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A Novel 1,5-Benzoheteroazepine Synthesis via a One-Pot Coupling–Isomerization–Cyclocondensation Sequence§

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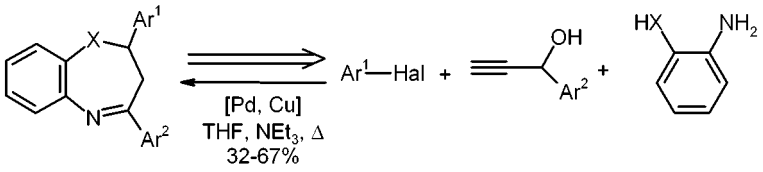
ABSTRACT



Ar¹ = electron deficient (hetero)aryl Ar² = aryl X = NH, O, S

2,4-Di(hetero)aryl substituted 2,3-dihydro 1,5-benzoheteroazepines (hetero = NH, O, S) can be readily sythesized in a one-pot process initiated by a coupling–isomerization sequence of an electron poor (hetero)aryl halide and a terminal propargyl alcohol subsequently followed by a cyclocondensation with 2-amino, 2-hydroxy, or 2-mercapto anilines. In addition, the structures were established unambiguously by an X-ray structure analysis of 7a.

Benzodiazepines (**1** and **2**) constitute an important class of psychopharmaca.[1] In particular, derivatives of 1,5-benzodiazepines **2** have aroused considerable interest as CNS active anticonvulsant drugs[2] and also as in vitro nonnucleoside inhibitors of HIV-1 reverse transcriptase[3] (Figure 1).

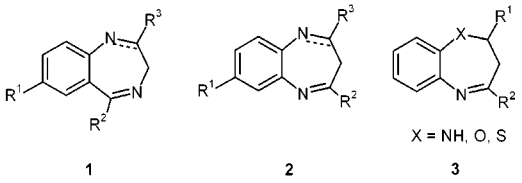


Figure 1.

Besides these only nitrogen containing benzoannealed seven-membered heterocycles, their oxaza and thiaza analogues **3** have become increasingly interesting since 1,5-benzothiazepines show antifungal, antibacterial,[4] antifeedant,[5] antiinflammatory, analgesic,[6] and anticonvulsant[7] activity.

§ Dedicated to Prof. Richard R. Schmidt on the occasion of his 65th birthday.

† X-ray crystal structure analysis.

(1) For reviews, see: (a) Archer, G. A.; Sternbach, L. H. *Chem. Rev.* **1968**, *68*, 747. (b) Popp, F. D.; Noble, A. C. *Adv. Heterocycl. Chem.* **1967**, *8*, 21. (c) Sternbach, L. H. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 34. (d) Vanderheyden, J. L.; Vanderheyden, J. E. *J. Pharm. Belg.* **1981**, *36*, 354. (e) Jones, G. R.; Singer, P. P. *Adv. Anal. Toxicol.* **1989**, *2*, 1. (f) Newkome, G. R. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, New York, Toronto, Sydney, Paris, Frankfurt, 1996; Vol. 9, p 181.

(2) For synthetic and pharmacological studies, see: (a) Zellou, A.; Cherrah, Y.; Hassar, M.; Essassi, E.-M. *Ann. Pharm. Fr.* **1998**, *56*, 169. (b) Savelli, F.; Boido, A.; Mule, A.; Piu, L.; Alamanni, M. C.; Pirisino, G.; Satta, M.; Peana, A. *Farmaco* **1989**, *44*, 125. (c) Nawojski, A.; Nawrocka, W.; Liszkiewicz, H. *Pol. J. Pharmacol. Pharm.* **1985**, *37*, 69. (d) Wilimowski, M.; Orzechowsa-Juzwenko, K.; Barczynska, J.; Kedzierska-Gozdzik, L.; Witkowska, M.; Wojewodzki, W.; Dus, E.; Plawiak, T.; Gryska, J.; Maska, H. *Pol. J. Pharmacol. Pharm.* **1983**, *35*, 89. (e) Srivastava, V. K.; Satsangi, R. K.; Kishore, K. *Arzneim.-Forsch.* **1982**, *32*, 1512.

(3) For synthetic and pharmacological studies, see: (a) Parker, K. A.; Dermatakis, A. *J. Org. Chem.* **1997**, *62*, 4164. (b) Hargrave, K. D.; Schmidt, G.; Engel, W.; Austel, V. Patent Application: U.S. 91-650141 19910204. Patent Priority: U.S. 89-340937 19890420; U.S. 89-372728 19890628; U.S. 89-438922 19891117; U.S. 90-600554 19901019.

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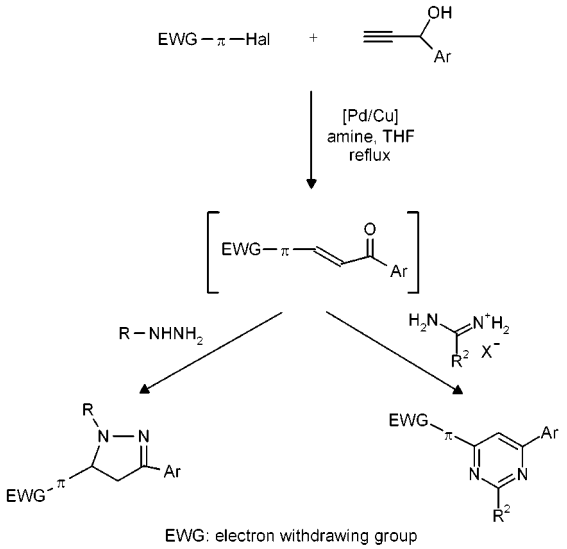
Retrosynthetically, 1,5-benzoheteroazepines are synthesized by cyclocondensation of the corresponding 2-substituted anilines with suitable enones or 1,3-dicarbonyl compounds (and synthetic equivalents).[4−7,8] However, the enones and, in particular, chalcones (i.e., 1,3-diaryl enones) are usually prepared by an aldol condensation and have to be isolated and purified prior to the cyclization step. Therefore, we set out to develop a novel synthesis of 1,5-benzoheteroazepines, preferentially in a straightforward highly convergent manner, that also can be conducted in the sense of a one-pot process. Here, we wish to communicate a facile one-pot synthesis of 2,4-di(hetero)aryl substituted 2,3-dihydro 1,5-benzodiazepines, -oxazepines, and -thiazepines (**3**, R^1 = (het)aryl, R^2 = aryl) based upon a coupling−isomerization sequence with a subsequent cyclocondensation with 2-amino, 2-hydroxy, or 2-mercapto anilines.

Recently, we found that palladium/copper catalyzed cross-coupling reactions of electron poor halogen substituted π-systems and 1-aryl prop-2-yn-1-ols do not furnish the expected propargyl alcohols but rather the isomeric enone components.[9] Mechanistically, this isomerization, occurring after the cross-coupling reaction, is purely base catalyzed and opens a new access to electron deficient propenones. With this powerful tool for the construction of chalcones (1,3-diaryl propenones) in hand and considering the mild reaction conditions for the Sonogashira coupling reaction, we have developed novel one-pot pyrazoline[9] and pyrimidine[10] syntheses (Scheme 1).

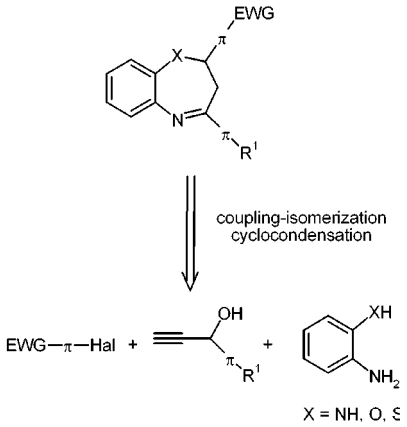
Scheme 1. One-Pot Pyrazoline and Pyrimidine Synthesis Based upon a Coupling−Isomerization Sequence



EWG: electron withdrawing group

Since cyclocondensations of 2-heteroatom substituted anilines with chalcones (1,3-diaryl propenones) give 1,5-benzoheteroazepines,[3−7] retrosynthetically, an extension of the coupling−isomerization-based methodology to a one-pot synthesis of 1,5-benzoheteroazepines can be easily envisioned. Upon cyclocondensing *o*-phenylene diamine, 2-amino phenol, or 2-amino thiophenol as suitable 1,4-dinucleophilic components with the initially formed enone functionality, the benzoannealed seven-membered heterocycles are to be readily formed (Scheme 2). In particular,

Scheme 2. Retrosynthetic Concept for a Three-Component 1,5-Benzoheteroazepine Synthesis



the mild reaction conditions of Sonogashira couplings[11] not only allow the presence of sensitive functional groups without tedious protection and deprotection steps but are also advantageous for base-mediated processes such as cyclocondensations. In addition, this strategy could also be extended to a combinatorial approach to 1,5-benzoheteroazepines (**3**).

Thus, we have submitted *p*-iodo nitrobenzene (**4a**), 4-bromo pyridine (**4b**), or *p*-bromo benzonitrile (**4c**), aryl propynols **5**,[12] and 2-heteroatom substituted anilines **6** to the reaction conditions of the Sonogashira coupling in a boiling mixture of triethylamine and THF.[13] In all cases the isolated products were the beige to yellow 1,5-benzoheteroazepines **7** in 32−67% yield (Table 1).[14] As already shown for the one-pot synthesis of pyrazolines and pyrimidines the electron withdrawing nature of the (hetero)aryl halide **4** is crucial for the successful coupling−isomerization step.[9,10]

The proton and carbon NMR spectroscopic data support the formation of the 1,5-benzoheteroazepine, in particular in the ^{1}H NMR spectra of **7** by the indicative appearance of

(4) (a) Mane, R. A.; Ingle, D. B. *Ind. J. Chem., Sect. B* **1982**, *21B*, 973. (b) Jadhav, K. P.; Ingle, D. B. *Ind. J. Chem., Sect. B* **1983**, *22B*, 180. (c) Attia, A.; Abdel-Salam, O. I.; Abo-Ghalia, M. H.; Amr, A. E. *Egypt. J. Chem.* **1995**, *38*, 543.

(5) Reddy, R. J.; Ashok, D.; Sarma, P. N. *Ind. J. Chem., Sect. B* **1993**, *32B*, 404.

(6)) Satyanarayana, K.; Rao, M. N. A. *Ind. J. Pharm. Sci.* **1993**, *55*, 230.

(7) DeSarro, G.; Chimirri, A.; DeSarro, A.; Gitto, R.; Grasso, S.; Zappala, M. *Eur. J. Med. Chem.* **1995**, *30*, 925.

(8) Lloyd, D.; McNab, H. *Adv. Heterocycl. Chem.* **1998**, *71*, 1.

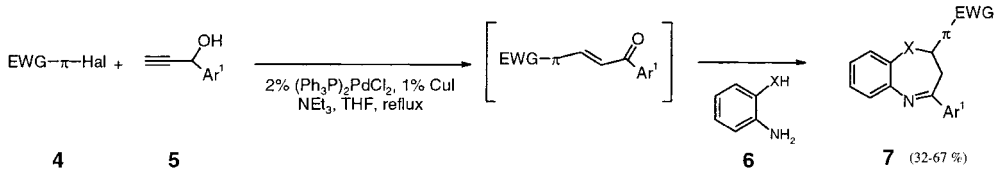
(9) Müller, T. J. J.; Ansorge, M.; Aktah, D. *Angew. Chem., Int. Ed.* **2000**, *39*, 1253.

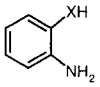
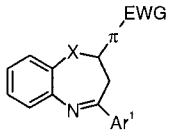
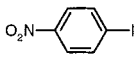
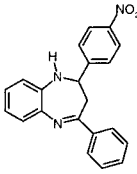
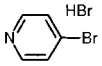
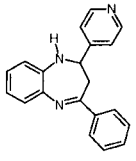
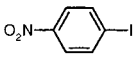
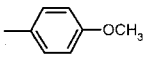
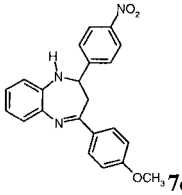
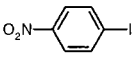
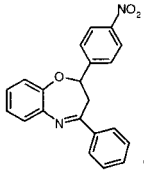
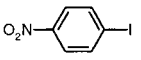
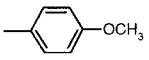
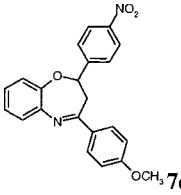
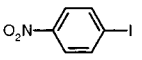
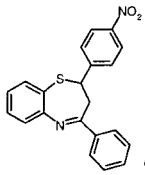
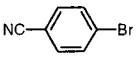
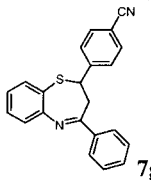
(10) Müller, T. J. J.; Braun, R.; Ansorge, M. *Org. Lett.* **2000**, *2*, 1967.

(11) (a) Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1980**, 627. (b) Sonogashira, K. In *Metal Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998, p 203.

(12) The propynols **5** were synthesized according to Krause, N.; Seebach, D. *Chem. Ber.* **1987**, *120*, 1845.

Table 1. Three-Component 1,5-Benzoheteroazepine Synthesis Based upon a Coupling−Isomerization−Cyclocondensation Sequence[a]



Entry	EWG-π-Hal **4**	Propargyl alcohol **5**	2-Hetero aniline **6**	1,5 Benzoheteroazepine **7** (Yield %)[b]
				
1	 **4a**	Ar¹ =  **5a**	X = NH **6a**	 **7a** (52 %)
2	 **4b**	Ar¹ =  **5a**	X = NH **6a**	 **7b** (53 %)
3	 **4a**	Ar¹ =  **5b**	X = NH **6a**	 **7c** (42 %)
4	 **4a**	Ar¹ =  **5a**	X = O **6b**	 **7d** (35 %)
5	 **4a**	Ar¹ =  **5b**	X = O **6b**	 **7e** (32 %)
6	 **4a**	Ar¹ =  **5a**	X = S **6c**	 **7f** (67 %)
7	 **4c**	Ar¹ =  **5a**	X = S **6c**	 **7g** (67 %)

[a] Reaction conditions: 1.0 equiv of the (hetero)aryl halide **4**, 1.05 equiv of the propargyl alcohol **5**, 0.02 equiv of $(Ph_3P)_2PdCl_2$, 0.01 equiv of CuI, 1.1 equiv of the 2-hetero aniline **6**, THF/NEt_3 2:1 (10 mL/mmol halide). [b] Yields refer to isolated yields of compounds **7** after recrystallization estimated to be ≥95% pure as determined by NMR spectroscopy and elemental analysis.

the ABM-spin system with the characteristic geminal and vicinal coupling constants for the methylene group resonances (^2J = 13.5 Hz, ^3J = 4.4 Hz, ^3J = 7.1 Hz) and the vicinal coupling constants for the methine resonances (^3J = 4.4 Hz, ^3J = 7.0 Hz). Furthermore, the structure of **7** was unambiguously supported by an X-ray crystal structure analysis (Figure 2) of compound **7a**[15] (Table 1, entry 1).

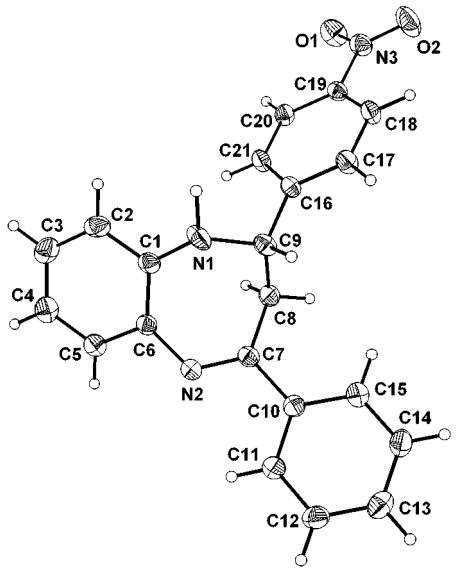


Figure 2. ORTEP plot of compound **7a**.

In conclusion, we could show that the mild reaction conditions of the coupling−isomerization sequence of electron poor (hetero)aryl halides with 1-aryl propargyl alcohols giving rise to chalcones can be extended to a one-pot three component synthesis of 2,4-di(hetero)aryl substituted 2,3-dihydro 1,5-benzodiazepines, -oxazepines, and -thiazepines. Further studies directed to extend these one-pot heterocycle syntheses are currently underway.

Acknowledgment. The financial support of the Fonds der Chemischen Industrie and the Dr.-Otto-Röhm Gedächtnisstiftung is gratefully acknowledged. The authors wish to express their appreciation to Prof. H. Mayr for his generous support.

Supporting Information Available: Tables of data collection parameters, bond lengths and angles, positional and thermal parameter, and least-squares planes for **7a**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL006721K

(13) **Typical Procedure (7g, entry 7).** To a magnetically stirred solution of 0.25 g (1.00 mmol) of 4-bromo benzonitrile (**4c**), 22 mg (0.02 mmol) of $Pd(PPh_3)_2Cl_2$, and 2 mg (0.01 mmol) of CuI in a degassed mixture of 6 mL of THF and 3.5 mL of triethylamine under nitrogen was added dropwise a solution of 139 mg (1.05 mmol) of 1-phenyl propyn-1-ol (**5a**) in 6 mL of THF at room temperature over a period of 30 min. The mixture was heated to reflux temperature for 16 h. After cooling to room temperature 138 mg (1.10 mmol) of 2-amino thiophenol (**6c**) was added, and the reaction mixture was heated to reflux temperature for 8 h. After cooling the solvents were removed in vacuo, and the residue was dissolved in dichloromethane and filtered through a short pad of silica gel. The solvents were evaporated in vacuo and the residue was recrystallized from dichloromethane/pentane to give 228 mg (67%) of analytically pure **7g** as yellow needles. Mp 180−181 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.03 (t, J = 12.8, 1 H), 3.30 (dd, J = 4.9 Hz, J = 12.9 Hz, 1 H), 4.97 (dd, J = 7.7 Hz, J = 12.6 Hz, 1 H), 7.16 (dt, J = 7.5 Hz, J = 1.4 Hz, 1 H), 7.32 (dd, J = 7.8, J = 1.9, 1 H), 7.41 (d, J = 8.3 Hz, 2 H), 7.61−7.46 (m, 7 H), 8.04 (dd, J = 7.6, J = 1.4, 2 H). ^{13}C NMR ($CDCl_3$, 300 MHz): δ 36.7 (CH_2), 59.4 (CH), 111.3 ($C_{quat.}$), 118.3 ($C_{quat.}$), 121.6 ($C_{quat.}$), 125.2 (CH), 125.3 (CH), 126.6 (CH), 127.1 (CH), 128.6 (CH), 130.0 (CH), 131.0 (CH), 132.4 (CH), 134.7 (CH), 137.1 ($C_{quat.}$), 148.6 ($C_{quat.}$), 152.2 ($C_{quat.}$), 168.1 ($C_{quat.}$). MS (70 eV, m/z (%)): 340 (M^+, 8), 211 ($M^+ - NCC_6H_4CH{=}CH_2$, 100). IR (KBr): $\tilde{\nu}$ 2229 cm^{-1}, 1609, 1574, 1452. UV/vis ($CHCl_3$): λ_{max} (ϵ) 244 nm (28700). Anal. Calcd for $C_{22}H_{16}N_2S$ (340.45): C, 77.62; H, 4.74; N, 8.23; S, 9.42. Found: C, 77.48; H, 4.76; N, 8.26; S, 9.52.

(14) All compounds have been characterized spectroscopically and by correct elemental analysis.

(15) Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-149968 (**7a**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. (Fax: + 44-1223/336-033; e-mail: deposit@ccdc.cam.ac.uk).