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[A0074]

A Coupling-Isomerization Sequence As An Entry To A Novel Three Component One-Pot Synthesis of 1,5-Benzoheteroazepines

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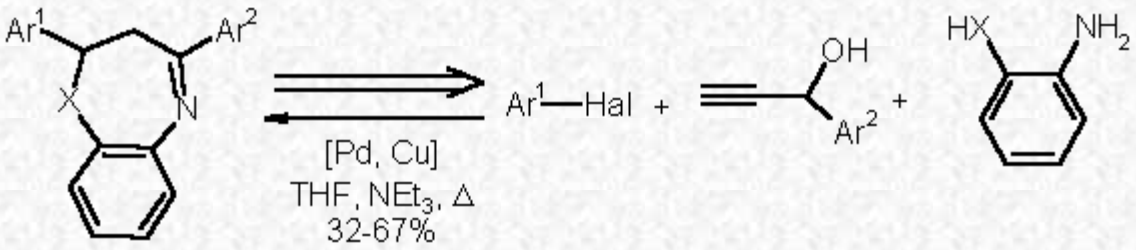
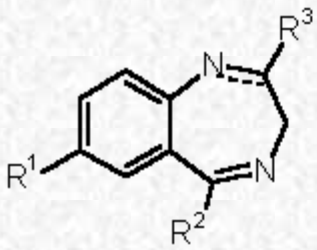
Abstract: 2,4-Di(hetero)aryl substituted 2,3-dihydro 1,5-benzodiazepines, -oxazepines, and thiazepines can be readily synthesized in a three component one-pot process initiated by a coupling-isomerization sequence of an electron poor (hetero)aryl halide and a terminal propargyl alcohol subsequently followed by a cyclocondensation with 2-amino, 2-hydroxy, or 2-mercapto anilines.

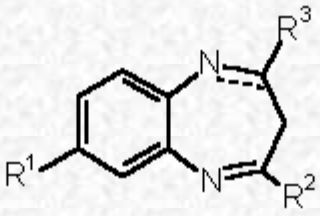


Ar¹ = electron deficient (hetero)aryl
Ar² = aryl
X = NH, O, S

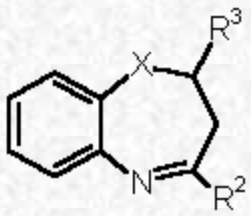
1,4- and 1,5-Benzodiazepines (**1** and **2**) constitute an important class of psychopharmaca [1], in particular, as tranquilizers and also as potent virucides and non-nucleoside inhibitors of HIV-1 reverse transcriptase [1,2]. Besides these only nitrogen containing benzoannealed seven-membered heterocycles their oxaza and thiaza analogues **3** have become increasingly interesting since 1,5 benzothiazepines show anti-fungal, anti-bacterial [3], anti-feedant [4], anti-inflammatory, analgesic [5], and anti-convulsant [6] activity.



1



2



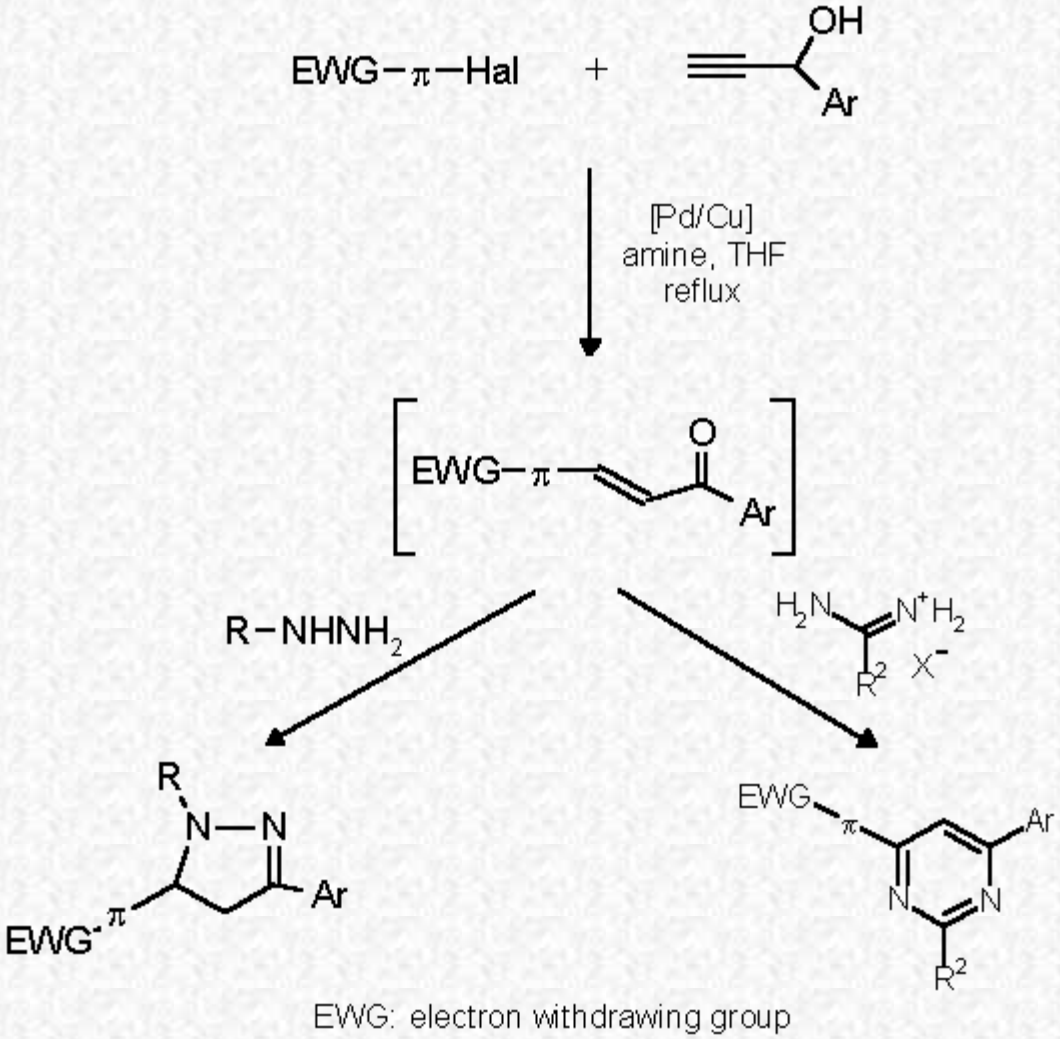
X = NH, O, S

3

Chart 1.

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) [3-6,7]. 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.

Scheme 1. One-pot pyrazoline and pyrimidine synthesis based upon a coupling-isomerization sequence.

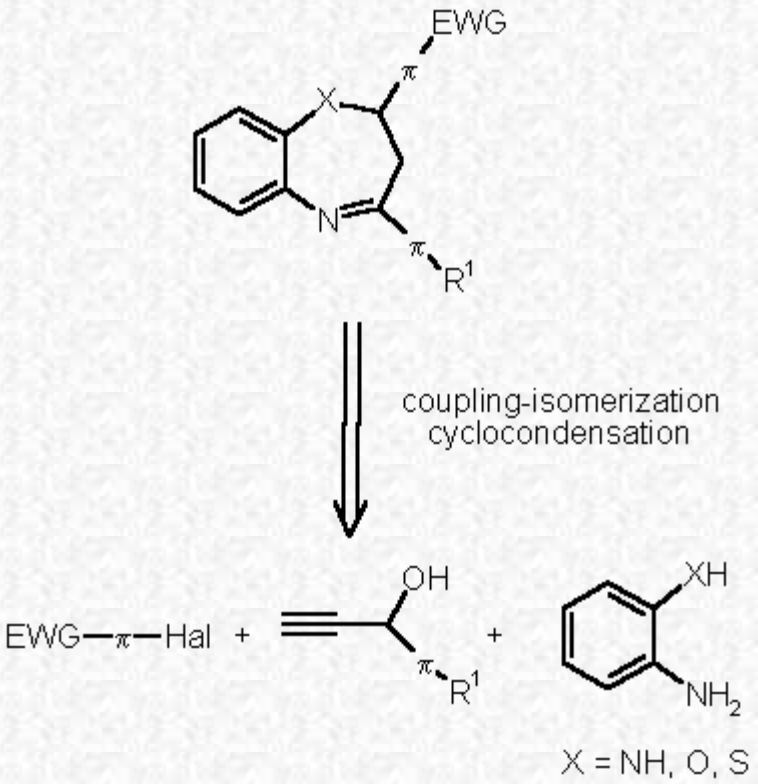


Recently, we found that palladium/copper catalyzed cross-coupling reactions of electron poor halogen substituted p-systems and 1-aryl prop-2-yn-1-ols do not furnish the expected propargyl alcohols but the isomeric enone components [8]. Mechanistically, this isomerization occurring after the cross-coupling 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 [8] and pyrimidine [9] syntheses (Scheme 1).

Since cyclocondensations of 2-heteroatom substituted anilines with chalcones (1,3-diaryl propenones) give 1,5-benzoheteroazepines [2-6], retrosynthetically, an extension of the coupling-isomerization-based methodology to a one-pot synthesis of 1,5-benzoheteroazepines can be easily envisioned. Upon cyclocondensing *ortho*-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, the mild reaction conditions of Sonogashira couplings [10] 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**).

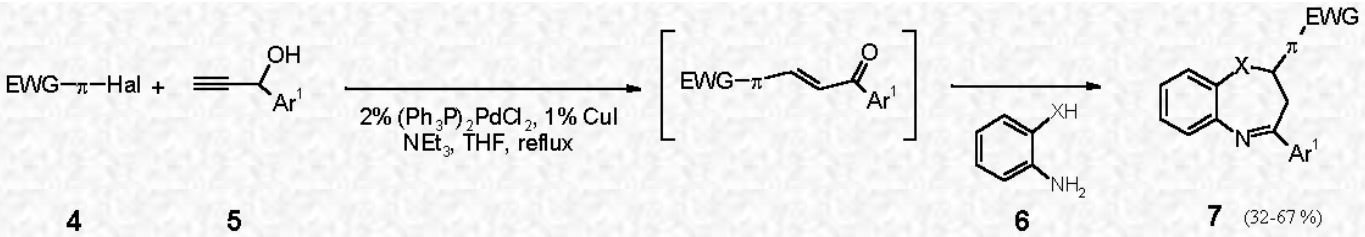
Scheme 2. Retrosynthetic concept for a three component 1,5-benzoheteroazepine synthesis.

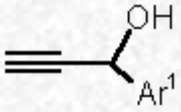
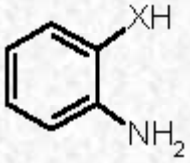
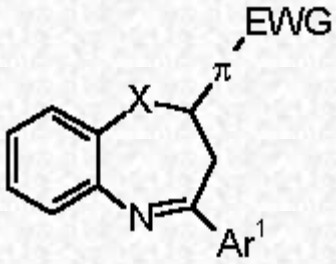
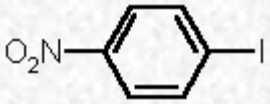
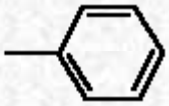
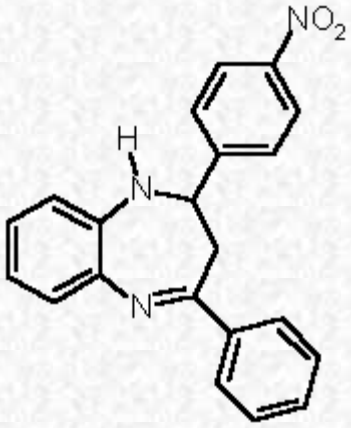
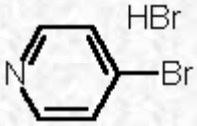
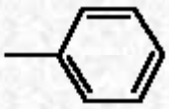
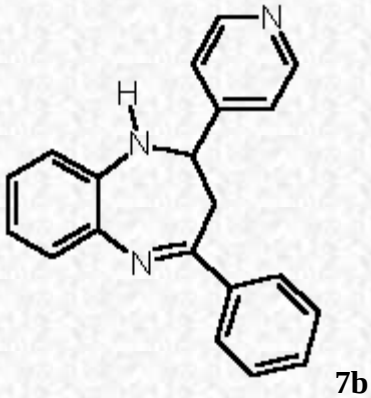
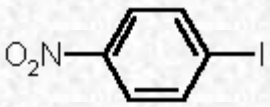
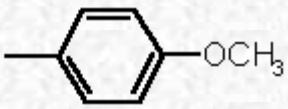


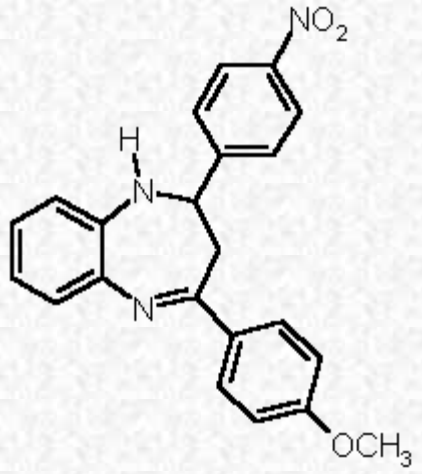
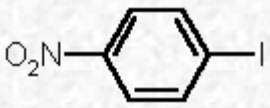
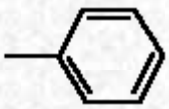
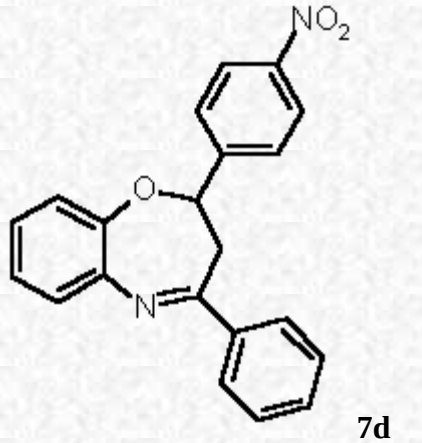
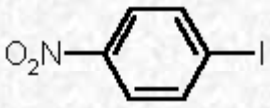
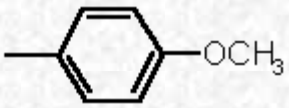
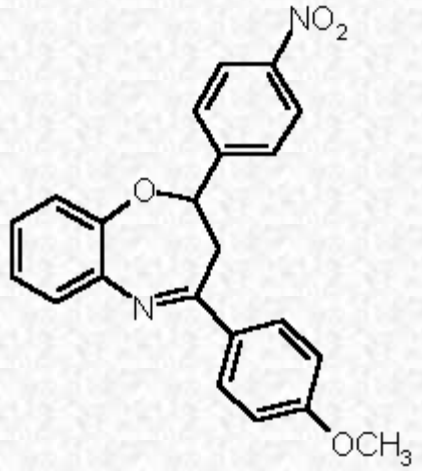
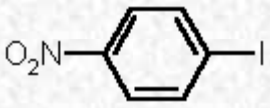
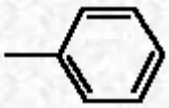
Thus, we have submitted *p*-iodo nitrobenzene (**4a**), 4-bromo pyridine (**4b**), or *p*-bromo benzonitrile (**4c**), aryl propynols **5** [11] and 2-heteroatom substituted anilines **6** to the reaction conditions of the Sonogashira coupling in boiling mixture of triethylamine and THF [12]. In all cases the isolated products were the beige to yellow 1,5-benzoheteroazepines **7** in 32-67 % yield (Table 1) [13]. As already shown for the one-pot synthesis of pyrazolines and pyrimidines the electron withdrawing nature of the (hetero)aryl halide **3** is crucial for the successful coupling-isomerization step [8,9].

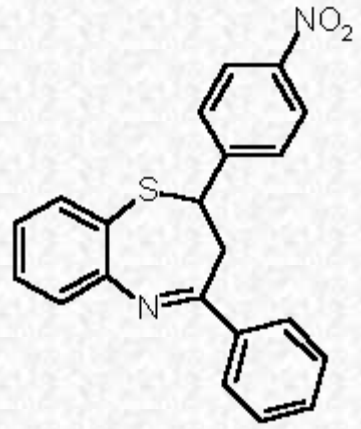
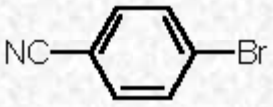
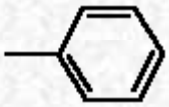
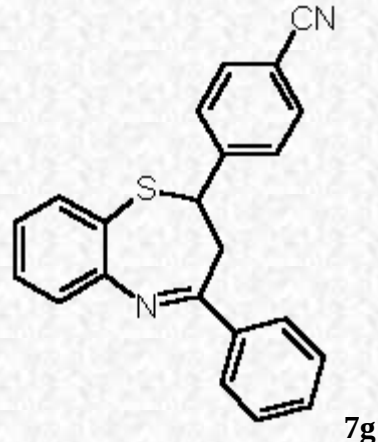
The proton and carbon NMR spectroscopic data support the formation of the 1,5-benzoheteroazepine, in particular, in the ^{1}H NMR spectra of **7** by the indicative appearance of the ABM-spin system with the characteristic geminal and vicinal coupling constants for the methylene group resonances (^{2}J = 13.5 Hz, ^{3}J = 4.4 Hz, ^{3}J = 7.1 Hz) and the vicinal coupling constants for the methine resonances (^{3}J = 4.4 Hz, ^{3}J = 7.0 Hz). Furthermore, the structure of **7** was unambiguously supported by an X-ray crystal structure analysis (Figure 1) of compound **7a** (Table 1, Entry 1).

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



Entry	EWG-p-Hal **3**	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 (10mL/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.

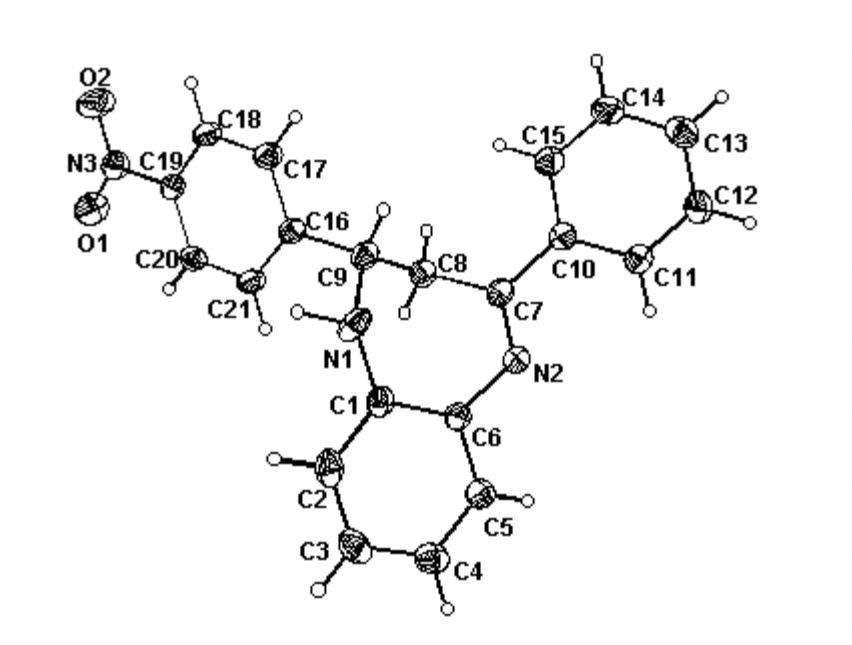


Figure 1

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. Since 2-heteroatom substituted anilines can act as chelating ligands as well transition metal templated syntheses of 14-membered rings [14] for novel ligands in catalysis can be easily envisioned. Further studies directed to extend these one-pot heterocycle syntheses are currently underway.

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[10] (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**, 203.

[11] The propynols **4** were synthesized according to Krause, N.; Seebach, D. *Chem. Ber.* **1987**, *120*, 1845.

[12] **Typical procedure** (**7g**, entry 7): To a magnetically stirred solution of 0.25 g (1.00 mmol) 4-brome benzonitrile (**4c**), 22 mg (0.02 mmol) of $Pd(PPh_3)_2Cl_2$, and 2 mg (0.01 mmol) of CuI in degassed mixture of 6 mL of THF and 3.5 mL of triethylamine under nitrogen a solution of 139 mg (1.05 mmol) of 1-phenyl propyn-1-ol (**5a**) in 6 mL of THF was added dropwise 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 temp. for 8 h. After cooling the solvents were removed *in vacuo* and the residue dissolved in dichloromethane and was 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): d 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): d 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} (e) 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.

[13] All compounds have been characterized spectroscopically and by correct elemental analysis.

[14] Hideg, K.; Lloyd, D. *J. Chem. Soc. C* 1971, 20, 3441.

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