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Microwave-Enhanced Synthesis of N-Shifted Buflavine Analogues via a Suzuki–Ring-Closing Metathesis Protocol

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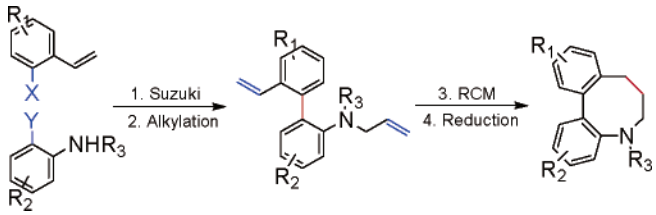
ABSTRACT



A novel, microwave-enhanced six-step synthesis was devised for the synthesis of N-shifted buflavine analogues. Microwave-enhanced Suzuki–Miyaura cross-coupling and ring-closing metathesis reactions were used as the key steps. Microwave irradiation was found to enhance the ring-closing metathesis reaction to generate the otherwise difficultly obtainable medium-sized ring system of the target molecules.

The apogalanthamine analogues represent an intriguing class of natural products belonging to the *Amaryllidaceae alkaloid* family.[1] They feature a rare 5,6,7,8-tetrahydrobenzo[*c*,*e*]-azocine skeleton composed of a biaryl-incorporated eight-membered *N*-heterocyclic ring. Buflavine (**1**) (Figure 1), isolated from *Boophane flava*,[2] an endemic *Amaryllidaceae alkaloid* species from South Africa, is a typical member of this family, exhibiting interesting biological activities such as α-adrenolytic and anti-serotonin activities.[3] However, after the pioneering work of Kobayashi,[4] little work has been published regarding the synthesis of apogalanthamine analogues (Figure 1). Only three total syntheses of buflavine have been reported,[5] while minor efforts have been made to generate structural analogues of these molecules for the purpose of biological and pharmacological screening.[6]

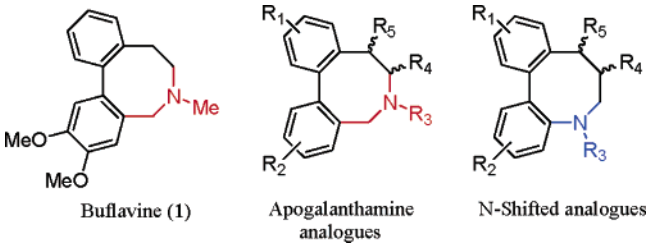


Figure 1. 5,6,7,8-Tetrahydrobenzo[*c*,*e*]azocines.

We have recently demonstrated the usefulness of microwave-irradiation in promoting Suzuki−Miyaura reactions[7] of highly electron-rich substrates[8] en route toward the

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(1) Ueyo, S.; Kobayashi, S. *Chem. Pharm. Bull.* **1953**, *1*, 139. Kobayashi, S.; Uyeo, S. *J. Chem. Soc.* **1957**, *638*. Ishida, Y.; Sadamune, K.; Kobayashi, S.; Kihara, M. *J. Pharmacobiodyn.* **1983**, *6*, 391. Kihara, M.; Miyake, Y.; Iitomi, M.; Kobayashi, S. *Chem. Pharm. Bull.* **1985**, *33*, 1260.

(2) Viladomat, F.; Bastida, J. E.; Codina, C.; Campbell, W. E.; Mathee, S. *Phytochemistry* **1995**, *40*, 307.

(3) Ishida, S.; Sasaki, Y.; Kimura, Y.; Watanabe, K. *J. Pharmacobiodyn.* **1985**, *8*, 917. Ishida, K.; Watanabe, K.; Kobayashi, S.; Kihara, M. *Chem. Pharm. Bull.* **1977**, *25*, 1851. Renard-Nozaki, J.; Kim, T.; Imakura, Y.; Kihara, M.; Kobayashi, S. *Res. Virol.* **1989**, *140*, 115.

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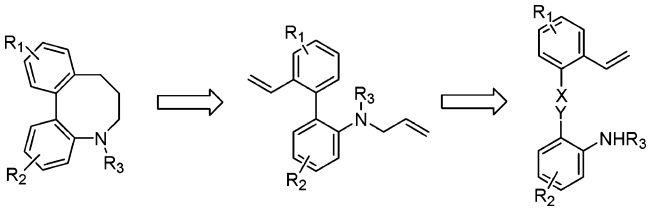
synthesis of apogalanthamine analogues. As a part of our ongoing research on microwave-enhanced transition-metal-catalyzed synthesis[9] of difficultly obtainable medium-sized-ring natural product analogues, we devised a novel strategy for the synthesis of the hitherto unknown N-shifted buflavine analogues (Figure 1), which we wish to delineate herein.

Our approach comprises a microwave-assisted Suzuki−Miyaura cross-coupling reaction followed by a ring-closing metathesis[10] (RCM) reaction (Scheme 1). The required biaryl

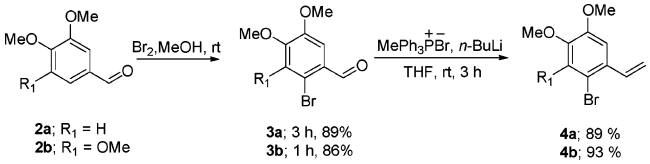
Scheme 1. Retrosynthetic Analysis



skeleton can easily be generated from the corresponding suitably functionalized styrene derivatives and anilines. After Suzuki−Miyaura cross-coupling reaction, the obtained biaryl system might be converted to the corresponding ring-closed targets by an RCM reaction. However, there is scarce literature precedent using the RCM for the generation of such medium-sized rings.[11] The increased ring strain of the target molecule, moreover reinforced by the incorporated biaryl unit, will impose severe challenges to perform this RCM.

Our initial goal was to synthesize the *o*-bromostyrenes needed for the biaryl coupling protocol. We decided to incorporate electron-rich methoxy substituents in the biaryl unit in order to keep a maximum resemblance with bufalvine (**1**). Furthermore, these electron-rich substituents will tend to slow the oxidative addition of the palladium catalyst to the C−Br bond,[7,8] making it a challenge to our cross-coupling strategy. Commercially available 3,4-dimethoxybenzaldehyde (**2a**) and 3,4,5-trimethoxybenz aldehyde (**2b**) were brominated regioselectively using bromine in methanol (Scheme 2).

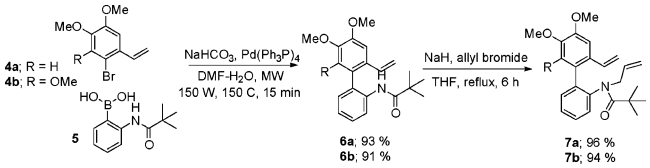
Scheme 2. Synthesis of *o*-Bromostyrenes **4a**,**b**



The reactions were completed in 1−3 h at rt, and the products **3a** and **3b** were isolated in high yields of 89% and 86%, respectively. The aldehydes were then converted to the corresponding styrenes **4a** and **4b** via Wittig reaction (Scheme 2) with methyl(triphenyl)phosphonium bromide in THF at rt, using *n*-BuLi as the base. The reactions were found to proceed smoothly, and the corresponding styrenes **4a**,**b** were isolated in excellent yields of 89% and 93%, respectively.

To explore the Suzuki−Miyaura reaction, we chose 2-pivaloylaminophenylboronic acid **5** as the coupling partner (Scheme 3). The boronic acid was synthesized in two steps

Scheme 3. Suzuki−Miyaura Reaction in the Synthesis of Biaryl Amines **7a**,**b**



from aniline following the literature procedure,[12] via directed *ortho* metalation.[13] Following our previous experience with

(4) Kobayashi, S.; Kihara, M.; Yamasaki, K.; Ishida, Y.; Watanabe, K. *Chem. Pharm. Bull.* **1975**, *23*, 3036. Kobayashi, S.; Kihara, M.; Shizu, S.; Katayama, S.; Ikeda, H.; Kitahiro, K.; Matsumoto, H. *Chem. Pharm. Bull.* **1977**, *25*, 3312. Kihara, M.; Kobayashi, S. *Yakugaku Zasshi*. **1978**, *26*, 155. Kihara, M.; Ohnishi, K.; Kobayashi, S. *J. Heterocycl. Chem.* **1988**, *25*, 161. Kobayashi, S.; Kihara, M.; Shingu, T. *Yakugaku Zasshi*. **1980**, *100*, 302. Kobayashi, S.; Kihara, M.; Miyake, Y. *Heterocycles* **1985**, *23*, 159.

(5) Patil, P. A.; Snieckus, V. *Tetrahedron Lett.* **1998**, *39*, 1325. Hoarau, C.; Couture, A.; Deniau, E. c.; Grandclaudon, P. *J. Org. Chem.* **2002**, *67*, 5846. Sahakitpichan, P.; Ruchirawat, S. *Tetrahedron Lett.* **2003**, *44*, 5239.

(6) Baudoin, O.; Cesario, M.; Guenard, D.; Gueritte, F. *J. Org. Chem.* **2002**, *67*, 1199. Herrbach, A.; Marinetti, A.; Baudoin, O.; Guenard, D.; Gueritte, F. *J. Org. Chem.* **2003**, *68*, 4897.

(7) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. Suzuki, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; p 49. Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147; Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633, and references therein.

(8) Appukkuttan, P.; Orts, A. B.; Chandran, R. P.; Goeman, J. L.; Van der Eycken, J.; Dehaen, W.; Van der Eycken, E. *Eur. J. Org. Chem.* **2004**, 3277. Appukkuttan, P.; Van der Eycken, E.; Dehaen, W. *Synlett* **2005**, 127.

(9) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225. Lidström, P.; Westman, J.; Lewis, A. *Comb. Chem. High Throughput Screening* **2002**, *6*, 441. Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* **2002**, *35*, 717. Loupy, A. *Microwaves in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2002; and references therein. Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250. Hayes, B. L. *Aldrichim. Acta* **2004**, *37*, 66.

(10) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036. Grubbs, R. H.; Blackwell, H. E. *Angew. Chem., Int. Ed.* **1998**, *37*, 3281. Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3812. Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* 2001, *34*, 18. Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117. Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199.

(11) Fürstner, A.; Radkowski, K.; Wirtz, C.; Goddard, R.; Lehmann, C. W.; Mynott, R. *J. Am. Chem. Soc.* **2002**, *124*, 7061. Banfi, L.; Basso, A.; Guanti, G.; Riva, R. *Tetrahedron Lett.* **2003**, *44*, 7655. Rodriguez, C.; Ravelo, J. L.; Martin, V. S. *Org. Lett.* **2004**, *6*, 4787. Kim, Y. J.; Lee, D. *Org. Lett.* **2004**, *6*, 4351. Vassilikogiannakis, G.; Margaros, I.; Tofi, M. *Org. Lett.* **2004**, *6*, 205. Qadir, M.; Cobb, J.; Sheldrake, P. W.; Whittall, N.; White, A. J. P.; Hii, K. K.; Horton, P. N.; Hursthouse, M. B. *J. Org. Chem.* **2005**, *70*, 1545. Qadir, M.; Cobb, J.; Sheldrake, P. W.; Whittall, N.; White, A. J. P.; Hii, K. K.; Horton, P. N.; Hursthouse, M. B. *J. Org. Chem.* **2005**, *70*, 1552.

(12) Guillier, F.; Nivoliers, F.; Godard, A.; Marsais, F.; Queguiner, G.; Siddiqui, M. A.; Snieckus, V. *J. Org. Chem.* **1995**, *60*, 292. Rocca, P.; Marsais, F.; Godard, A.; Queguiner, G. *Tetrahedron* **1993**, *49*, 49.

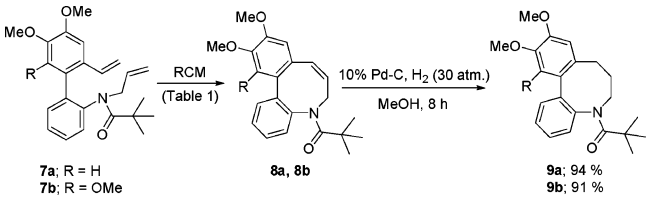
(13) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. Snieckus, V. *Pure Appl. Chem.* **1990**, *62*, 671. Chauder, B.; Green, L.; Snieckus, V. *Pure Appl. Chem.* **1999**, *71*, 1521. Hartung, C. G.; Snieckus, V. *Mod. Arene Chem.* **2002**, 330. Anctil, E. J.-G.; Snieckus, V. *J. Organomet. Chem.* **2002**, *653*, 150.

the Suzuki−Miyaura cross-coupling reaction between an electron-rich aryl halide and *ortho*-substituted boronic acids,[8] we decided to carry out the reaction under microwave irradiation. Thus, styrene **4a** and boronic acid **5** (1.3 equiv) were suspended in a 1:1 mixture of DMF and H_2O (3 mL) together with $NaHCO_3$ as the base (3.0 equiv) and $Pd(Ph_3P)_4$ as the catalyst (5 mol %) in a 10 mL sealed glass vial. The mixture was irradiated at 150 °C for 15 min, using a maximum power level of 150 W. The cross-coupling was found to proceed smoothly, and the product **6a** was isolated in an excellent yield of 93% (Scheme 3).

Following the same procedure, the cross-coupling between styrene **4b** and boronic acid **5** was carried out under microwave irradiation and the product **6b** was isolated in an excellent yield of 91% (Scheme 3). To generate the intermediate for the RCM, the remaining task was the creation of the *N*-allyl handle by allylating the aniline nitrogen (Scheme 3). Refluxing the intermediates **6a**,**b** with NaH and allylbromide in dry THF for 6 h was found to drive the allylation to completion, and the biaryl compounds **7a**,**b** were isolated in excellent yields of 96% and 94%, respectively.

Our next goal was to carry out the RCM reaction to generate the required biaryl-incorporated medium-sized rings **8a**,**b** (Scheme 4). As expected, this conversion was rather

Scheme 4. RCM of the Intermediates **7a**,**b** and Further Conversion to the Target Molecules **9a**,**b**



troublesome. In a first run, **7a** (0.1 mmol) was stirred with Grubbs first-generation (G-1) catalyst (3 mol %) in dry and degassed CH_2Cl_2 at rt. Unfortunately, no reaction was observed even after 24 h, and the starting material was found untouched (Table 1, entry 1). The use of Grubb's second-generation catalyst (G-2) as well as the Hoveyda second-generation (H-2) catalyst also failed to provide any change to the course of the reaction (Table 1, entries 2 and 3). On the contrary, when the reaction was carried out at reflux temperature in CH_2Cl_2 for 3 h with G-1 (3 mol %) as the catalyst, the product **8a** was isolated in 17% yield, together with unreacted starting material **7a** (Table 1, entry 4). Increasing the reaction time to 6 or 12 h failed to improve the outcome of the reaction (Table 1, entries 5 and 6). Therefore, we decided to perform the reaction at elevated temperature in $CHCl_3$, resulting in a slightly higher yield of 22%, while in refluxing toluene a moderate 28% was obtained (Table 1, entries 7−8).

However, the use of G-2 was found to increase the yields substantially, and we could isolate **8a** in a moderate yield

Table 1. Ring-Closing Metathesis To Generate Targets **8a**,**b**[a]

entry	starting material	product	catalyst	time (h)	solvent	*T* (°C)	yield (%)
1	**7a**	**8a**	G-1	24	CH_2Cl_2	rt	0
2	**7a**	**8a**	G-2	24	CH_2Cl_2	rt	0
3	**7a**	**8a**	H-2	24	CH_2Cl_2	rt	0
4	**7a**	**8a**	G-1	3	CH_2Cl_2	reflux	17
5	**7a**	**8a**	G-1	6	CH_2Cl_2	reflux	17
6	**7a**	**8a**	G-1	12	CH_2Cl_2	reflux	17
7	**7a**	**8a**	G-1	3	$CHCl_3$	reflux	22
8	**7a**	**8a**	G-1	3	PhMe	reflux	28
9	**7a**	**8a**	G-2	3	CH_2Cl_2	reflux	32
10	**7a**	**8a**	G-2	3	$CHCl_3$	reflux	42
11	**7a**	**8a**	G-2	3	PhMe	reflux	58
12	**7a**	**8a**	H-1	3	PhMe	reflux	29
13	**7a**	**8a**	H-2	3	PhMe	reflux	43
14	**7a**	**8a**	G-2	5 min[b]	PhMe	150	69[a]
15	**7b**	**8b**	G-1	3	PhMe	reflux	41
16	**7b**	**8b**	G-2	3	PhMe	reflux	55
17	**7b**	**8b**	H-2	3	PhMe	reflux	43
18	**7b**	**8b**	G-2	5 min[b]	PhMe	150	68[a]

[a] All reactions were carried out in a 0.25 mmol scale with 3 mol % of catalyst in 5 mL of solvent. [b] Reactions were carried out under microwave irradiation in 3 mL of solvent at a maximum power level of 150 W. All yields correspond to the isolated pure compounds, as determined by the NMR experiments.

of 32% when the reaction was carried out with G-2 in refluxing CH_2Cl_2, 42% in refluxing $CHCl_3$, and a good yield of 58% in refluxing toluene each upon stirring for 3 h (Table 1, entries 9−11, respectively). Changing the catalytic system to the Hoveyda catalyst, the product was isolated in slightly lower yields of 29% in the case of using H-1 and 43% in the case of H-2, in refluxing toluene (Table 1, entries 12 and 13). As it seemed to be advantageous to perform the RCM at higher temperature, we decided to investigate the reaction upon microwave irradiation. When a sample of **7a** was irradiated in toluene, at 150 °C and a maximum power level of 150 W, the yield was found to increase to 69%, while the reaction time could be decreased to a mere 5 min (Table 1, entry 14). Applying the same conditions, the trimethoxy analogue **8b** was synthesized in 5 min under microwave irradiation in a good yield of 68% (Scheme 4, Table 1, entry 18) and under conventional heating conditions in a 55% yield (Table 1, entry 16). To complete the sequence, the dihydrodibenzo[*b*,*d*]azocines **8a**,**b** were converted into the corresponding tetrahydrodibenzo[*b*,*d*]azocines **9a**,**b** via a simple palladium-catalyzed hydrogenation protocol applying a high-pressure Parr hydrogenation apparatus (Scheme 4). The reactions were run for 8 h in MeOH at 30 atm of H_2 pressure. The products **9a**,**b** were isolated in excellent yields of 94% and 91%, respectively.

In conclusion, we have developed a novel microwave-enhanced, transition-metal-mediated protocol for the synthesis of hitherto unknown N-shifted buflavine analogues. The key biaryl generating step was performed via a palladium-catalyzed Suzuki−Miyaura reaction upon focused microwave irradiation. RCM reactions were successfully employed in generating the rigid, medium-sized ring system of the target molecules. Again, microwave irradiation was found to be highly beneficial in overcoming the high activation barrier of the reaction. The synthesis of a small

library of the title molecules as well as attempts to vary the ring size is under current investigation.

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Supporting Information Available: Complete experimental procedures, both under conventional heating and microwave irradiation, as well as full characterization data (^{1}H, ^{13}C, and DEPT NMR, CI-MS, and HRMS (EI)) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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