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Syntheses of 2-arylated 1-benzazocines via Beckmann rearrangement

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Abstract—One-step and highly efficient syntheses of 2-aryl-1-benzazocines via Beckmann rearrangement of 5*H*-benzocyclohepten-5-one oxime mesylates in dry toluene was described, in which aryl Grignard reagents were used for the first time to induce Beckmann rearrangement directly without any additional protic agents. Iodotrimethylsilane was also employed to promote Beckmann rearrangement of the mesylates, followed by the treatment of the intermediate imidoyl iodide with phenylmagnesium bromide to complete the synthesis of benzazocines.

Azocines (azacyclooctatetraenes) have received much attention because of their increasing usefulness, both as synthetic intermediates and therapeutic agents.[1] Most of the evidence available regarding the difficulties associated with the formation of an eight-membered ring comes from the preparative studies. Thus, the search for synthetic methods for the preparation of such systems has been a major objective all the time.[2] Many methods utilized to prepare such systems, especially the highly unsaturated azocines, are specific and often consist of a single example.[3] 2-Methoxy[4,5] and 2-ethoxyazocines[6] (Fig. 1) seem to be the only reported synthetic examples of the fully unsaturated azocines. The methoxy or ethoxy groups at the 2-position of azocines were formed by O-alkylation of the corresponding lactams, the traditional products of Beckmann rearrangement, with the Meerwein's reagents (trialkyloxonium fluoroborate).

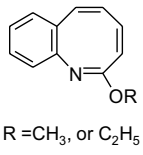

Figure 1.

We now wish to present here our exploratory work on the development of a general and convenient synthesis of 2-aryl substituted benzazocines without the lactam stages, in which the chemistry of Beckmann rearrangement was developed by the use of aryl Grignard reagents (Fig. 2).

Beckmann rearrangement is a powerful method for the preparation of amides from the corresponding ketoxime in organic synthesis; however, this generally requires high reaction temperature and large amount of strong Brönsted acid. The use of excessive amount of such chemicals, the large amount of by-products, and the corresponding problem of corrosion make this process environmentally questionable.[7] In order to overcome these problems, we chose the aprotic medium for the Beckmann rearrangement.

As oxime derivatives, oxime sulfonates could be used preferentially because of their ready availability from

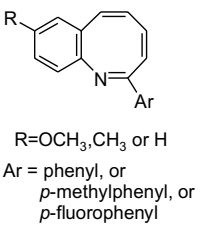

Figure 2.

Keywords: 2-Arylated 1-benzazocines; Beckmann rearrangement; Aryl Grignard reagents.
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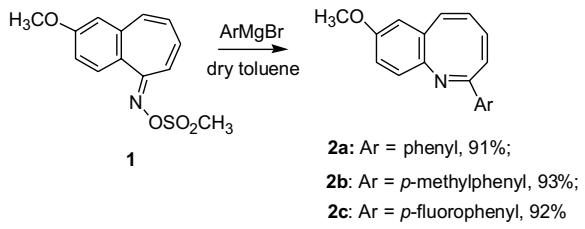
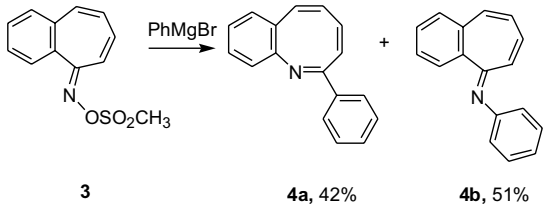
oxime using *p*-toluenesulfonyl chloride or methanesulfonyl chloride and high enough reactivity to initiate Beckmann rearrangement. In case of unstable oxime tosylates,[8] the corresponding mesylates were obtained in almost quantitative yields. When 2-methoxy-5*H*-benzocyclohepten-5-one oxime mesylate (**1**) in dry toluene[9] was treated directly with PhMgBr at −20 °C under an argon atmosphere, Beckmann rearrangement occurred. The eight-membered ring compound, 8-methoxy-2-phenyl-1-benzazocine (**2a**), was isolated and recrystallized from petroleum ether in 91% yield. Compound **2a** was a tub-like molecule analyzed by NMR and X-ray.[10] This reaction proceeded under mild conditions in nonpolar aprotic media and can be repeated well (Scheme 1). The same rearrangement results were obtained by trying the other aryl Grignard reagents, such as *p*-methylphenylmagnesium bromide (*p*-MePhMgBr) and *p*-fluorophenylmagnesium bromide (*p*-FPhMgBr). 8-Methoxy-2-(*p*-methylphenyl)-1-benzazocine (**2b**) and 8-methoxy-2-(*p*-fluorophenyl)-1-benzazocine (**2c**) were obtained in 93% and 92% yields, respectively.



Scheme 1.



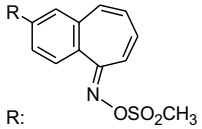
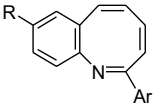
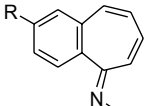
Scheme 2.

In our ongoing research toward Beckmann rearrangement promoted directly by ArMgBr, a series of experiments were carried out by varying the substituent of the substrates. When attempts were directed toward 2-phenyl-1-benzazocine (**4a**)[11] with the similar method, we surprisingly found that the reaction did not give the only one eight-membered ring product. A mixture of two products was formed instead. They were isolated by flash chromatography and the structures were identified by MS and NMR spectra. The desired benzazocine **4a** was obtained in 42% yield (Scheme 2). The other product was 2-methyl-*N*-(5*H*-benzocyclohepten-5-yilidene) aniline (**4b**),[12] an unrearranged seven-membered ring derivative, obtained in 51% yield. Unrearranged compounds were isolated from the Beckmann rearrangement for the first time, in which the nucleophilic reagents directly replaced the leaving groups of the substrates.

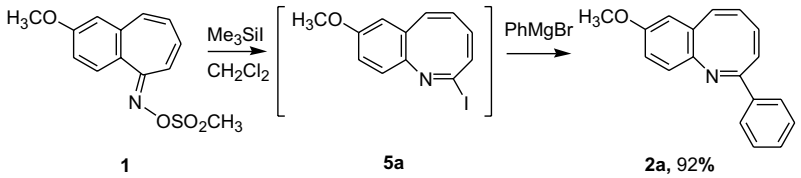
For the rearrangement to the corresponding benzazocines, the other experiments with *para*-substituted mesylates were carried out under the same conditions. The results are summarized in Table 1. Comparing the yields of eight-membered ring products of different substituted substrates, as for OCH_3, CH_3, and H, we found that the methoxy group made the biggest contribution to Beckmann rearrangement promoted by aryl Grignard reagents. Whatever the ArMgBr was, Beckmann arrangement of mesylate **1** gave the entire arrangement product in excellent yield (91–93%). Group CH_3 and H substituted substrates gave the mixture of rearranged and unrearranged products. When R was CH_3, the yield of eight-membered ring product was higher than when R was H with the same ArMgBr. The yield of unrearranged product was low accordingly. To the same nucleophilic reagent, such as *p*-MePhMgBr, the yields of the three products were 93% ($R = OCH_3$), 67% ($R = CH_3$), and 45% (R = H), respectively.

On the other hand, the higher yield of benzazocines was obtained by using the more active aryl Grignard reagents. The nucleophilic ability order was *p*-MePhMgBr > PhMgBr > *p*-FPhMgBr. When R was CH_3, for example, the yields of the three 2-arylated benzazocines were 67%, 65%, and 61%, respectively. The same

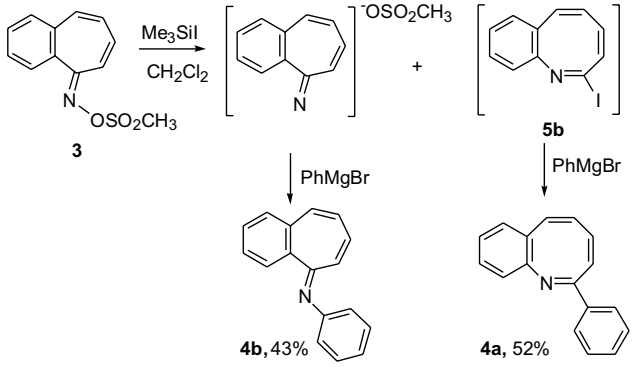
Table 1. Beckmann rearrangement of benzocyclohepten-5(*H*)-one oxime mesylates in dry toluene

Entry	R: 	ArMgBr	Yield[a] (%) 	Yield[a] (%) 
1	OCH_3	*p*-MePh	93	0
2	OCH_3	Ph	91	0
3	OCH_3	*p*-FPh	92	0
4	CH_3	*p*-MePh	67	27
5	CH_3	Ph	65	27
6	CH_3	*p*-FPh	61	30
7	H	*p*-MePh	45	49
8	H	Ph	42	51
9	H	*p*-FPh	40	54

[a] Isolated yields.



Scheme 3.



Scheme 4.

results were obtained by treating **3** with the three aryl Grignard reagents; the yields were 45%, 42%, and 40%. But it was the substituent of the substrate, not the nucleophilic reagent, that was the main factor of the reaction.

For this electrophilic reaction, more active nucleophilic reagent should be used to accomplish this transformation in higher yield. Imidoyl iodide is a highly intriguing class of activated amides in view of the ready susceptibility toward nucleophilic attack.[13] As reported by Hisashi Yamamoto and co-workers,[14] a few α-phenylated aliphatic amines were prepared by the Beckmann rearrangement of oxime derivatives with iodotrimethylsilane (TMSI) or diethylaluminum iodide, to give the intermediates imidoyl iodides and then phenylated by the use of PhMgBr. We considered that the syntheses of 2-arylated 1-benzazocines might be achieved with the same method. When **1** and **3** in $CDCl_3$ in NMR tube were treated, respectively, with TMSI at 25 °C for 10 min under an argon atmosphere, two ^1H NMR spectra were obtained. One ^1H NMR spectrum suggested that 8-methoxy-2-iodo-1-benzazocine (**5a**)[15] was in almost 100% transformation. The other spectrum indicated clearly to be a mixture of two compounds, 2-iodo-1-benzazocine (**5b**)[16] (~55%) and **4b** (~45%). The amounts were determined with the integral area of H signals suggested by the ^1H NMR spectrum. On treatment of the reactive intermediates with PhMgBr, the α-phenyl benzazocines derivatives were produced. The yields of **2a** and **4a** were 92% and 52%, respectively. The unrearranged compound **4b** was also isolated in 43% yield (Schemes 3 and 4).

In conclusion, we have successfully developed an easy and efficient method to furnish 2-arylated benzazocines through Beckmann rearrangement, prompted directly by aryl Grignard reagents in aprotic media. Different groups of the substrates resulted in the different products and different yields of the corresponding benzazocines. This was also confirmed by TMSI-promoted Beckmann rearrangement, although imidoyl iodide is a highly intriguing class of activated amides in view of the ready susceptibility toward nucleophilic attack. This would enrich the azocine systems both as synthetic intermediates and as therapeutic agents. This would be important for the development of the realization of nonaromatic character of azocine systems.

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9. Other solvents, such as THF, CH_2Cl_2, ethyl ether, and benzene, have been tried; toluene and benzene were the best media for the Beckmann rearrangement. This rearrangement almost did not occur in CH_2Cl_2.
10. A typical procedure: PhMgBr (0.5 mL of a 3 M ethereal solution, 1.5 mmol) was added to a solution of benzotropone oxime mesylate (**1**) (279 mg, 1 mmol) in dry toluene (5 mL) at −20 °C. The resulting solution was stirred at −20 °C for 30 min and at 0 °C for 1 h. The reaction was carried out under an argon atmosphere all the time. Water was used to quench the reaction, and the aqueous layer was separated and extracted with ether. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (elution with ethyl acetate/petroleum ether/diethyl amine 1:9:1, v/v). Compound **2a** (238 mg) was obtained as a yellow crystal from petroleum ether in 91% yield. Mp 87–89 °C ^1H NMR (500 MHz, $CDCl_3$): δ 3.79 (3H, s, OCH_3), 6.16 (1H, dd, $J = 4.2$, 12.0 Hz, H-5), 6.31 (1H, dd, $J = 4.2$, 11.5 Hz, H-4), 6.42 (1H, d, $J = 11.5$ Hz, H-3), 6.54 (1H, d, $J = 2.5$ Hz, H-7), 6.57 (1H, d, $J = 12.0$ Hz, H-6), 6.88 (1H, dd, $J = 2.5$, 8.5 Hz, H-9), 6.95 (1H, d, $J = 8.5$ Hz, H-10), 7.42 (2H, t, $J = 7.0$ Hz, H-3′, H-5′), 7.47 (1H, t, $J = 7.0$ Hz, H-4′), 7.93 (2H, dd, $J = 2.5$, 7.0 Hz, H-2′, H-6′); ^{13}C (125.7 MHz, $CDCl_3$): δ

55.40 (OCH_3), 113.38 (C-7), 114.34 (C-9), 123.60 (C-10), 127.91 (C-2′, C-6′), 128.34 (C-3′, C-5′, C-6a), 130.16 (C-3), 130.82 (C-4′), 131.20 (C-5), 132.69 (C-6), 134.98 (C-4), 137.80 (C-1′), 144.60 (C-10a), 156.09 (C-8), 167.50 (C-2); EI-MS (*m*/*z*, relative intensity) 261 (M^+, 100), 246 ([M^+-CH_3], 26), 230 ([M^+-OCH_3], 23), 184 ([$M^+-C_6H_5$], 9); EI-HRMS Calcd for $C_{18}H_{15}NO$: 261.1154. Found: 261.1157.

11. As a yellow solid, **4a** was unstable and decomposed very quickly to a colored tarry material when being exposed to the air at room temperature or when being heated for the melting point.
12. *N*-(5*H*-Benzocyclohepten-5-yilidene) aniline (**4b**). A yellow solid crystallized using petroleum ether. Mp 57–58 °C ^1H NMR (500 MHz, $CDCl_3$) δ 6.44 (3H, complex, H-6, H-7, H-8), 6.92 (2H, d, $J = 8.0$ Hz, H-2′, H-6′), 7.06 (1H, d, $J = 12.0$ Hz, H-9), 7.10 (1H, dd, $J = 7.5$, 8.0 Hz, H-4′), 7.36 (2H, dd, $J = 7.5$, 8.0 Hz, H-3′, H-5′), 7.46 (1H, d, $J = 7.5$ Hz, H-1), 7.53 (1H, dd, $J = 7.5$, 7.0 Hz, H-2), 7.59 (1H, dd, $J = 7.5$, 7.0 Hz, H-3), 8.27 (1H, d, $J = 7.0$ Hz, H-4); ^{13}C (125.7 MHz, $CDCl_3$) δ 120.08 (C-2′, C-6′), 123.62 (C-4′), 126.51 (C-8), 128.22 (C-6), 129.10 (C-3′, C-5′), 129.44 (C-4), 129.76 (C-2), 130.30 (C-3), 130.54 (C-7), 131.03 (C-1), 135.33 (C-9a), 136.52 (C-9), 138.35 (C-4a), 150.50 (C-1′), 163.96 (C-5); EI-MS (*m*/*z*, relative intensity) 231 (M^+, 61), 128 ([$M^+-C_6H_5CN$], 100); EI-HRMS Calcd for $C_{17}H_{13}N$: 231.1048. Found: 231.1044.
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15. General procedure for TMSI-promoted Beckmann rearrangement: To a solution of oxime mesylates **1** (1 mmol) in dry methylene chloride (10 mL) was added trimethylsilyl iodide (157 μL, 1.1 mmol) at 0 °C under an argon atmosphere. After the mixture was stirred at 15 °C for1 h and cooled to −20 °C, an ethereal solution of PhMgBr (1.5 mL of a 1 M solution, 1.5 mmol) was added at −20 °C. Then the mixture was stirred at this temperature for 1.5 h, poured onto saturated $NaHCO_3$ solution, and extracted with methylene chloride. The combined extracts were dried over Na_2SO_4, concentrated, and purified by flash column chromatography on silica gel (elution with ethyl acetate/petroleum ether/diethyl amine 1:9:1, v/v). Compound **2a** (240 mg) was obtained as a yellow crystal in 92% yield. 2-Iodo-1-benzazocin-8-OCH_3 (**5a**). ^1H NMR (500 MHz, $CDCl_3$) δ 3.83 (s, 3H), 6.10 (d, $J = 12.5$ Hz, 1H), 6.36 (dd, $J = 4.5$, 12.5 Hz, 1H), 6.68 (s, 1H), 6.71 (dd, $J = 4.5$, 12.5 Hz, 1H), 6.88 (d, $J = 12.5$ Hz, 1H), 6.97 (d, $J = 7.5$ Hz, 1H), 7.32 (d, $J = 7.5$ Hz, 1H).
16. 2-Iodo-1-benzazocine (**5b**). ^1H NMR (500 MHz, $CDCl_3$) δ 5.54 (dd, $J = 4.0$, 11.0 Hz, 1H), 6.09 (dd, $J = 4.0$, 11.5 Hz, 1H), 6.22 (d, $J = 12.5$ Hz, 1H), 6.60 (d, $J = 12.5$ Hz, 1H), 6.84 (d, $J = 8.0$ Hz, 1H), 6.91 (d, $J = 8.0$ Hz, 1H), 7.04 (t, $J = 8.0$ Hz, 1H), 7.20 (t, $J = 8.0$ Hz, 1H).