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Stereospecific Photochemical Ring Expansion of Lithiated Benzamides

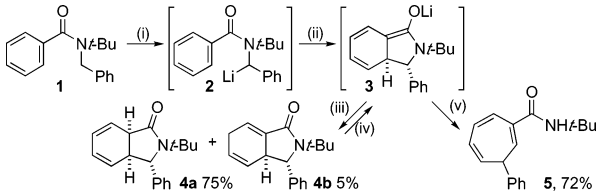
Jonathan Clayden,* Faye E. Knowles, and Christel J. Menet
Department of Chemistry, University of Manchester, Oxford Road, Manchester, M13 9PL, U.K.

Received April 28, 2003; E-mail: j.p.clayden@man.ac.uk

The six carbon atoms of a benzenoid aromatic ring can be a valuable resource for constructing more complex, nonaromatic targets,[1] and photochemistry[2] has a good track record as a tool for breaking open the aromatic sextet. In this Communication, we reveal a mild new photochemical reaction which, by means of base and a simple halogen spotlamp, achieves the stereospecific transformation of tertiary benzamides into a range of seven-membered cyclic trienes and dienones, or their norcaradiene analogues.

As we have previously shown, the extended enolate **3** may be made by lithiating **1** to form organolithium **2** in the presence of HMPA.[3] Protonation of **3** yields the dearomatized tetrahydroisoindolinones **4** in 80% yield (Scheme 1). However, when the enolate

Scheme 1. A Cycloheptatriene from a Benzamide[a]

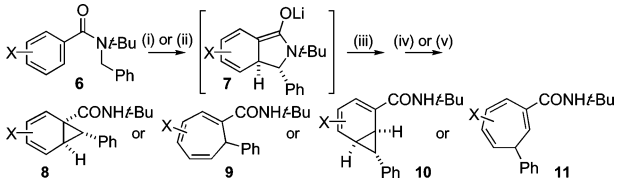


[a] Reagents: (i) *t*-BuLi, HMPA, −78 °C; (ii) −78 °C, 16 h; (iii) NH_4Cl; (iv) LDA, THF, 0 °C; (v) *hν*, >500 nm, 500 W, 3 h.

3 (which can be re-formed from **4** with LDA) was cooled to −78 °C and the resulting red solution was placed under a 500 W tungsten-filament halogen lamp, a rearrangement took place over a period of 3 h. Workup gave the cycloheptatriene **5** in 72% yield, an overall insertion of the *N*-benzyl group of **1** between the ortho and meta carbons of its aromatic ring.

Similar treatment of other *N*-benzylbenzamides **6**[4] led to related, but not always identical, rearrangements (Scheme 2). A range of

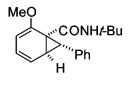
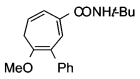
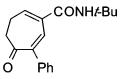
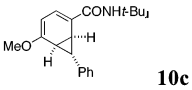
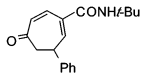
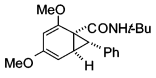
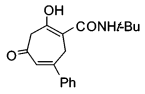
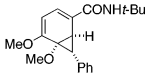
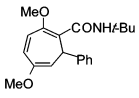
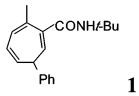
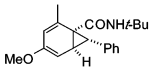
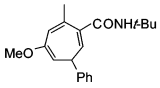
Scheme 2. Rearrangement of Lithiated Benzamides[a]



[a] Reagents: (i) LDA, THF, 0−20 °C, 2 h; (ii) *t*-BuLi, HMPA, THF, −78 °C, 16 h; (iii) *hν*, 500 nm, 500 W, −78 °C, 3 h; (iv) NH_4Cl (aq); (v) HCl (aq).

enolates **7** were irradiated, and the outcomes are collected in Table 1. The four classes of products **8**−**11** fall into two pairs of regioisomers, each pair related by a disrotatory thermal electrocyclization. Presumably, the lithium salts of norcaradienes **8** or **10** are the initial products in all cases, but ring opening on workup or before may give the cycloheptatrienes **9** or **11**. Aqueous acid, which hydrolyzes enol ether products to ketones, can promote formation of cycloheptatrienones. Whether the isolated product has the regiochemistry of **8** or **10** also depends on workup conditions (acid gives **11** not only from **10** but from **8** as well) but principally on ortho substitution in the starting amide (thus **6a**, **6d**, and **6h** give **8**, while **6c** and **6e** give **10**).

Table 1. Dearomatizing Ring Expansions of Benzamides

Entry	S.M.	X =.	Protocol	Product	Yield
1	**6a**	2-MeO	(i), (iii), (iv)	 **8a**	80
2	**6b**	3-MeO	(ii), (iii), (iv)	 **11b**	63
3	**6b**	3-MeO	(ii), (iii), (v)	 **11b'**	54
4	**6c**	4-MeO	(i), (iii), (iv)	 **10c**	73[a] 69[b]
5	**6c**	4-MeO	(i), (iii), (v)	 **11c**	73
6	**6d**	2,4-di-MeO	(ii), (iii), (iv)	 **8d**	33
7	**6d**	2,4-di-MeO	(ii), (iii), (v)	 **11d**	21
8	**6e**	3,4-di-MeO	(i), (iii), (iv)	 **10e**	75
9	**6f**	2,5-di-MeO	(ii), (iii), (iv)	 **9f**	24
10	**6g**	2-Me	(i), (iii), (iv)	 **11g**	72
11	**6h**	2-Me-4-MeO	(ii), (iii), (iv)	 **8h**	48
12	**6h**	2-Me-4-MeO	(ii), (iii), (v)	 **11h**	47

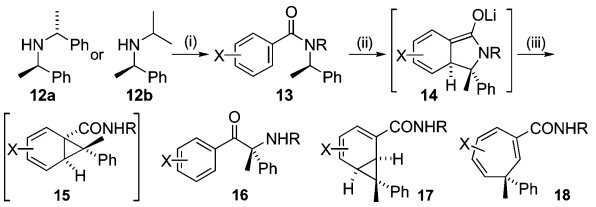
[a] Structure proved by X-ray diffraction. [b] With **12**Li as base (78% ee).

Introducing chirality into the starting materials or producing the enolate intermediates of the rearrangements enantioselectively both offered new opportunities for the asymmetric synthesis of chiral 6,3- and 7-ring systems and illuminated some features of the rearrangement's mechanism. Enantiomerically enriched (78% ee[5]) enolate **7c** (formed by cyclization of **6c** with lithiated **12b**) rearranged to the norcaradiene **10c** in 69% yield and with 74% ee, showing that the photochemical rearrangement of **7** to **9** can be stereospecific. Stereospecificity is also evident in the rearrangement

10.1021/ja035827i CCC: $25.00

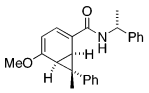
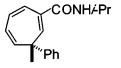
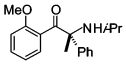
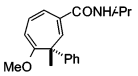
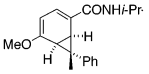
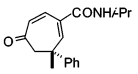
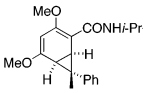
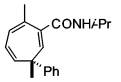
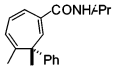
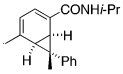
of amides derived from chiral amines **12a** and **12b** (Scheme 3 and Table 2). **17a** is formed as a single diastereoisomer from **13a**, and

Scheme 3. Rearrangement of Chiral Benzamides[a]



[a] Reagents: (i) ArCOCl, Et_3N, CH_2Cl_2; (ii) *t*-BuLi, DMPU, −78 to +20 °C; (iii) *hν*, >500 nm, 500 W, −78 °C, 3 h, then NH_4Cl.

Table 2. Stereospecific Ring Expansions of Chiral Benzamides

Entry	S.M.	R =	X =.	Product	Yield	ee
1	**13a**		4-MeO	 **17a**	52	>98[a]
2	**13b**	*i*-Pr	–	 **18b**	80	>99
3	**13c**	*i*-Pr	2-MeO	 **16c**	55	n/d
4	**13d**	*i*-Pr	3-MeO	 **18d**	20	90
5	**13e**	*i*-Pr	4-MeO	 **17e**	94	>99
6	**13e**	*i*-Pr	4-MeO	 **18e**	94	n/d
7	**13f**	*i*-Pr	2,4-di-MeO	 **17f**	53	92
8	**13g**	*i*-Pr	2-Me	 **18g**	49	80
9	**13h**	*i*-Pr	3-Me	 **18h**	40	92
10	**13i**	*i*-Pr	4-Me	 **17i**	85	86

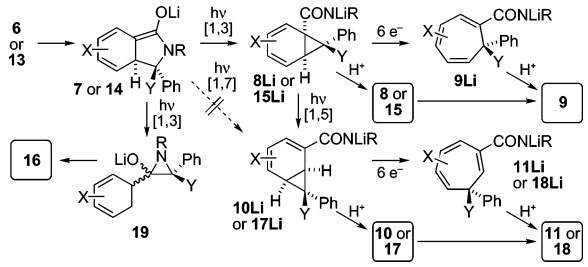
[a] Diastereoisomeric excess.

the enantiomeric purity of amides formed by acylation of **12a** is also largely preserved throughout the cyclization−rearrangement sequence. Norcaradienes **17** or cycloheptatrienes **18** were formed in up to 94% yield, but in no case was **15** or its cycloheptatriene isomer (analogous to **8** and **9**) isolated, even from ortho-substituted amides **13c** and **13f**. A rearrangement not seen with **6**, giving the ketone **16c**, was observed with **13c**.

The lowest measured product ee was 80%: stereospecificity persists through the deprotonation, cyclization,[6] and rearrangement steps. Overall, transformation of **13** to **17** or **18** amounts to a remarkable stereospecific insertion of a chiral carbenoid into the aromatic structure of the benzene ring.

The relative stereochemistry of the products[7] was proved by a combination of X-ray crystallography and NOE studies and, in most cases,[8] is consistent with rearrangement via stereospecific photochemical sigmatropic rearrangements of the enolates **7** and **14**, whose UV−visible spectra show absorptions in the region of 550 nm. Scheme 4 shows a proposed mechanistic pathway. Photochemical [1,3]-sigmatropic rearrangement (suprafacial and retentive)[9] of **7** or **14** gives norcaradiene **8**Li or **15**Li, or aziridine **19** whose protonation with ring opening yields **16**. From **8**Li or **15**Li, rearrangement may continue, forming **10**Li or **17**Li by 1,5-sigmatropic rearrangement,[10] presumably photochemical, because this then allows the observed stereochemistry to be formed by an invertive suprafacial migration.[11] Protonation of **8**Li, **10**Li, **15**Li, or **17**Li yields norcaradienes **8**, **10**, **15**, or **17**; six-electron disrotatory ring opening and protonation or hydrolysis (in either order) yields cycloheptatrienes **9**, **11**, or **18**.

Scheme 4. Mechanism of the Rearrangements



We are currently applying this reaction of extreme practical simplicity ((1) base, (2) halogen lamp) to the synthesis of further cyclopropane and cycloheptenone targets.

Acknowledgment. We are grateful to the EPSRC, Aventis CropScience, and GlaxoSmithKline for studentships, to Pfizer and AstraZeneca for unrestricted support, and to Dr. Darren Mansfield and Dr. Ian Baldwin for helpful discussions.

Supporting Information Available: Characterization data for rearrangement products; X-ray crystallographic data for **10c** (PDF and CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) Clayden, J.; Knowles, F. E.; Menet, C. J. *Tetrahedron Lett.* **2003**, *44*, 3397.
(7) The absolute stereochemistry of **16**−**18** is deduced from the retentive stereospecificity of the cyclization of **13e**: see ref 6.
(8) Protonation of the enolate **7** derived by cyclization of **6a** indicates that it is formed as a mixture of diastereoisomers, so at least in this case the rearrangement must be stereoselective and not simply stereospecific.
(9) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: New York, 1976, Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Academic Press: New York, 1970. This rearrangement can be viewed as a reverse aza-vinylcyclopropane rearrangement (Hudlicky, T.; Reed, J. W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 899. Cloke, J. B. *J. Am. Chem. Soc.* **1929**, *51*, 1174. Cloke, J. B.; Maginnity, P. M. *J. Am. Chem. Soc.* **1951**, *73*, 49. Ellis, M. C.; Stevens, R. V. *Tetrahedron Lett.* **1967**, 5185). For other photochemical N → C rearrangements, see: Archier-Jay, D.; Besbes, N.; Laurent, A.; Laurent, E.; Lesniak, S.; Tardivel, R. *Bull. Soc. Chim. Fr.* **1989**, 537. Amougay, A.; Letsch, O.; Pete, J.-P.; Piva, O. *Tetrahedron* **1996**, *52*, 2405. Becker, H.-D.; Skelton, B. W.; White, A. H. *Aust. J. Chem.* **1983**, *36*, 2073.
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(11) Such rearrangements are notoriously disrespectful of the Woodward−Hoffmann rules, see: Klärner, F.-G. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 268. Baldwin, J. E.; Broline, B. M. *J. Am. Chem. Soc.* **1974**, *96*, 2857.

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