Construction of aryl-substituted triquinanes through the interrupted Nazarov reaction†

Curtis J. Rieder, Ryan J. Fradette and F. G. West*

Received (in College Park, MD, USA) 16th January 2008, Accepted 7th February 2008
First published as an Advance Article on the web 25th February 2008
DOI: 10.1039/b800800k

The first examples of intermolecular trapping of Nazarov cyclopentenyl cation intermediates by simple arenes to furnish α-arylcyclopentanones are described.

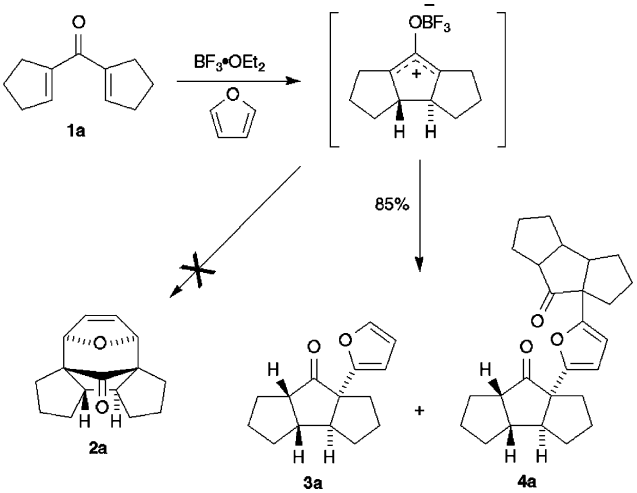
The Nazarov cyclization is a well established method for construction of substituted cyclopentanoid ring systems.[1] Recently, we have shown that the electrophilic 2-oxidocyclopentenyl cation intermediate is subject to capture by a variety of pendent nucleophilic traps.[2] We have been especially interested in trapping by arenes, as this process furnishes α-arylcyclopentanones from simple reactants. The intramolecular version of the reaction is effective, producing complex fused or bridged tricyclic systems from either dienone[3] or dichlorocyclopropane[4] precursors containing pendent arene traps. However, the corresponding bimolecular process could not be observed with dienone substrates that had been successfully captured intermolecularly by a variety of other traps.[5] Here we describe the first successful examples of intermolecular arylation of the Nazarov intermediate, using bicyclic dienone precursors and a variety of electron-rich arene traps.

Initial studies focused on dicyclopentenyl ketone **1a**. This substrate had previously been shown to undergo a variety of productive intermolecular trapping processes; in particular, its efficient [3+2] trapping by allylsilanes[5b] to furnish bridged/fused tetracyclic adducts was encouraging. With this in mind, we set out to explore the corresponding [4+3] trapping,[5c] using one equivalent of furan (Scheme 1). To our surprise, none of the expected cyclooctene product **2a** was obtained. Instead, a mixture of furyltriquinanes **3a** and **4a** was isolated in good yield. Spectral analysis of **3a** confirmed the installation of a 2-furyl substituent at one of the bridgehead positions α to the cyclopentanone carbonyl group, consistent with electrophilic aromatic addition of the cyclopentenyl cation intermediate. The relative stereochemistry of **3a** was inferred from the known conrotatory electrocyclization mechanism together with the precedent for preferential nucleophilic trapping[5b] to form *cis* ring-fusions. Likewise, protonation of the enolate formed after nucleophilic capture is expected to proceed with high or complete selectivity for the more stable *cis*-fused ring system. Product **4a** arises from addition of a second equivalent of cyclopentenyl cation to the 5-position of the furan ring of **3a**, and this product could be suppressed by increasing the ratio of furan to **1a** to 10 : 1. It was not possible to determine the relative configurations of the two triquinane units of **4a**, given the large distance separating the two moieties.

Using the optimized conditions, **1a** was subjected to trapping experiments using a variety of simple arene traps (Table 1). Bridgehead arylated triquinanes **3b–d** were obtained in very good yields. Notably, 1,3-dimethoxybenzene was an effective trap, demonstrating that this new reactivity is not limited to heteroaromatic nucleophiles. However, no nucleophilic capture was observed with the less electron-rich anisole; instead, the simple Nazarov elimination product **5** was obtained (entry 5). The *cis* ring-fusion stereochemistry for **3a–d** was confirmed by 2D TROESY experiments, which indicated correlations between aryl protons and the neighboring bridgehead methines (see ESI† for details).

Next, other dienones were examined. Efficient trapping of **1a** by electron-rich arenes suggested that in those cases the simple eliminative termination step was slow enough to allow bimolecular electrophilic aromatic substitution to compete effectively. It is possible that elimination is conformationally impeded in the rigid, polycyclic intermediate cation. With this in mind, we chose to examine the homologous dienone **1b**, which could be prepared by addition of 1-lithiocyclopentene to cyclohexenecarboxaldehyde, followed by Dess–Martin oxidation.

Treatment of **1b** with furan under the optimized conditions noted above furnished two adducts in good yield, but which

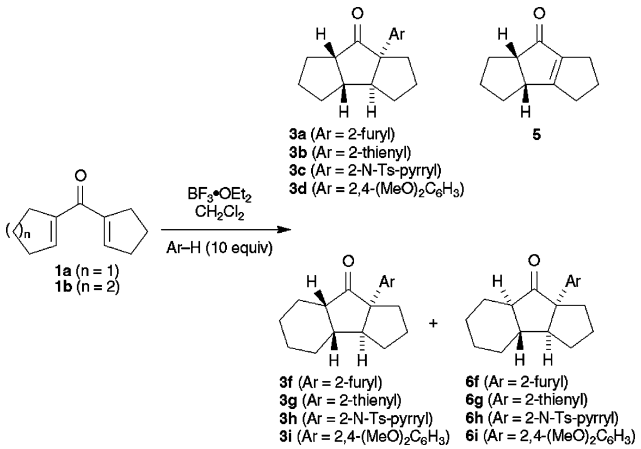


Scheme 1 Nucleophilic trapping of **1a** by furan.

Department of Chemistry, University of Alberta, E3-43 Gunning-Lemieux Chemistry Centre, Edmonton, AB, Canada T6G 2G2. E-mail: frederick.west@ualberta.ca; Fax: +1 780-492-8231; Tel: +1 780-492-8187

† Electronic supplementary information (ESI) available: Experimental procedures and spectral data for all new compounds. See DOI: 10.1039/b800800k

Table 1 Arene trapping of Nazarov cations derived from bicyclic dienones **1a,b**[a]

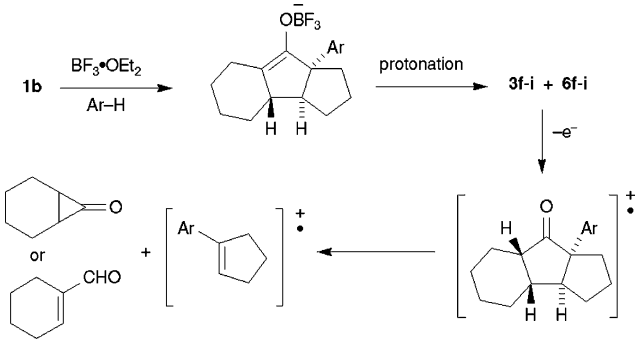


Entry	Dienone	Arene	Product (% yield)
1	**1a**	Furan	**3a** (79)
2	**1a**	Thiophene	**3b** (79)
3	**1a**	*N*-Ts-pyrrole	**3c** (78)
4	**1a**	1,3-Dimethoxybenzene	**3d** (79)
5	**1a**	Anisole	**5** (81)
6	**1b**	Furan	**3f** + **6f** (76; 2 : 1)
7	**1b**	Thiophene	**3g** + **6g** (80; 4 : 1)
8	**1b**	*N*-Ts-Pyrrole	**3h** + **6h** (29; 2 : 1)
9	**1b**	1,3-Dimethoxybenzene	**3i** (53) + **6i** (27)

[a] Standard procedure: $BF_3{\cdot}OEt_2$ (1.1 equiv) was added to a solution of dienone **1** and arene (10 equiv) in CH_2Cl_2 at rt. After 30 min, the reaction was quenched with sat. $NaHCO_3$. Crude product was purified by flash chromatography. All stated yields given are for homogeneous material following chromatographic purification.

were inseparable under all chromatographic conditions (Table 1, entry 6). Similar results were obtained with thiophene and *N*-tosylpyrrole, but 1,3-dimethoxybenzene gave rise to two separable products, **3i** and **6i**. Spectral analysis of these adducts indicated that each contained the expected saturated tricyclic ketone skeleton and a 1,2,4-trisubstituted aromatic ring. Careful examination of mass spectral fragmentation patterns revealed that both **3i** and **6i** underwent apparent loss of a neutral $C_6H_{10}CO$ fragment.‡ In contrast, triquinanes **3a–d** lose a C_5H_8CO fragment. The observation that the aryl group remains attached to the former cyclopentenyl fragment indicates that **3i** and **6i** result from nucleophilic trapping at the bridgehead position connecting the two 5-membered rings (Scheme 2). The two isomeric adducts presumably differ only in their relative configuration at the other α-methine bridgehead as a result of enolate protonation from both faces of the initial trapping product. Indeed, stirring pure **3i** or **6i** with DBU resulted in the formation of an equilibrium mixture of both isomers. Analysis of the other adducts generated from **1b** (entries 6–8) indicated similar fragmentation behavior, and they were assigned as **3f–3h** and **6f–6h** in analogy to **3i** and **6i**.

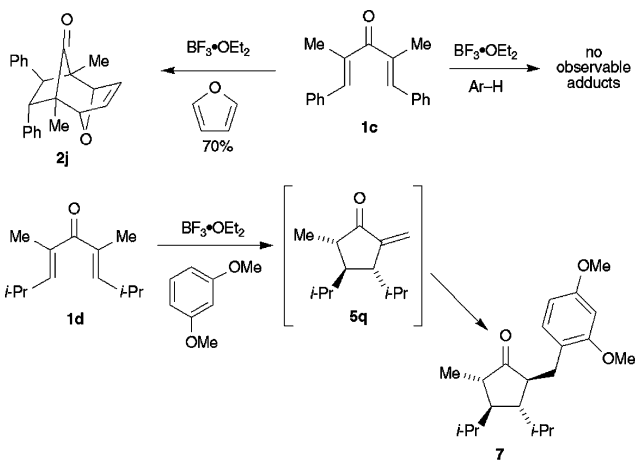
Two acyclic dienones **1c** and **1d** were also examined. Dibenzylidenepentanone **1c** was already known to react cleanly with furan to furnish the [4+3]-cycloadduct **2j**, with no evidence of trapping by simple arene substitution (Scheme 3).[5c] Treatment of **1c** with any of the other previously successful arene traps resulted in consumption of **1c** and recovery of arene, with no identifiable adducts. The same result was seen in the case of **1d** with furan, thiophene and *N*-tosylpyrrole. However, treatment with 1,3-dimethoxybenzene did result in an adduct isolated in good yield. Close inspection of this product revealed the presence of a trisubstituted arene, and *two* methine protons adjacent to a cyclopentanone carbonyl. Moreover, one of the two expected methyl groups was absent, while a benzylic methylene was found to be adjacent to one of the aforementioned α methines. Based on these data, structure **7** was assigned to this product. Coupling constants suggested an all-*trans* relative stereochemistry.



Scheme 2 Formation and MS fragmentation of arene trapping products from **1b**.

This unexpected product may result from conjugate addition of the arene to methylene cyclopentanone **5q**, resulting from elimination of the intermediate cyclopentenyl cation in an exocyclic mode. This regioselectivity is not unreasonable, as the customary Saytzeff elimination[6] would furnish a highly hindered cyclopentenone. To the best of our knowledge, reactivity of this type in the Nazarov reaction is unprecedented.[7,8] Unfortunately, to date we have not observed any other examples of this fascinating process.

Intermolecular arene trapping of the Nazarov intermediate allows for the 1-step construction of α-arylated cyclopentanones from two simple reactants. Bis(cycloalkenyl) ketones **1a,b** are efficiently trapped by electron-rich heteroaromatics and by dimethoxybenzene. Simple, acyclic dienones do not appear to participate in this process, although **1d** furnished an



Scheme 3 Trapping reactions of acyclic dienones.

adduct resulting from conjugate addition of dimethoxybenzene to the initially formed eliminative product of simple Nazarov cyclization. Further applications of this novel chemistry are under current study, and will be described in due course.

Notes and references

‡ For **3i**, **6i** and all other tricyclic arene adducts, the product of this apparent α-cleavage process furnished the base peak in the mass spectrum.

1 For recent reviews: (*a*) H. Pellisier, *Tetrahedron*, 2005, **61**, 6479–6517; (*b*) A. J. Frontier and C. Collison, *Tetrahedron*, 2005, **61**, 7577–7606; (*c*) M. A. Tius, *Eur. J. Org. Chem*., 2005, 2193–2206.

2 Recent examples: (*a*) S. Giese, R. D. Mazzola, Jr, C. M. Amann, A. M. Arif and F. G. West, *Angew. Chem., Int. Ed*., 2005, **44**, 6546–6549; (*b*) A. Rostami, Y. Wang, A. M. Arif, R. McDonald and F. G. West, *Org. Lett*., 2007, **9**, 703–706.

3 C. C. Browder, F. P. Marmsäter and F. G. West, *Can. J. Chem*., 2004, **82**, 375–385.

4 (*a*) T. N. Grant and F. G. West, *J. Am. Chem. Soc*., 2006, **128**, 9348–9349; (*b*) T. N. Grant and F. G. West, *Org. Lett*., 2007, **9**, 3789–3792.

5 (*a*) S. Giese and F. G. West, *Tetrahedron*, 2000, **56**, 10221–10228; (*b*) S. Giese, L. Kastrup, D. Stiens and F. G. West, *Angew. Chem., Int. Ed*., 2000, **39**, 1970–1973; (*c*) Y. Wang, B. D. Schill, A. M. Arif and F. G. West, *Org. Lett*., 2003, **5**, 2747–2750; (*d*) A. Yungai and F. G. West, *Tetrahedron Lett*., 2004, **45**, 5629–5632; (*e*) T. D. White and F. G. West, *Tetrahedron Lett*., 2005, **46**, 5629–5632; (*f*) B. Mahmoud and F. G. West, *Tetrahedron Lett*., 2007, **48**, 5091–5094; (*g*) D. Song, A. Rostami and F. G. West, *J. Am. Chem. Soc*., 2007, **129**, 12019–12022.

6 For a discussion of steric effects on the regiochemistry of E_1 eliminations, see: H. C. Brown and I. Moritani, *J. Am. Chem. Soc*., 1955, **77**, 3623–3628.

7 For recent examples of related indole alkylations, see: (*a*) W. Chen, W. Du, L. Yue, R. Li, Y. Wu, L.-S. Ding and Y.-C. Chen, *Org. Biomol. Chem*., 2007, **5**, 816–821; (*b*) L.-W. Xu, W. Zhou, L. Yang and C.-G. Xia, *Synth. Commun*., 2007, **37**, 3095–3104.

8 For preparation of a similar compound *via* arylcuprate 1,4-addition to a methylenecyclopentanone, see: A. B. Smith, III, B. A. Wexler and J. S. Slade, *Tetrahedron Lett*., 1980, **21**, 3237–3240.