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Diastereoselective synthesis of tetrasubstituted-octahydro-3,6-diazacarbazoles and tetrasubstituted-3,6-diazacarbazoles via double Pictet–Spengler reaction

Abdullah M. A. Shumaila [a], Vedavati G. Puranik [b], Radhika S. Kusurkar [a,*]

[a] Department of Chemistry, University of Pune, Pune 411007, Maharashtra, India
[b] Center for Materials Characterization, National Chemical Laboratory, Pune 411008, Maharashtra, India

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ABSTRACT

Pictet–Spengler condensation of 2,5-bis(2-phenyl-1-aminoethyl)pyrrole using glacial acetic acid afforded only one diastereomer of unreported tetrasubstituted-octahydro-3,6-diazacarbazoles. These were readily dehydrogenated to tetrasubstituted-3,6-diazacarbazoles. The stereoselectivity in the Pictet–Spengler reaction has been demonstrated using single crystal X-ray analysis.

Diazacarbazole is a ring system obtained by substituting two carbons of carbazole skeleton by two nitrogen atoms. They are frequently exploited as carbazole bioisosteres in the design of biologically interesting molecules.[1] Many of these compounds show diverse biological activities, such as Sarcoma 180 inhibitor,[2,3] potential antineoplastic[4] and cytotoxic activities towards L1210 leukaemia cells.[5]

The Pictet–Spengler reaction[6] has been shown to be useful and important for the synthesis of tetrahydro-isoquinoline, tetrahydro-β-carboline and tetrahydro-azaindole ring systems, which are present in numerous natural and synthetic organic compounds possessing various biological activities.[7–9] There are a few reports[3,5,10–12] available in the literature for the synthesis of substituted 3,6-diazacarbazoles and only one report for the synthesis of disubstituted-octahydro-3,6-diazacarbazoles using Pictet–Spengler condensation in HCl.[13] Considering the biological importance there is a need of good synthetic routes towards these compounds. In continuation with our earlier[7d,8b] work in diastereoselective Pictet–Spengler reactions using glacial acetic acid, we herein describe these reactions for the synthesis of new tetrasubstituted-octahydro-3,6-diazacarbazoles and their further dehydrogenation to 3,6-diazacarbazoles.

In the earlier work, silica gel has been used as a solid catalyst for Michael addition reactions where monoalkylated pyrroles were obtained selectively along with little amount of dialkylated pyrroles in some cases.[14] To achieve the exclusive formation of dialkylated pyrroles, the above reactions were carried out at 150 °C using excess amounts of nitro-olefins.

Thus, pyrrole **1** and nitro-olefin **2a** (in 1:3 ratio) were loaded on silica gel and heated at 150 °C for 15 min. This reaction furnished exclusively the expected dialkylated pyrrole **3a** in 91% yield as shown in Scheme 1. Subsequently, the same reaction was carried out using other nitro-olefins **2b–e** resulting in dialkylated products **3b–e** (Scheme 1, Table 1). All dialkylated pyrroles were characterised by comparing the spectral data with the reported values.[14,15] Thus a new method for an exclusive formation of dialkylated pyrroles was developed by using excess of nitro-olefins and heating at 150 °C. These products could serve as important intermediates for the synthesis of biologically active compounds.

After generalizing the conjugate addition of pyrrole, the nitro compound **3a** was reduced using freshly prepared Raney Nickel in methanol to obtain a new amino compound **4** as a diastereomeric mixture in the ratio of 1:1 (Scheme 2).

Further, treatment of amine **4** with benzaldehyde in the presence of glacial acetic acid in dichloromethane furnished tetraphenyl-octahydro-3,6-diazacarbazole **5a** melting at 229–231 °C in 43% yield as shown in Scheme 2. The product **5a** was a single diastereomer which was revealed from ^{1}H and ^{13}C NMR.[16] In

* Corresponding author. Tel.: +91 20 25601400; fax: +91 20 25691728.
E-mail address: rsk@chem.unipune.ac.in (R.S. Kusurkar).

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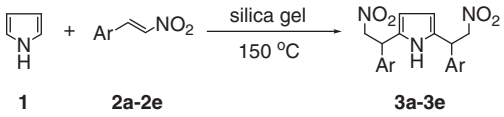


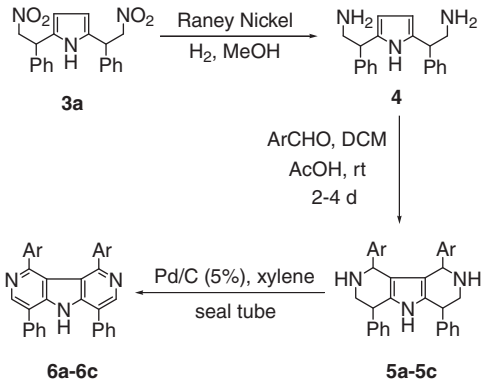
2a, **3a.** Ar = Phenyl; **2b**, **3b.** Ar = 4-Methoxyphenyl; **2c**, **3c.** Ar = 3,4-Dimethoxyphenyl; **2d**, **3d.** Ar = 2-Furyl; **2e**, **3e.** Ar = 2-Thienyl.

Scheme 1. Reaction of pyrrole with nitro-olefin.

Table 1
Time and yield for Michael adducts **3a–e**

Compd no.	Ar	Time (min)	Yield[a] (%)
3a	Phenyl	15	91
3b	4-Methoxyphenyl	20	89
3c	3,4-Dimethoxyphenyl	20	88
3d	2-Furyl	15	90
3e	2-Thienyl	15	91

[a] Products **3a–e** are mixture of diastereomers.



5a, **6a.** Ar = Phenyl; **5b**, **6b.** Ar = 4-Methoxyphenyl; **5c**, **6c.** Ar = 4-Nitrophenyl.

Scheme 2.

addition to this product, one diastereomer of starting amino compounds was recovered from the original reaction mixture in 33% yield which was confirmed by ^{1}H NMR. In the starting amino compound **4** (diastereomeric mixture), there were two singlets at 5.84 and 5.87 ppm with equal intensity where as in the recovered product only one singlet was observed at 5.83 ppm. The other regions in the ^{1}H NMR spectrum also indicated simplification of the signals consistent with the recovered product being a single diastereomer.[17]

To investigate the stereochemistry of the diastereomer **5a**, a single crystal was prepared and X-ray analysis was carried out which unambiguously showed that the diastereomer of **5a** has S, R, S and R relative configurations at C_1, C_4, C_5 and C_8, respectively, as shown in Figure 1.[18]

This indicated *trans* geometry at C_1 and C_4 and at C_5 and C_8 and *cis* geometry at C_1 and C_8 and at C_4 and C_5. From this observation it is revealed that amongst the mixture of two diastereomers of the starting amino compound, only one isomer reacted and other was recovered from the Pictet–Spengler condensation. The diastereoselectivity obtained in the above mentioned reaction can be attributed to slow and selective reaction in the presence of glacial acetic acid.

Further, dehydrogenation of **5a** by heating in a sealed tube at 120 °C with 5% Pd/C in xylene furnished 1,4,5,8-tetraphenyl-3,6-

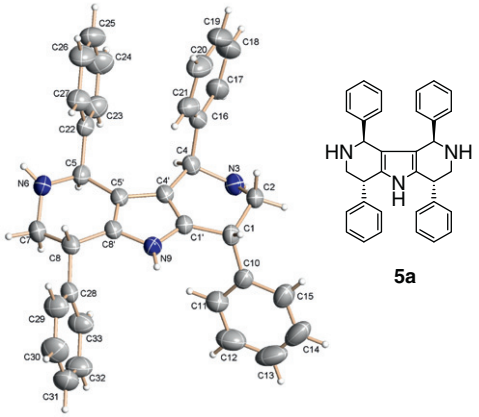


Figure 1. ORTEP diagram of compound **5a** ellipsoids is drawn at 50% probability.

diazacarbazole **6a**. The structure was confirmed using analytical and spectral data.[19]

After getting a successful diastereoselective reaction using acetic acid as a catalyst, it was decided to generalize the stereoselectivity in these reactions. Thus, condensation of the amine **4** with benzaldehydes having electron donating (4-methoxybenzaldehyde) and electron withdrawing (4-nitrobenzaldehyde) substituents afforded new compounds **5b** and **c**, respectively, in a diastereoselective manner (Scheme 2). Since the X-ray revealed the geometry of compound **5a** to be as shown in Figure 1, it was presumed that the compounds **5b** and **c** should have the similar geometry.

In the last step, dehydrogenation of tetrasubstituted-octahydro-3,6-diazacarbazoles **5b** and **c** furnished tetrasubstituted-3,6-diazacarbazole **6b** and **c**, respectively. During the Pictet–Spengler condensation step compounds **6a** and **b** were also obtained in very minor amounts. The presence of them was confirmed by TLC.

A diastereoselective method was established for the synthesis of octahydro-3,6-diazacarbazoles using Pictet–Spengler condensation in glacial acetic acid. This method was used for synthesizing three new tetrasubstituted-octahydro-3,6-diazacarbazoles **5a, b** and **c** which were dehydrogenated to tetrasubstituted-3,6-diazacarbazoles **6a, b** and **c**. The structure and stereochemistry of compound **5a** were unambiguously established as S, R, S and R at C_1, C_4, C_5 and C_8, respectively, using single crystal X-ray analysis. The importance of new tetrasubstituted-3,6-diazacarbazoles lies in their structural similarity with biphenyls and thus may exhibit atropisomerism.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.03.060.

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16. *1,4,5,8-Tetraphenyl-1,2,3,4,5,6,7,8-octahydro-9H-dipyrido-[4,3-b;3′,4′-d]pyrrole* **5a**: 43%, colourless crystals; mp 229–231 °C; R_f 0.41 (50% EtOAc/hexane); ν_{max} (KBr) 3308, 3217, 3140 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.41 (1H, br s, N*H* exchangeable with D_2O), 7.29–7.2 (4H, m, Ar*H*), 7.17 (2H, t, *J* 7.4 Hz, Ar*H*), 7.07 (4H, d, *J* 7.3 Hz, Ar*H*), 6.86 (10H, strong br s, Ar*H*), 4.89 (2H, s, C_4H,C_5H), 4.0 (2H, t, *J* 5.0 Hz, C_1H,C_8H), 3.36 (2H, dd, *J* 5.5, 12.7 Hz, C_2H,C_7H), 2.75 (2H, dd, *J* 5.0, 12.7 Hz, C_2H,C_7H), 1.72 (2H, br s, 2>N*H* exchangeable with D_2O); δ_C (75 MHz, DMSO-d_6) 145.6 (2 × carbons), 143.2 (2 × carbons), 128.1 (8 × carbons), 127.8 (4 × carbons), 126.7 (4 × carbons), 126.5 (2 × carbons), 125.8 (2 × carbons), 125.6 (2 × carbons), 115.2 (2 × carbons), 55.7 (2 × carbons), 47.9 (2 × carbons), 40.3 (2 × carbons); *m*/*z* 481 [M^+], 452 (100%), 423, 404, 91, 77; Anal. Calcd for $C_{34}H_{31}N_3$ requires: C, 84.79; H, 6.49; N, 8.72. Found: C, 84.98; H, 6.74; N, 8.48.
17. *2,5-Bis(2-phenyl-1-aminoethyl)pyrrol* **4** (diastereomeric mixture): 92%, brown solid, mp 77–79 °C; ν_{max} (KBr) 3319 (br), 3286 (br) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 9.39 (1H, br s, N*H* exchangeable with D_2O), 9.29 (1H, br s, N*H* exchangeable with D_2O), 7.31–7.11 (20H, m, Ar*H*), 5.87 (2H, s, Ar*H*), 5.84 (2H, s, Ar*H*), 3.87 (4H, dd, *J* 6.6, 12.6 Hz, C_2H), 3.17 (4H, dd, *J* 7.1, 12.4 Hz, C_1H), 3.07 (4H, dd, *J* 6.6, 12.4 Hz, C_1H), 1.64 (8H, br s, NH_2 exchangeable with D_2O); δ_C (75 MHz, $CDCl_3$) 142.0 (2 × carbons), 141.9 (2 × carbons), 132.4 (2 × carbons), 132.3 (2 × carbons), 128.49 (4 × carbons), 128.47 (4 × carbons), 128.1 (8 × carbons), 126.7 (4 × carbons), 105.0 (2 × carbons), 104.9 (2 × carbons), 47.7 (2 × carbons), 47.6 (2 × carbons), 47.2 (2 × carbons), 47.1 (2 × carbons); *m*/*z* 305 [M^+], 275, 259, 246 (100%), 156, 141, 91, 77. The ^1H NMR spectrum of recovered amino product: δ_H (300 MHz, $CDCl_3$) 10.48 (1H, br s, N*H* exchangeable with D_2O), 7.29–7.06 (10H, m, Ar*H*), 5.83 (2H, s, Ar*H*), 4.09 (2H, t, *J* 5.1 Hz, C_2H), 3.93 (4H, br s, 2 × NH_2 exchangeable with D_2O), 3.27 (2H, dd, *J* 5.1, 12.2 Hz, C_1H), 3.08 (2H, dd, *J* 6.6, 12.2 Hz, C_1H).
18. Crystallographic data in this paper have been deposited with the Cambridge Crystallographic Data Centre. Deposition number is CCDC 808489 for **5a**. Copy of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).
19. *1,4,5,8-Tetraphenyl-9H-dipyrido-[4,3-b;3′,4′-d]pyrrole* **6a**: 35%, white solid; mp 197–199 °C; R_f 0.29 (30% EtOAc/hexane); ν_{max} (KBr) 3421 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 11.73 (1H, br s, N*H* exchangeable with D_2O), 8.57 (2H, s, C_2H,C_7H), 7.76 (4H, d, *J* 7.0 Hz, Ar*H*), 7.65–7.21 (10H, m, Ar*H*), 7.06–6.91 (6H, m, Ar*H*); δ_C (75 MHz, DMSO-d_6) 148.5 (2 × carbons), 141.5 (2 × carbons), 137.4 (2 × carbons), 135.9 (2 × carbons), 135.5 (2 × carbons), 132.7 (2 × carbons), 129.2 (8 × carbons), 127.7 (4 × carbons), 127.6 (4 × carbons), 126.1 (2 × carbons), 125.9 (2 × carbons), 121.0 (2 × carbons); *m*/*z* 473 [M^+], 446, 396, 91 (100%), 77; Anal. Calcd for $C_{34}H_{23}N_3$ requires: C, 86.23; H, 4.90; N, 8.87. Found: C, 86.51; H, 4.63; N, 8.59.