged. The authors would like to thank Dr. Arpad Somogyi for help with mass spectra analysis and Dr. Neil Jacobsen and Mr. Travis Gregar for help with NMR experiments.

Supporting Information Available: Experimental procedures and spectroscopic data for compounds **4–12**, **15**, and **16**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(9) Thus far, we have been unable to selectively reduce the ethyl ester in **5** or **6**.

(10) **21** is available from the reaction of **4** and NaOCH₃.

(11) Thus far, our attempts to equilibrate the olefin in **5** with base have been unsuccessful.

(12) Sherman, E.; Dunlop, A. P. *J. Org. Chem.* **1960**, *25*, 1309–1311.

(13) Chamberlin, P.; Rooney, A. E. *Tetrahedron Lett.* **1979**, 383–386.

(14) Leroy, J. *Tetrahedron Lett.* **1992**, *33*, 2969–2972.

