Pergamon

Tetrahedron Letters 42 (2001) 2245–2248

TETRAHEDRON LETTERS

Competitive 3+2 and 2+2 cycloadditions of ester stabilized azaallyl anions to benzynes. Ring expansion of initial 3+2 products to isoquinolin-3-ones

Helmi Hussain, Ebrahim Kianmehr and Tony Durst*

Department of Chemistry, University of Ottawa, Ottawa, Canada K1N 6N5

Received 11 December 2000; revised 19 January 2001; accepted 22 January 2001

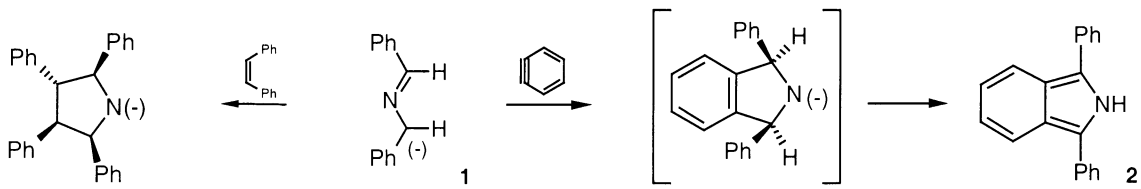
Abstract—Reaction of the azaallyllithiums derived from imines of α-amino esters with benzynes results in the formation of 1,3-dihydroisoindoles and 4-hydroxyisoquinolines via 3+2 and 2+2 cycloadditions, respectively. The initially formed 1-carboethoxy-1,3-dihydroisoindoles rearrange under basic reaction conditions to form 3-(2*H*)-isoquinolinones. © 2001 Published by Elsevier Science Ltd.

Cycloaddition of the 1,3-diphenyl-2-azaallyl anion **1** with reactive double and triple bonds was studied carefully in the 1970s as an example of an anionic 3+2 Woodward–Hoffmann symmetry controlled reaction.[1]

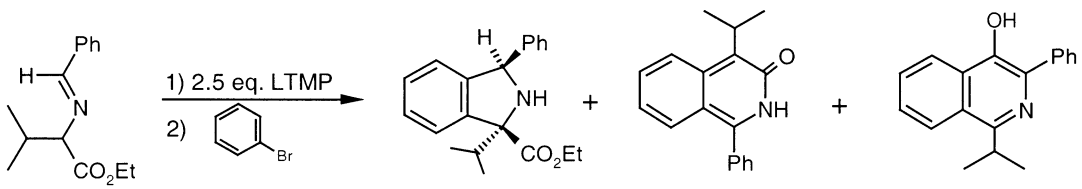
In a review of this topic, Kauffmann[2] cited an unpublished observation that reaction of **1** with benzyne resulted in the formation of 1,3-diphenylisoindole, **2**, presumably via initial formation of the corresponding 1,3-dihydroindole (Scheme 1). To the best of our knowledge, no subsequent reports of this reaction have appeared.

As part of our interest in the addition of nucleophiles to benzynes generated from bromo- or iodobenzenes with LTMP,[3a,b] we have examined the reaction of a number of azaallyllithium species **3** with several benzynes. These reactions led to the formation of a fascinating series of products that we interpreted as emanating from competitive 3+2 and 2+2 cycloaddition reactions followed by rearrangements. The precursors of **3** are readily derived from the reaction of α-amino esters with a variety of aldehydes.

Typically, addition of imines **4** to slightly more than 2 equiv. of LTMP in THF at −78°C followed by addition



Scheme 1.

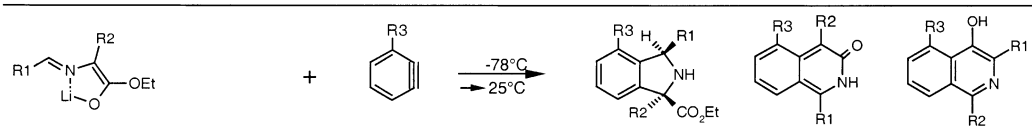


4a **5a, (38%)** **6a, (17%)** **7a, (14%)** (1)

* Corresponding author.

0040-4039/01/$ - see front matter © 2001 Published by Elsevier Science Ltd.
PII: S0040-4039(01)00130-7

Table 1. Reaction of azaallyllithium **3** with benzynes

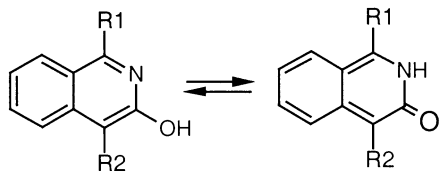


	5	6	7
a) R_1=Ph, R_2=CH(CH_3)$_2$, R_3=H	38	17	14
b) R_1=Ph, R_2=CH_3, R_3=H	8	43	13
c) R_1=Ph, R_2=CH(CH_3)$_2$, R_3=CH_3O	4	16	10
d) R_1=Ph, R_2=CH_3, R_3=CH_3O	-	22	12
e) R_1=p-$MeOC_6H_4$, R_2=CH(CH_3)$_2$, R_3=H	16	48	-
f) R_1=p-$MeOC_6H_4$, R_2=CH(CH_3)$_2$,R_3=CH_3O	-	22	13
g) R_1=PhCH=CH-, R_2=CH(CH_3)$_2$, R_3=H	6	19	10
h) R_1=CH_3CH=CH-, R_2= CH(CH_3)$_2$, R_3=H	35	12	-
i) R_1=c-C_6H_{11}, R_2=CH_3,R_3=H	30	-	-
j) R_1=p-(CH_3)$_2$$NC_6H_4$, R_2=CH(CH_3)$_2$, R_3=H	22	53	-

of bromobenzenes and subsequent warming to room temperature, led to formation of two or three isolable products. In the specific example shown in Eq. (1), imine **4a**, derived from (L)-valine methyl ester and benzaldehyde, was converted into the 1,3-dihydroisoindole, **5a**, 1-phenyl-4-isopropyl-3(2*H*)-isoquinolinone, **6a**, and 1-isopropyl-3-phenyl-4-hydroxyisoquinoline, **7a**, in 38, 17 and 14% isolated yields, respectively.[4] Similar results were obtained with the benzalimine of (L)-ethyl alanine. These results, and those of the reaction with related lithiated imines with benzyne and 3-methoxybenzyne (1–2 mmol scale), are summarized in Table 1.[4]

The 1,3-dihydroisoindoles **5** were always obtained as single stereoisomers as shown by NMR. The relative stereochemistry, a *cis* relationship between the 1-carboethoxy group and the 3-aryl or alkyl substituent, is consistent with a concerted cycloaddition between the benzynes and the azaallyllithium species, **3**, which allows lithium complexation to both oxygen and nitrogen.[5] This stereochemistry was verified in the case of **5e** by a single-crystal X-ray structure determination[6] (Fig. 1). The isoindole 2-carboxylates, available in a stereochemically defined form, represent new novel proline analogs.

The assignment of structure **6b**, the most polar of the three products, was problematic due to seemingly contradictory spectroscopic evidence. The ^{13}C NMR spectrum of **6b** showed a low field peak at $\delta = 207$ ppm, consistent with a ketone carbonyl carbon.[7] However, the only IR absorption assignable to a carbonyl group stretching frequency occurred at 1594 cm^{-1}, significantly lower than expected for an unsaturated ketone. The observed IR frequency is plausible for a highly conjugated amide, but the ^{13}C peak is far downfield from the typical amide carbon.[7] In the end, the structures of series of this compounds was secured by a single-crystal X-ray structure determination of **6b**, 1-phenyl-4-methyl-3(2*H*)-isoquinolone,[8] (Fig. 2),[6] and a comparison of the spectroscopic properties of **6b** with those of the other compounds in this series. All showed the unusually low ^{13}C NMR amide carbonyl resonance in the 192–207 ppm range. The C–C bond lengths in the carbocyclic ring of **6b** vary from 1.35 to 1.43 Å as required by the *o*-quinonoid structure. The preferred existence of these compounds as 3(2*H*)-isoquinolinones **6** rather than the tautomeric 3-hydroxyisoquinolines **8** has been noted previously.[9]



The relative stability of structures of type **6** versus **8** is reported to be highly dependent on the solvent and the nature of the substituents at C(1) and C(4).[9] Derivatives of 3(2*H*)-isoquinolinone have been reported to show diverse biological effects including antidepressant, cardiotonic and analgesic activity.[10,11]

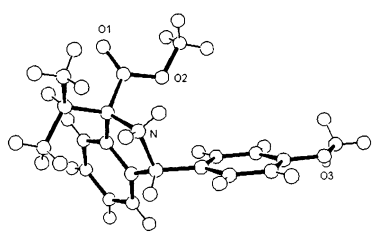


Figure 1. X-Ray structure of **5e**.

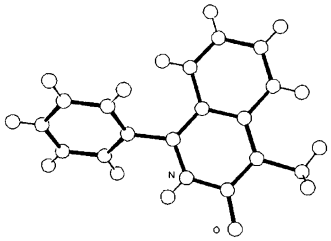


Figure 2. X-Ray structure of **6b**.

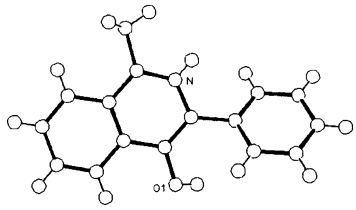
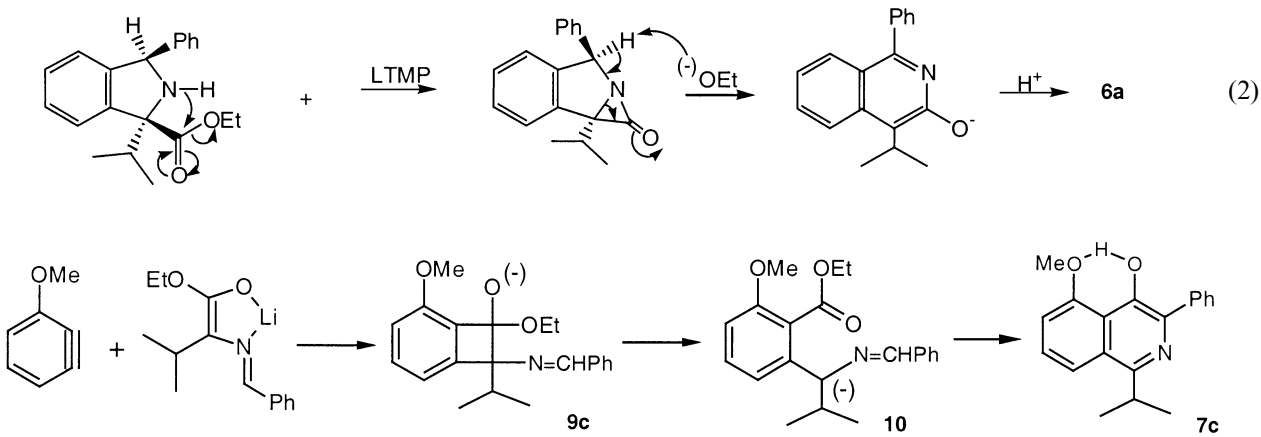


Figure 3. X-Ray structure of **7b**.



Scheme 2.

The 3(2*H*)-isoquinolinones are rearrangement products derived by prolonged exposure of the corresponding 1,3-dihydroindoles with base at temperatures above 0°C. A plausible mechanism for the conversion of **5a**[12] to **6a** is shown in Eq. (2). This observation allows one to design reaction conditions which favor the formation of either **5** or **6**. For example, when the reaction of **4h** with benzyne was quenched after 3 h of reaction time at −78°C, the dihydroisoindole **5h** was obtained in 66% yield; no **6h** was observed. This compares with the results shown in Table 1 where the reaction mixtures were quenched after warming to 25°C; 3(2*H*)-isoquinolinones were generally the major product under these conditions.

We propose that the 4-hydroxyisoquinolines **7**, including **7c**, are the result of an initial 2+2 cycloaddition involving the ketene acetal-like double bond (Scheme 2). The formation of a benzocyclobutene intermediate, such as **9**, could occur via a concerted or a stepwise sequence. Ring opening of alkoxybenzocyclobutene is known to be rapid even at very low temperature.[13] Such ring opening in **9** leads to the azaallyl intermediate **10**, which is set for cyclization and subsequent aromatization to **7c**. The structure of these compounds and the regiochemistry of the 2+2 cycloaddition to 3-methoxybenzyne was proven by NMR experiments and a subsequent X-ray structure determination of **7b**[6,14] (Fig. 3). The hydroxyl group in **7a**, **b**, and **e** occurred as a broad signal at ca. $\delta = 5.6$ ppm. In contrast, in **7c**, **d**, and **f** the absorption for this peak was a sharp singlet near $\delta = 9.5$ ppm due to intramolecular hydrogen bonding with the *peri*-methoxy group at C(5). The regiochemistry observed in **7c** is consistent with, but does not demand, a stepwise process for the formation of **9** from **3c** and 3-methoxybenzyne.

Acknowledgements

Financial support of the NSERC (Canada) is greatly appreciated. The authors also thank Dr. Sasmita Triphathy for valuable discussions.

References

1. Woodward, R. B.; Hoffmann, R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 781.
2. Kauffmann, T. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 627.
3. (a) Tripathy, S.; Leblanc, R.; Durst, T. *Org. Lett.* **1999**, *1*, 1973; (b) Tripathy, S.; Hussain, H.; Durst, T. *Tetrahedron Lett.* **2000**, *41*, 8401.
4. All compounds reported were characterized by ^{1}H and ^{13}C NMR (200 and 500 MHz), IR and MS including HRMS.
5. Barr, D. A.; Dorrity, M. S.; Grigg, R.; Malone, J. F.; Montgomery, J.; Rajviroongit, S.; Stevenson, P. *Tetrahedron Lett.* **1990**, *31*, 6569 and references cited therein.
6. X-Ray structure determinations were carried out by Dr. G. Yap. Details will be given in an upcoming full paper.
7. Silverstein, R. M.; Webster, F. X. *Spectrometric Identification of Organic Compounds*; John Wiley & Sons: New York, 1998.

8. NMR (500 MHz, $CDCl_3$) of **6b**. ^1H δ: 2.42 (s, 3H), 7.27 (ddd, $J=6.8$, 6.7, 1.0 Hz, 1H), 7.45–7.63 (m, 6H), 7.81 (d, $J=8.4$ Hz, 1H), 7.90 (d, $J=8.6$ Hz, 1H), 10.35 (bs, 1H); ^{13}C δ: 10.3, 106.9, 121.6, 122.6, 123.1, 127.6, 128.1, 128.3, 129.8, 138.7, 138.9, 155.7, 157.0, 206.0.
9. (a) Suzuki, H.; Abe, H. *J. Org. Chem.* **1994**, *59*, 6116; (b) For a review, see: Suzuki, H.; Abe, H. *Adv. Heterocyclic Chem.* **1990**, *52*, 156.
10. Wu, M.-J.; Chang, L.-J.; Wei, L.-M.; Lin, C.-F. *Tetrahedron* **1999**, *55*, 13193.
11. Hazai, L. *Advances in Heterocyclic Chemistry*; Academic Press: New York, 1991; Vol. 52, p. 155.
12. NMR (200 MHz, $CDCl_3$) of **5a**. ^1H δ: 0.73 (d, $J=6.6$ Hz, 3H), 1.01 (d, $J=6.6$ Hz, 3H), 1.34 (t, $J=7.17$ Hz, 3H), 2.60 (sept., $J=6.63$ Hz, 1H), 3.14 (s, 1H), 4.22–4.35 (m, 2H), 5.42 (s, 1H), 6.93 (d, $J=7.10$ Hz, 1H), 7.18–7.34 (m, 7H), 7.59 (d, $J=7.14$ Hz, 1H); ^{13}C δ: 14.9, 16.8, 18.5, 38.1, 62.3, 69.5, 78.9, 123.9, 124.0, 128.1, 128.3, 128.6, 129.0, 129.3, 142.4, 145.0, 145.7, 175.5.
13. (a) Fitzgeraid, J. J.; Pagano, A. R.; Sakoda, V. M.; Olofson, R. A. *J. Org. Chem.* **1994**, *59*, 4117; (b) Choy, W.; Yang, H. *J. Org. Chem.* **1988**, *53*, 5796.
14. NMR (500 MHz, $CDCl_3$) of **7b**. ^1H δ: 2.12 (s, OH), 2.88 (s, 3H), 7.23 (t, $J=7.3$ Hz, 1H), 7.36 (t, $J=7.5$ Hz, 2H), 7.56 (t, $J=7.5$ Hz, 1H), 7.64 (t, $J=7.5$ Hz, 1H), 7.68 (d, $J=7.3$ Hz, 2H), 8.0 (d, $J=8.3$ Hz, 1H), 8.21 (d, $J=8.3$ Hz, 1H); ^{13}C δ: 22.0, 122.9, 126.0, 127.6, 128.3, 128.5, 129.2, 129.5, 129.6, 129.8, 135.5, 137.7, 143.6, 150.6.