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Diversity-Oriented Synthesis of Dibenzoazocines and Dibenzoazepines via a Microwave-Assisted Intramolecular A^3-Coupling Reaction

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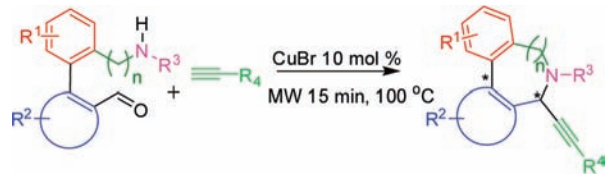
ABSTRACT



An unprecedented, diversity-oriented strategy for the generation of 6,7-dihydro-5*H*-dibenzo[*c*,*e*]azepines and 5,6,7,8-tetrahydrodibenzo[*c*,*e*]azocines by a microwave-assisted copper-catalyzed intramolecular A^3-coupling reaction is presented.

In light of the increased demand for the diversity-oriented[1] generation of biaryl-containing medium-sized rings,[2] different approaches have been developed for these biologically interesting classes of compounds. As an example, the apogalanthamine analogues (**1**)[3] (Figure 1) belonging to the Amaryllidaceae alkaloid family feature a rare 5,6,7,8-tetrahydrodibenzo[*c*,*e*]azocine skeleton which comprises a biaryl ring system linked with an eight-membered *N*-heterocyclic ring. Buflavine[4] (**2**) (Figure 1), isolated from *Boophane flava*, an endemic Amaryllidaceae alkaloid species from South Africa, is a typical member of this family, exhibiting interesting biological activities such as α-adrenolytic and antiserotonin activities.[3a−c,5] Five total syntheses of buflavine have been reported in the literature[6] to date, while minor efforts have been done for the synthesis of apogalanthamines and their structural analogues (6,7-dihydro-5*H*-dibenzo[*c*,*e*]azepines and 5,6,7,8-tetrahydrodibenzo[*c*,*e*]azocines (compounds **3** in Figure 1) after the pioneering work of Kobayashi et al.[7] While the biaryl moiety can be directly

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(1) (a) Burke, M. D.; Berger, E. M.; Schreiber, S. L. *Science* **2003**, *302*, 613. (b) Burke, M. D.; Lalic, G. *Chem. Biol.* **2002**, *9*, 535. (c) Schreiber, S. L. *Science* **2000**, *287*, 1964.
(2) (a) Mehta, G.; Singh, V. *Chem. Rev.* **1999**, *99*, 881. (b) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95.
(3) (a) Ishida, Y.; Sasaki, Y.; Kimura, Y.; Watanabe, K. *J. Pharmacobiodyn.* **1985**, *8*, 917. (b) Ishida, Y.; Sadamune, K.; Kobayashi, S.; Kihara, M. *J. Pharmacobiodyn.* **1983**, *6*, 391. (c) Ishida, Y.; Watanabe, K.; Kobayashi, S.; Kihara, M. *Chem. Pharm. Bull.* **1977**, *25*, 1851.
(4) Viladomat, F.; Bastida, J. E.; Codina, C.; Campbell, W. E.; Mathee, S. *Phytochemistry* **1995**, *40*, 307.
(5) Renard-Nozaki, J.; Kim, T.; Imakura, Y.; Kihara, M.; Kobayashi, S. *Res. Virol.* **1989**, *140*, 115.
(6) For an overview, see: Appukkuttan, P.; Van der Eycken, E. *Eur. J. Org. Chem.* **2008**, 5867.

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accessed via Ullmann-type coupling, (asymmetric) Suzuki−Miyaura cross-coupling reaction[8a−c] or intramolecular oxidative coupling,[8d,e] the construction of the medium-sized ring is still a major challenge for the construction of such structures.

As a part of our ongoing interest in the synthesis of buflavine analogues[8f−h] in particular and of medium-sized rings in general[9] via the application of microwave irradiation,

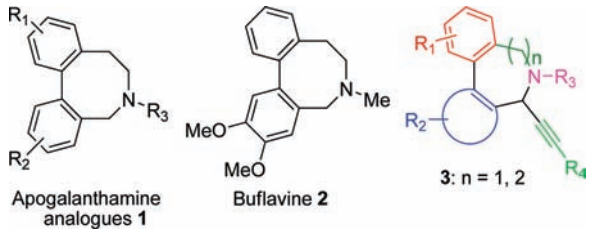
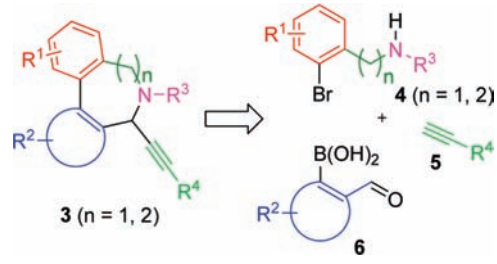


Figure 1. Structure of the apogalanthamine analogues (**1**), buflavine (**2**), and the proposed new analogues **3**.

we became interested in the development of an alternative route for these compounds via an intramolecular A^3-coupling reaction. This multicomponent reaction has attracted much attention in recent years[10] as it easily allows for the introduction of diversity in a single step under mild conditions using inexpensive transition-metal catalysts. This A^3-coupling reaction can be performed in, e.g., an ionic liquid[11] or water[12] as reaction medium, and high enantioselectivities could be achieved using QUINAP or Pybox chiral ligands.[10b,f] Moreover, it has been recently demonstrated that the process is suited for scale up using microwave-assisted continuous flow conditions.[13] We have already demonstrated the applicability of the A^3-coupling reaction for the synthesis of (−)-steganacin and (−)-steganone aza analogues, and very recently, we reported a new method to access polyalkyl-substituted secondary propargylamine via A^3-coupling using scarcely explored primary aliphatic amines.[14]

In this report, we describe the first application of an intramolecular A^3-coupling reaction for the construction of medium-sized rings. Our approach gives access to 6,7-dihydro-5*H*-dibenzo[*c*,*e*]azepines as well as to 5,6,7,8-tetrahydrodibenzo[*c*,*e*]azocines, thus allowing the introduction of five points of diversity (Scheme 1).

Scheme 1. Retrosynthesis for the Generation of the 6,7-Dihydro-5*H*-dibenzo[*c*,*e*]azepine and the 5,6,7,8-Tetrahydrodibenzo[*c*,*e*]azocine Skeleton via an Intramolecular A^3-Coupling Reaction



In our approach to construct medium-sized ring derivatives, the required biaryl moiety was obtained via a Suzuki−Miyaura cross-coupling reaction of a suitable *o*-bromobenzylamine or an *o*-bromophenethylamine **4** and an electron-poor *o*-formyl(hetero)arylboronic acid **6** (Scheme 1). We have previously demonstrated that this kind of electronically unfavorable combination of binding partners highly benefits from the application of microwave irradiation.[8f−h,9d] For our optimization study, the starting biaryl compound **7a** was synthesized according to our optimized microwave-assisted procedure.[9b] In continuation of our research regarding A^3 couplings, we investigated the intramolecular reaction of biaryl compound **8a** that was in situ formed via Boc deprotection of the generated **7a** upon treatment with TFA/DCM (1:3) at 0 °C. The latter intermediate delivers both the aldehyde and the amine moiety, which were reacted with *p*-tolylacetylene using CuBr (20 mol %) as the catalyst in toluene under microwave irradiation at a ceiling temperature of 100 °C and a maximum power of 80 W for 25 min (Table 1, entry 1). The desired compound **3a** was obtained in a high yield of 95%. Other copper salts such as CuI and CuCl also worked equally well (Table 1, entries 2 and 3). The yield remained high even when the reaction time was decreased to 15 min (Table 1, entry 4). The amount of CuBr catalyst could be reduced to 10 mol % without affecting the yield of **3a** (Table 1, entries 5 and 7). Further

(7) (a) Kobayashi, S.; Kihara, M.; Shizu, S.; Katayama, S.; Ikeda, H.; Kitahiro, K.; Matsumoto, H. *Chem. Pharm. Bull.* **1977**, *25*, 3312. (b) Kihara, M.; Vangveravong, S.; Ohnishi, K.; Imakura, Y.; Kobayashi, S. *Chem. Pharm. Bull.* **1989**, *37*, 1744.

(8) (a) Joncour, A.; Decor, A.; Liu, J. M.; Dau, M.; Baudoin, O. *Chem.—Eur. J.* **2007**, *13*, 5450. (b) Joncour, A.; Decor, A.; Thoret, S.; Chiaroni, A.; Baudoin, O. *Angew. Chem., Int. Ed.* **2006**, *45*, 4149. (c) Baudoin, O. *Eur. J. Org. Chem.* **2005**, 4223. (d) Hamamoto, H.; Anilkumar, G.; Tohma, H.; Kita, Y. *Chem. Commun.* **2002**, 450. (e) Takada, T.; Arisawa, M.; Gyoten, M.; Hamada, R.; Tohma, H.; Kita, Y. *J. Org. Chem.* **1998**, *63*, 7698. (f) Appukkuttan, P; Dehaen, W; Van der Eycken, E. *Chem.—Eur. J.* **2007**, *13*, 6452. (g) Appukkuttan, P.; Van der Eycken, E. Microwave-Assisted Natural Product Chemistry. In *Topics in Current Chemistry*; Microwave Methods in Organic Synthesis; Springer: New York, 2006; Vol. 266, p 1. (h) Appukkuttan, P; Dehaen, W; Van der Eycken, E. *Comb. Chem. High Throughput Screening* **2007**, *10*, 790.

(9) (a) Mont, N; Mehta, V. P; Appukkuttan, P; Beryozkina, T; Toppet, S; Van Hecke, K; Van Meervelt, L; Voet, A; De Maeyer, M; Van der Eycken, E. *J. Org. Chem.* **2008**, *73*, 7509. (b) Donets, P; Van der Eycken, E. V. *QSAR Comb. Sci* **2007**, *26*, 1239. (c) Beryozkina, T; Appukkuttan, P; Mont, N; Van der Eycken, E *Org. Lett.* **2006**, *8*, 487. (d) 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.

(10) (a) Gommermann, N.; Knochel, P. *Chem.—Eur. J.* **2006**, *12*, 4380. (b) Gommermann, N; Knochel, P. *Chem. Commun.* **2005**, 4174. (c) Wei, C. M.; Mague, J. T.; Li, C. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5749. (d) Wei, C. M.; Li, Z. G.; Li, C. J. *Synlett* **2004**, 1472. (e) Gommermann, N.; Koradin, K.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 5763. (f) Wei, C. M.; Li, C. J. *J. Am. Chem. Soc.* **2002**, *124*, 5638. (g) Zani, L.; Bolm, C. *Chem. Commun.* **2006**, 4263.

(11) Zhang, X.; Corma, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4358.

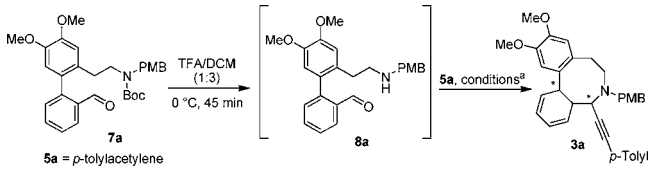
(12) Shi, L.; Tu, Y.-Q.; Wang, M.; Zhang, F.-M.; Fan, C.-A. *Org. Lett.* **2004**, *6*, 1001.

(13) Shore, G.; Yoo, W.-J.; Li, C.-J.; Organ, M. G. *Chem.—Eur. J.* **2010**, *16*, 126.

(14) Bariwal, J. B.; Ermolat'ev, D. S.; Van der Eycken, E. V. *Chem.—Eur. J.* **2010**, *16*, 3281.

lowering the catalyst concentration resulted in a prolonged reaction time to reach completion. The same was noticed when the ceiling temperature was decreased to 80 °C. When the solvent was changed from toluene to dioxane an important drop of the yield was observed (Table 1, entry 6). Best conditions were found when the reaction was run with 10 mol % of CuBr catalyst for 15 min under microwave irradiation as described above (Table 1, entry 7).

Table 1. Investigation of the Reaction Parameters for the Intramolecular A^3-Coupling Reaction



entry	catalyst (mol %)	time (min)	yield[b] (%)
1	CuBr (20)	25	95
2	CuI (20)	25	96
3	CuCl (20)	25	93
4	CuBr (20)	15	94
5	CuBr (10)	25	94
6	CuBr (20)	25	78[c]
7	**CuBr (10)**	**15**	**95**
8	Cu/C (20)	25	82
9	Cu/C (10)	25	80

[a] Reaction conditions: compound **7a** (1.0 mmol), *p*-tolylacetylene (1.5 mmol), dry toluene (1.0 mL), MW, 80 W, 100 °C. [b] Yields obtained for the diastereomeric mixture calculated over two steps. [c] Dioxane was used as solvent.

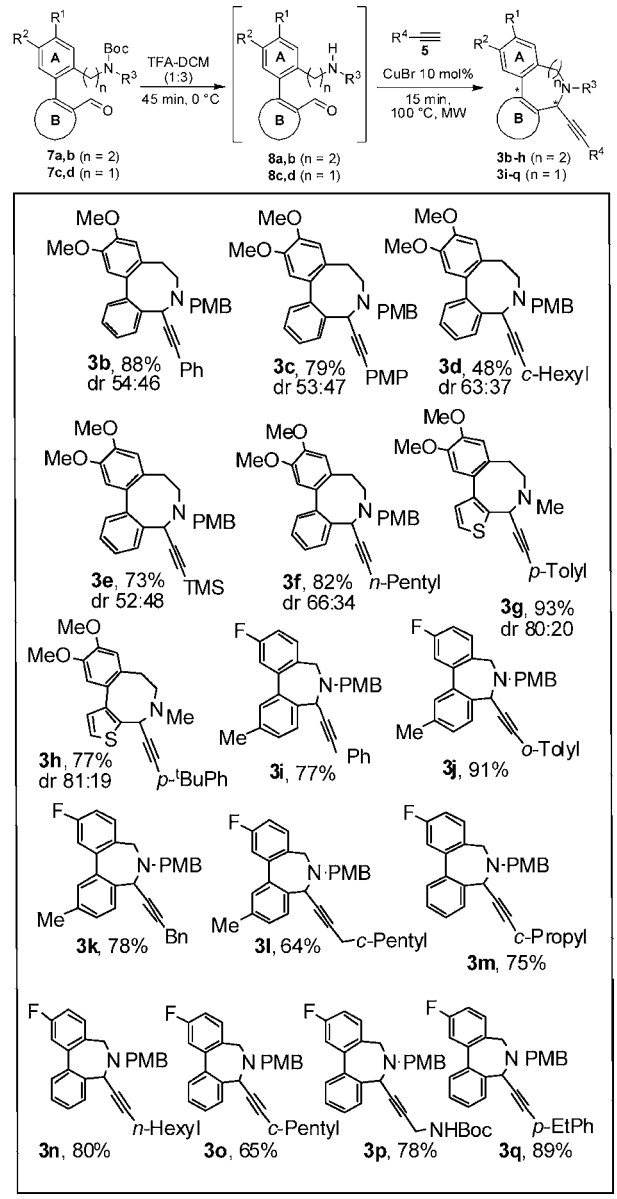
Interestingly, this intramolecular A^3 coupling could also be run using copper-in-charcoal as catalyst[15] (Cu ≈ 15% by weight). In this case, compound **3a** could be isolated in a slightly decreased yield of 80−82% (Table 1, entries 8 and 9). The possibility to apply heterogeneous catalysis opens the way for performing the reaction as a flow process, as will be further demonstrated. It has been observed that the target compound **3a** appeared at rt as a diastereomeric mixture (≈55:45; determined by HPLC and NMR) that could not be separated by column chromatography due to rapid interconversion via rotation along the biaryl axis.

However, attempts to crystallize the diastereomeric mixture provided single diastereomers of **3a** in crystalline form. The structures of these crystalline diastereomers were unequivocally confirmed by X-ray crystallography. Compound **3a** crystallized in the centrosymmetric space group $P2_1/c$; hence, both enantiomers are present in the structure.[16] Using the optimized conditions for our intramolecular A^3 coupling

(15) Lipshutz, B. H.; Taft, B. R. *Angew. Chem.* **2006**, *118*, 8415; *Angew. Chem. Int. Ed.* **2006**, *45*, 8235.

(16) CCDC 772382 (**3a**) and CCDC 772381 (**3g**) contain the supplementary crystallographic data for these structures. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/conts/retrieving.html. (See the Supporting Information for crystal structures of compound **3a** and **3g** and two enantiomers overlapped for compound **3a**).

Scheme 2. Investigation of the Scope of the Intramolecular A^3-Coupling Reaction



(Table 1,entry 7), we further investigated the scope of this reaction evaluating different substrates (Scheme 2). To our delight, all compounds were obtained in fairly good to excellent yields.

The A^3-coupling reaction seemed to work equally well for the formation of a 5,6,7,8-tetrahydrodibenzo[*c*,*e*]azocine (Scheme 2, **3b**−**h**) as for a 6,7-dihydro-5*H*-dibenzo[*c*,*e*]azepine (Scheme 2, **3i**−**q**) skeleton. Also, the incorporation of a thiophene ring in the biaryl axis does not seem to hamper the medium-sized ring formation (Scheme 2, **3g**,**h**). All of the eight-membered ring derivatives **3a**−**f**, where ring B is phenyl, appeared as an interconvertable diastereomeric mixture (∼1:1) according to their NMR spectra.

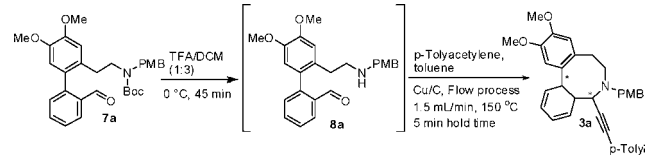
However, for compounds **3g**,**h** where ring B is replaced by a thiophene ring, a diastereomeric ratio of ∼20:80 was

observed. The structure of the major (a*R*,5*S*) diastereoisomer of compound **3g** was unequivocally proven by X-ray crystallography. The compound **3g** crystallized in the chiral space group $P2_1$; hence, only one enantiomer is present in the structure.[16] Interestingly, the seven-membered compounds **2a**−**i** were obtained as single diastereoisomers.[17]

The possibility to catalyze this intramolecular A^3-coupling process with copper-in-charcoal (Cu/C) (Table 1, entries 8 and 9) opens the way to perform this reaction under continuous flow conditions. We have recently reported Cu(I)-catalyzed azide−alkyne cycloaddition reactions (CuAAC) using a high-temperature/pressure continuous flow reactor incorporating immobilized Cu/C as a catalyst.[18] For the A^3 coupling **8a** to **3a** the initially optimized batch conditions (100 °C, 25 min, Table 1) were not transferrable to a flow experiment, due to the long reaction time, i.e., residence time, in the reactor. For this reason, the reaction temperature was increased to 150 °C and the reaction time thereby decreased to 5 min, providing a similar isolated product yield (79%) of **3a**. Transferring the conditions from the microwave batch experiment to continuous flow (X-Cube reactor),[16] we found that at a flow rate of 1.5 mL/min were able to obtain a good yield of the desired intramolecular A^3-coupling product **3a** (67%) (Scheme 3). It has to be noted that lower flow rates lead to significant amounts of homocoupling of the terminal alkyne (Glaser coupling), which can be rationalized by the stoichiometric amounts of Cu under flow conditions.[19]

In summary, we have developed an unprecedented strategy for the construction of 6,7-dihydro-5*H*-dibenzo[*c*,*e*]azepines and 5,6,7,8-tetrahydrodibenzo[*c*,*e*]azocines via a microwave-assisted copper-catalyzed intramolecular A^3-coupling reaction. This method allows the introduction of five different points of diversity in the azepine and azocine skeleton in a short and concise way. All compounds were obtained in good yields and purities over two synthetic steps. Furthermore, we proved that this reaction could easily be performed in a microwave-assisted continuous flow process opening the way for the generation of these compounds on a larger scale.

Scheme 3. Intramolecular A^3-Coupling Reaction Performed As a Continuous Flow Process



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Supporting Information Available: Experimental procedures and characterizations of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL1008729

(17) Pira, S. L.; Wallace, T. W.; Graham, J. P. *Org. Lett.* **2009**, *11*, 1663.

(18) Fuchs, M; Goessler, W; Pilger, C; Kappe, C. O *Adv. Synth. Catal* **2010**, *352*, 323.

(19) Similar changes in selectivity have been observed in Pd-catalyzed Heck reactions under continuous flow conditions. Glasnov, T. N; Findenig, S; Kappe, C. O *Chem.−Eur. J.* **2009**, *15*, 1001.