Pergamon

Tetrahedron Letters, Vol. 35, No. 28, pp. 4887-4890, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

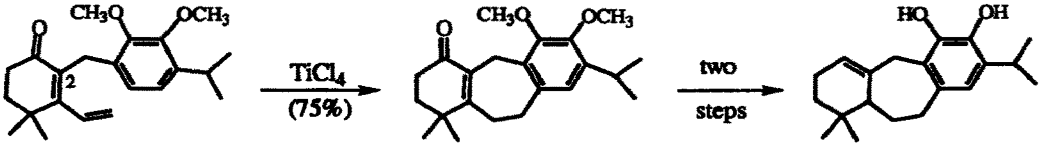
0040-4039(94)00942-2

Cyclialkylations of Conjugated Dienones with Furans

George Majetich,* Yong Zhang and Shuang Liu
Department of Chemistry, *The University of Georgia*,
Athens, Georgia 30602

Abstract: Fused tricyclic compounds with the salient features of the guaianolides and the pseudoguaianolides were prepared using a furan-based cyclialkylation strategy.

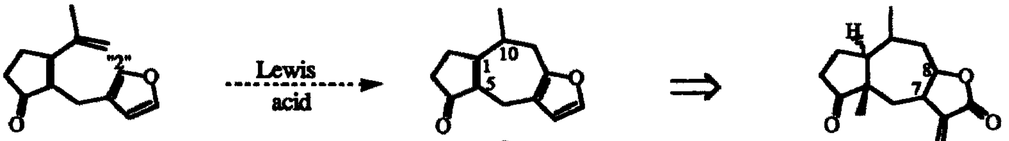
In 1940 Brunson and Kroeger popularized the term "cyclialkylation" to describe intramolecular Friedel-Crafts alkylation.[1] Recently we reported that Lewis acid-activated conjugated dienones add to electron-rich arenes, such as those present in 2-benzyl-dienone **1**, to create tricyclic compounds containing a central cycloheptane ring, as shown below.[2a] This cyclialkylation was featured in a concise synthesis of the diterpene barbatusol.[2b]



1

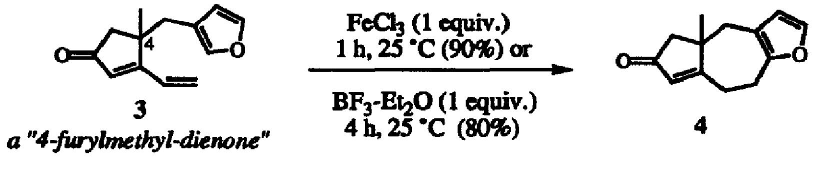
barbatusol

Like other aromatic compounds, furans undergo electrophilic substitutions. However, low reaction temperatures and mild catalysts are required in order to minimize the destruction of the starting furans and / or products. Electrophilic substitution of furans, which are more reactive than arenes, takes place predominantly at the 2-position. These properties suggest that the 5,7-carbocyclic framework characteristic of the pseudoguaianolides could be formed using the furan-based cyclialkylation shown below.[3] This annulation strategy was attractive since the furan ring in cyclization product **2** can be elaborated into an α-methylene lactone, while the cyclopentenone moiety allows the control of the C(1), C(5) and C(10) asymmetric centers.[4] Here we report that Lewis acid-activated conjugated dienones can intramolecularly substitute furans to produce fused tricyclic compounds with the salient features of the guaianolides and the pseudoguaianolides.



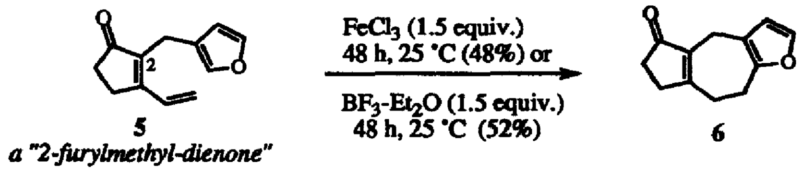
2

Previous work has shown that 4-benzyl-dienone cyclialkylations are more facile than those of 2-benzyl-dienones (cf. 1).[2a] This generality also extends to furan-based cyclialkylations. For example, treatment of 4-furylmethyl-dienone 3[5] with stiochiometric amounts of either $FeCl_3$ or BF_3-Et_2O at room temperature produced tricyclic enone 4 in good yield within hours. In contrast, the cyclization of 2-furylmethyl-dienone 5[6] was less efficient and required excess catalyst and long reaction times.



3
a "4-furylmethyl-dienone"

4

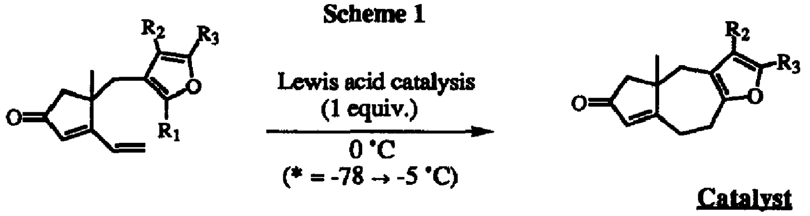


5
a "2-furylmethyl-dienone"

6

Several substituted 4- and 2-furylmethyl-dienones were prepared in hopes that functionalizing the furan ring would improve the efficacy of these cyclialkylations (Schemes 1 and Scheme 2, respectively).[7] In the case of silylated dienone 7, which involves *ipso*-substitution,[8] the loss of the silyl group was predicted. In contrast, loss of the silyl moiety in the cyclization of substrate **10** and its retention in the cyclization of silylated dienone **8** were unexpected. Dienones in which the furan ring bears either an electron-withdrawing group (cf. **11**), or an electron-donating group (i.e., **13**), cyclize in

Scheme 1

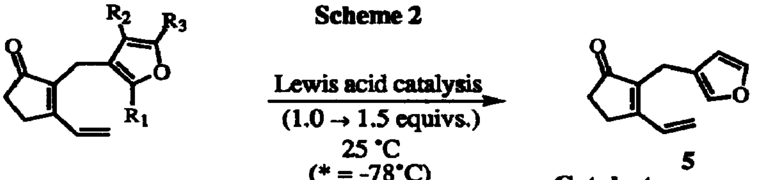


Cyclization Precursor	**Product**	**Catalyst**	
		$FeCl_3$	*BF_3-Et_2O*
$R_1 = Si(CH_3)_3$, $R_2 = R_3 = H$ (7)	$R_2 = R_3 = H$ (4)	89% (5 min)	81% (5 min)
$R_1 = H$, $R_2 = Si(CH_3)_3$, $R_3 = H$ (8)	$R_2 = Si(CH_3)_3$, $R_3 = H$ (9)	85% (5 min)	87% (50 min)
$R_1 = R_2 = H$, $R_3 = Si(CH_3)_3$ (10)	$R_2 = R_3 = H$ (4)	96% (10 min)	92% (15 min)
$R_1 = R_2 = H$, $R_3 = Br$ (11)	$R_2 = H$, $R_3 = Br$ (12)	95% (25 min)	97% (4 hrs)*
$R_1 = R_2 = H$, $R_3 = SC_6H_5$ (13)	$R_2 = H$, $R_3 = SC_6H_5$ (14)	93% (30 min)	95% (30 min)

high yield under mild reaction conditions.

Treatment of silylated furans **15**, **16**, and **17** with $FeCl_3$ or BF_3-Et_2O at room temperature resulted in rapid protodesilylation of the furan ring (Scheme 2). Prolonged reaction times (>2 days) or heating at elevated temperatures were required to convert dienone **5**, which was formed *in situ*, to tricycle **6**, albeit in low yield (25% < 50%) because of the vigorous conditions employed.[9]

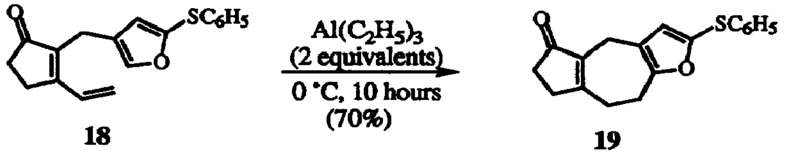
Scheme 2



5

Cyclization Precursor	Catalyst	
	$FeCl_3$	*BF_3-Et_2O*
R_1 = $Si(CH_3)_3$, R_2 = R_3 = H (**15**)	91% (10 min)	95% (10 min)
R_1 = H, R_2 = $Si(CH_3)_3$, R_3 = H (**16**)	20% (60 min)* and 60% unreacted **16**	25% (10 min) and 55% unreacted **16**
R_1 = R_2 = H, R_3 = $Si(CH_3)_3$ (**17**)	55% (20 min) and 25% unreacted **17**	69% (10 min)

On the other hand, 2-furylmethyl-dienone **18**, which has an electron-rich furan ring, undergoes facile cyclialkylation to produce **19**. Indeed, this annulation occurs in 70% yield at 0 °C over a ten-hour period using triethylaluminum, a weak Lewis acid; stronger Lewis acids, such as BF_3-Et_2O, $FeCl_3$ or $TiCl_4$, resulted in polymerization.



18 **19**

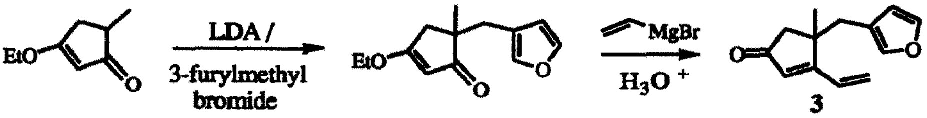
To summarize, furan-based cyclialkylations can be used to prepare furan-containing 5,7,5-fused tricycles. These processes work best when either 4-furylmethyl-dienones or 2-furylmethyl-dienones with electron-rich furans are cyclized. Synthetic applications featuring this new methodology are forthcoming.

Acknowledgments: Acknowledgment is made to the Donors of The Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

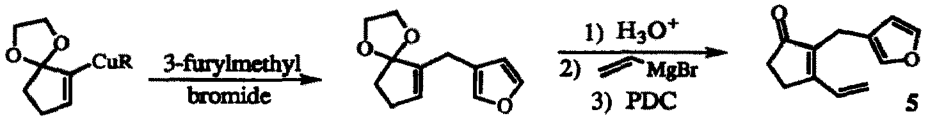
Bibliographic References:

1. Brunson, H. A.; Kroeger, J. W. J. Am. Chem. Soc. **1940**, *62*, 36.

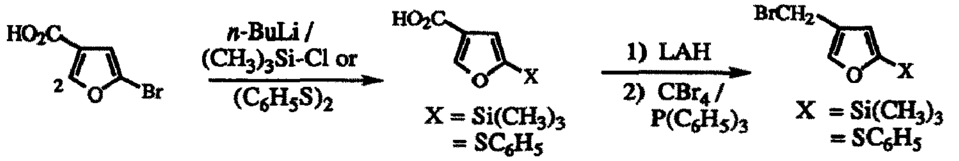
2. a) Majetich, G.; Zhang, Y.; Feltman, T. L.; Belfoure, V. Tetrahedron Lett. **1993**, *34*, 441.
   b) Majetich, G.; Zhang, Y.; Feltman, T. L.; Duncan, S. Jr. Ibid. **1993**, *34*, 445.
3. For examples of "furan-terminated cyclizations" for the construction of pseudoguaianolides, see: Tanis, S. P.; Robinson, E. D.; McMills, M. C.; Watt, W. J. Am. Chem. Soc. **1992**, *114*, 8349.
4. The C(1), C(5) and C(10) stereochemistry of the helenanolide graveolide was established from a bicyclic analogue of tricycle **2**, lacking only the furan ring, using a reductive alkylation strategy. See: Majetich, G.; Song, J. S.; Leigh, A. J.; Condon, S. M. J. Org. Chem. **1993**, *58*, 1030.
5. The synthesis of dienone **3** (shown below) is representative of the procedures also used to prepare substrates **7**, **8**, **10**, **11** and **13**. See also ref. 7.



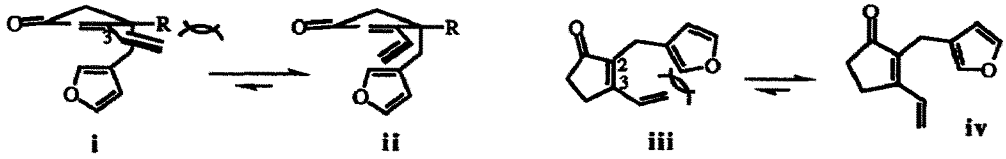
6. The four-step synthesis of dienone **5** (shown below) is representative of the procedures also used to prepare substrates **15**, **16**, **17** and **18**. For a detailed discussion of this protocol, see: a) Majetich, G.; Leigh, A. J.; Condon, S. M. Tetrahedron Lett. **1992**, *32*, 605. See also ref. 7.



7. LiAlH$_4$ reduction of 5-bromo-3-furoic acid [Ferraz, J. P.; Amaral, L. D. J. Org. Chem. **1976**, *41*, 2350], followed by treatment of the resulting alcohol with CBr$_4$/(C$_6$H$_5$)$_3$P gave the bromide needed for the preparation of dienone **11**.[5] The bromide required for precursors **7**[5] and **15**[6] was prepared by first silylating 3-furoic acid at the 2-position, followed by LiAlH$_4$ reduction and bromination [CBr$_4$/(C$_6$H$_5$)$_3$P]. The bromide used for the preparation of **8**[5] and **16**[6] was prepared from a known alcohol [Liotta, D.; Saindane, M.; Ott, W. Tetrahedron Lett. **1983**, *24*, 2473], by treatment with CBr$_4$/(C$_6$H$_5$)$_3$P. The transformations shown below enabled the preparation of precursors **10**,[5] **13**,[5] **17**,[6] and **18**.[6]



8. For a discussion of electrophilic substitution of silylated arenes via an *ipso*-attack mechansim, see: Eaborn, C. J. Organometal. Chem. **1975**, *100*, 43.
9. Conformation considerations make 4-furylmethyl-dienones more reactive than 2-furylmethyl-dienones. In the 4-series, steric interactions between the C(3) vinyl group and the furan-containing side-chain favor the cisoid dienone conformation which facilitates cyclialkylation (cf. **i** → **ii**). In the 2-series, steric interactions between the C(2) and C(3) substituents (cf. **iii**) cause the transoid conformer (**iv**) to predominate, thereby precluding cyclization. This unfavorable equilibrium slows the reaction rate and is overcome only by using harsh conditions, which unfortunately promote decomposition of both the cyclization precursors and products.



(*Received in USA* 23 *November* 1993; *revised* 8 *February* 1994; *accepted* 13 *May* 1994)