INTRAMOLECULAR DIELS-ALDER REACTION OF BENZYNES: A NOVEL STRATEGY FOR THE CONSTRUCTION OF TETRAHYDROBENZAZEPINE SKELETONS

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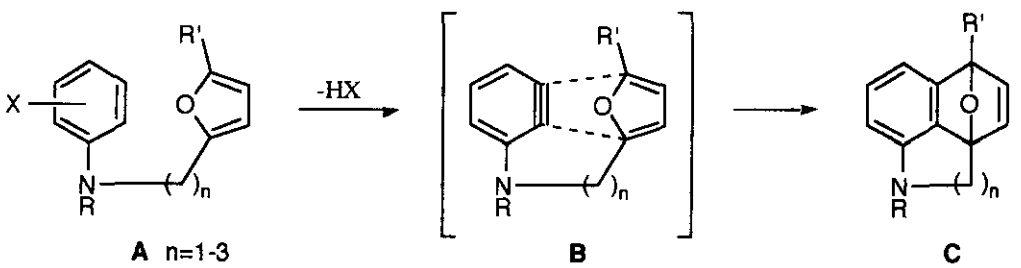
Abstract—Intramolecular Diels-Alder reaction of benzynes, generated from ortho-haloaniline derivatives by the action of lithium 2,2,6,6-tetramethylpiperidide, with furans has been developed as a novel route for the construction of tetrahydro-benzazepine skeletons.

There is considerable current interest in the intramolecular Diels-Alder (IMDA) strategy for the construction of polycyclic molecules and several important developments have been achieved in this area.[1] Although it has been well recognized that benzynes are one of the most reactive dienophiles and widely utilized for Diels-Alder reactions,[2] there are only few reports of IMDA reactions where benzynes serve as useful dienophiles.[3] In this paper we would like to describe a novel method for preparing tetrahydrobenzazepine skeletons (**C**, n=3)[4] by using the IMDA reaction between a benzyne **B** and a furan as generally outlined in Scheme 1

Scheme 1



Our initial attempts under a variety of conditions using **A** (n=1) to provide indole skeletons **C** (n=1) failed completely due to the significant decomposition of the substrates. Although we could not determine their structures, it might be concluded that the difficulty might be ascribed to the ready fragmentation of a furan functionality *via* deprotonation at the allylic position.[5, 6] Since no efficient means to obtain some other homologs

Scheme 2

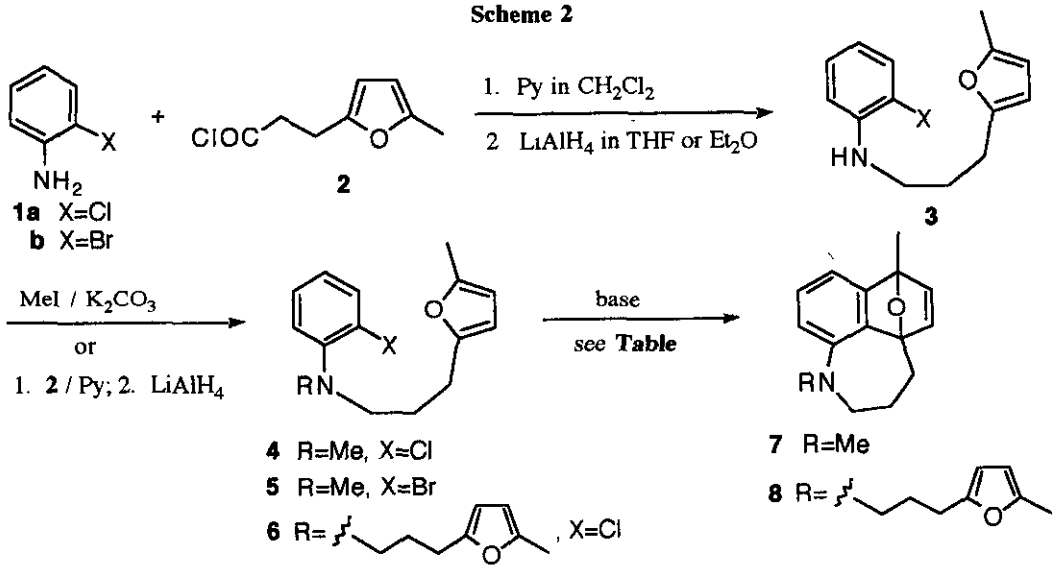


Table. Intramolecular Diels-Alder Reactions of **4**, **5**, and **6**

Run	Substrate	Reaction Conditions	Product	Yield, %[a]
1	**4**	n-BuLi (4 equiv), THF, -78 °C → room temperature, 24 h	**7**	10
2	**4**	LDA (4 equiv.), THF, -40 °C → room temperature, 20 h	**7**	40
3	**4**	LiTMP (4 equiv.), THF, -78 °C → room temperature, 24 h	**7**	49
4	**5**	$NaNH_2$ (5 equiv.), THF, room temperature, 20 h	no products	
5	**5**	$NaNH_2$ (5.5 equiv.)-NaO-t-Bu (1.1 equiv.), THF, 60 °C, 60 h	no products	
6	**5**	$NaCH_2SOMe$ (3.5 equiv), DMSO, 100 °C, 16 h	**7**	<5
7	**6**	n-BuLi (3 5 equiv.), THF, -78 °C → room temperature, 24 h	no products	
8	**6**	LDA (3.5 equiv.), THF, -40 °C → room temperature, 20 h	**8**	29
9	**6**	LiTMP (3.5 equiv.), THF, -78 °C → room temperature, 24 h	**8**	34

a) Isolated yields after purification by preparative tlc.

A (n=2) could be found, we then turned our attention to prepare **A** (n=3) to realize the above mentioned IMDA strategy, while these compounds possess a rather longer side chain.

Considering the availability of starting materials and the simplicity for benzyne formation, the compounds (**4-6**) were elected as target molecules. The synthetic route was straightforward as shown in Scheme 2. Condensation of *o*-chloro- or *o*-bromoanilne (**1a** or **1b**) with 2-(5-methylfuryl)propanoyl chloride (**2**)[7] followed by reduction with $LiAlH_4$ gave **3**, which was further transformed into **4** and **5** by methylation with MeI/K_2CO_3 in almost quantitative yields. Alternatively, compound (**6**) was also prepared from **3** by successive treatment with **2** and $LiAlH_4$ in high yield.

With the required substrates (**4-6**) were in hand, the stage was set for the IMDA reactions. The effect of a variety of bases to generate benzyne intermediates was determined as summarized in the Table. Apparently, the use of lithium amide in THF for dehydrochlorination (Runs 2, 3, 8, and 9) is superior to a combination of either sodium amide or NaH-DMSO and bromide (**5**) (Runs 4-6). Optimum results (34-49% yields) of benzyne adducts were accomplished when a THF solution of the substrate (**4**) or (**6**) was slowly added to the cold (-78 °C) solution of 3.5-4 equiv. of lithium 2,2,6,6,-tetramethylpiperidide (LiTMP)[8] in THF (Runs 3 and 9) Usually, the mixture was allowed to warm to room temperature and stirred overnight to complete the cycloaddition reaction.

The structures of **7**,[9] mp 83.5-84.5 °C, and **8**[10] were clearly confirmed by the ^1H nmr analyses. For example, the formation of **7** can be explained by large downfield shifts of the furan-H resonances from δ 5.70 (2H, s) to δ 6.19 (1H, d, *J*=8 Hz) and 6.65 (1H, d, *J*=8 Hz) during the reaction, consistent with the formation of a 1,4-dihydro-1,4-epoxynaphthalene skeleton. In addition, the methyl signal on a furan ring (δ 2.20) was appeared in a higher field (δ 1.74).

Contrary to our expectation, the difunctional compound (**6**) gave a rather decreased yield compared with **4** (Run 9). This maybe arise from the relative instability of the adduct formed. In fact, adducts (**7**) and (**8**) were rather sensitive to the air and slowly decomposed on standing at room temperature.

The successful preparation of tetrahydrobenzazepine derivatives (**7**) and (**8**) in this study established the utility of IMDA approach to derive such a complex molecule. Work to extend these discoveries to the other polycyclic systems are in progress.

ACKNOWLEDGMENT

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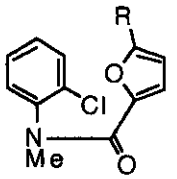
6 Instead, the use of the following compounds for the IMDA reactions was also fruitless.



R = $SiMe_3$ or NO_2

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9. Compound **7**: Ir (Nujol) 1600, 1585, 1565, 1490, and 1450 cm^{-1}; ^1H nmr (CCl_4) δ 1 74 (3H, s), 1.8-2.4 (4H, m), 2.84 (3H, s), 3.0-3.4 (2H, m), 6.19 (1H, d, *J*=8 Hz), 6.65 (1H, d, *J*=8 Hz), 6 4-6.8 (3H, m).

10. Compound **8**: viscous oil; ir (Neat) 1600, 1575, 1490, and 1450 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.83 (3H, s), 1.4-2.4 (6H, m), 2 23 (3H, s), 2.63 (2H, t, *J*=7.5 Hz), 3.0-3 4 (4H, m), 5.83 (2H, s), 6.37 (1H, d, *J*=8 Hz), 6.77 (1H, d, *J*=8 Hz), 6.5-6.9 (3H, m); ms (rel intensity; 70 eV) *m/z* 335 (M^+, 92), 309 (67), 226 (100), 95 (62).

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