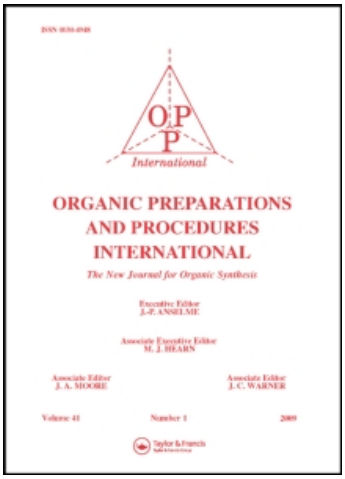


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

A CONVERGENT SYNTHETIC ROUTE TO 2-OXOPYRIDO[2,3-*a*]CARBAZOLES *via* 2-OXOPYRANO[2,3-*a*]CARBAZOLES FROM 1-OXO-1,2,3,4-TETRAHYDROCARBAZOLES

I. Antony Danish[a]; K. J. Rajendra Prasad[a]
[a] Department of Chemistry, Bharathiar University, Coimbatore, INDIA

To cite this Article Danish, I. Antony and Prasad, K. J. Rajendra(2004) 'A CONVERGENT SYNTHETIC ROUTE TO 2-OXOPYRIDO[2,3-*a*]CARBAZOLES *via* 2-OXOPYRANO[2,3-*a*]CARBAZOLES FROM 1-OXO-1,2,3,4-TETRAHYDROCARBAZOLES', Organic Preparations and Procedures International, 36: 4, 371 — 374
To link to this Article: DOI: 10.1080/00304940409458682
URL: http://dx.doi.org/10.1080/00304940409458682

A CONVERGENT SYNTHETIC ROUTE TO 2-OXOPYRIDO[2,3-*a*]CARBAZOLES *via* 2-OXOPYRANO[2,3-*a*]CARBAZOLES FROM 1-OXO-1,2,3,4-TETRAHYDROCARBAZOLES

Submitted by I. Antony Danish and K. J. Rajendra Prasad*
(2/3/04)

Department of Chemistry, Bharathiar University
Coimbatore-641 046, INDIA

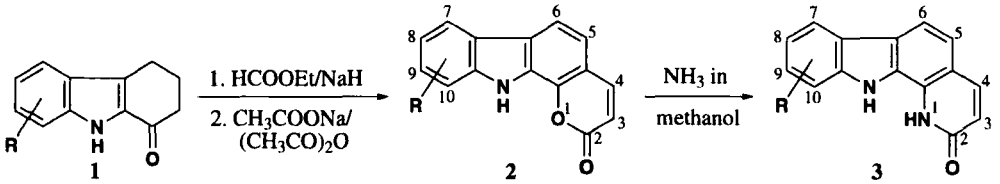
Among the carbazole alkaloids, pyridocarbazoles have gained much attention due to their well known anticancer[1-3] and anti-HIV[4] properties. In particular, a large number of pyrido[3,2-*b*]carbazoles, namely ellipticine derivatives, have been tested for their cytotoxic and antitumour activities.[5,6] The reported methods have used indoles,[7-9] 3-aminocarbazoles,[10] stilbenes[11] and quinolines[12] as starting materials, albeit in only low yields due either to the large number of steps or due to the formation of several isomers. Although earlier reports from our laboratory have described the preparation of the pyrano[2,3-*a*]carbazoles from 1-hydroxycarbazoles,[13,14] the methods suffer from some limitations such as multiple steps, low yield and difficulty in preparing the starting materials. This prompted us to search for an easy route to prepare pyridocarbazoles from 1-oxo-1,2,3,4-tetrahydrocarbazoles (**1**) *via* pyrano[2,3-*a*]carbazoles (**2**). Herein we report an efficient synthesis of 2-oxopyrido[2,3-*a*]carbazoles under mild reaction conditions in excellent yields.

Treatment of 1-oxo-1,2,3,4-tetrahydrocarbazoles [15] (**1**) with ethyl formate in the presence of sodium hydride, followed by reaction with acetic anhydride and anhydrous sodium acetate afforded 2-oxopyrano[2,3-*a*]carbazoles (**2**) in good yields. Reaction of **2** with dry ammonia gas in methanol resulted in the formation of 2-oxopyrido[2,3-*a*]carbazoles (**3**) in excellent yields.

The IR spectrum of product **2a** exhibited a strong band at 1747 cm^{-1} which has been well documented as in the α-pyrones.[16] The intense band at 3373 cm^{-1} is due to the NH stretching vibrations. The ^1H NMR spectrum showed the presence of the methyl protons as a three-proton singlet at δ 2.52. The aromatic protons at C_3 to C_9 resonated as a multiplet in the region δ 6.92-8.02. A broad singlet at δ 8.15 is ascribable to the carbazole NH proton. The mass spectrum showed the molecular ion peak, *m/z* at 249 (55%). Further, the elemental analysis agreed well with the molecular formula of $C_{16}H_{11}NO_2$. From these data, the structure of the product was established as 2-oxo-10-methylpyrano[2,3-*a*]carbazole (**2a**). Similarly, **1b**, **1c** and **1d** yielded the respective 2-oxopyrano[2,3-*a*]carbazoles **2b**, **2c** and **2d**.

The reaction of **2a** with gaseous ammonia in methanol afforded a product which melted at 178-180°C. The IR spectrum of the product exhibited strong absorptions at 3455, 3390 and 1618 cm^{-1}corresponding to the stretching vibrations for the two NH moieties and the amide C=O,

respectively. The ^{1}H NMR spectrum showed a three-proton singlet at δ 2.53 for the C_{10} methyl group. A broad singlet at δ 5.38 was due the NH proton at N_1. The aromatic protons at C_3 to C_9 appeared as a multiplet in the region δ 6.81-7.85. A broad singlet at δ 8.19 was accounted for the carbazole NH proton. The molecular ion peak at *m/z* 248 (33%) and the elemental analysis agreed well with the molecular formula $C_{16}H_{12}N_2O$. Based on the spectral and elemental analysis the structure of the product thus obtained was established as 2-oxo-10-methylpyrido[2,3-*a*]carbazole (**3a**). The generality of the reaction was tested with other 2-oxopyrano[2,3-*a*]carbazoles (**2b-d**). In all cases, the corresponding 2-oxopyrido[2,3-*a*]carbazoles (**3b-d**) were obtained. Analytical and spectral data were consistent with the proposed structures **2** and **3** (*Scheme 1*).



1, a) R = 8-CH_3; b) R = 7-CH_3; c) R = 6-CH_3; d) R = H: **2,3**, a) R = 10-CH_3; b) R = 9-CH_3; c) R = 8-CH_3; d) R = H

Scheme 1

Table. Mps, Yields, Elemental Analysis and Spectral Data of **2** and **3**

Cmpd	Mp (°C)	Yield (%)	IR (cm^{-1})	^{1}H NMR (δ)	Elemental Analysis (Found) C	H	N
2a	185-187	75	3373 1747	2.52 (s, 3H), 6.92-8.02 (m, 7H), 8.15 (br s, 1H)	77.09 (76.85)	4.45 (4.38)	5.62 (5.52)
2b	160-162	70	3404 1764	2.50 (s, 3H), 7.04-8.05 (m, 7H), 8.10 (br s, 1H)	77.09 (76.95)	4.45 (4.40)	5.62 (5.58)
2c	202-205	73	3421 1760	2.17 (s, 3H), 7.03-8.08 (m, 7H), 8.12 (br s, 1H)	77.09 (77.22)	4.45 (4.32)	5.62 (5.54)
2d	169-171	72	3415 1760	7.19-8.08 (m, 9H)	76.59 (76.68)	3.98 (3.86)	5.95 (5.82)
3a	178-180	90	3455 3390 1618	2.53 (s, 3H), 5.38 (br s, 1H), 6.81-7.85 (m, 7H), 8.19 (br s, 1H)	77.40 (77.32)	4.87 (4.95)	11.28 (11.20)
3b	157-159	92	3433 3271 1618	2.52 (s, 3H), 5.55 (br s, 1H),6.79-8.21 (m, 7H), 8.37 (br s, 1H)	77.40 (77.49)	4.87 (4.82)	11.28 (11.38)
3c	180-182	90	3460 3390 1616	2.53 (s, 3H); 5.35 (br s) 6.82-7.85 (m, 7H), 8.19(br s, 1H)	77.40 (77.59)	4.87 (4.78)	11.28 (11.20)
3d	196-197	85	3433 3255 1616	5.76 (b s, 1H), 6.86-8.07 (m, 8H), 8.48 (br s, 1H)	76.91 (76.83)	4.30 (4.21)	11.96 (11.85)

EXPERIMENTAL SECTION

Melting points were determined with a Mettler FP 51 melting point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu FTIR-8000 infra red spectrometer using KBr. ^{1}H-NMR spectra were obtained on a Varian AMX 400 FT-NMR spectrometer using TMS as an internal reference in $CDCl_3$ and the chemical shifts are quoted in parts per million (ppm). Mass spectra were performed on a Jeol-JMS-D-300 mass spectrometer. Microanalyses were done on a Carlo Erba 1106 CHN analyzer. Ethyl formate, acetic anhydride and sodium acetate were obtained from Qualigens, India and used as received and sodium hydride was from LOBA Chemie Pvt. Ltd. (as a 60% suspension of mineral oil).

Preparation of 2-Oxopyrano[2,3-*a*]carbazoles (2).- To a suspension of sodium hydride (2.40 g, 0.1 mole in 60% mineral oil suspension) in dry benzene (10 mL) in a round bottom flask fitted with a calcium chloride filled guard tube, cooled at 0°C, ethyl formate (5 mL, 0.062 mole) was added in portions with stirring. To this mixture, a solution of the 1-oxo-1,2,3,4-tetrahydrocarbazole **1** (0.003 mole) in dry benzene (20 mL) was added slowly with stirring. The reaction mixture was stirred at room temperature for 30 hrs. After this period the reaction was quenched in ice cold water (50 mL) to decompose the excess of sodium hydride (***CAUTION: Great care must be taken while adding water to sodium hydride***) and neutralization with ice cold HCl (1:1) to precipitate a yellow solid. The latter was dissolved in acetic anhydride (10 mL) and anhydrous sodium acetate (1 g) was added. The reaction mixture was refluxed at 170°C for 10 hrs under a nitrogen atmosphere and then poured into crushed ice. The resulting semi-solid was extracted with ethyl acetate, washed with water and dried over anhydrous sodium sulfate. Removal of the solvent yielded a crude product which was purified by passing it through a silica gel (Acme's synthetic chemicals, 60-120 mesh, 30 cm column) packed column and eluting with petroleum ether-ethyl acetate mixture (90:10) to yield 2-oxopyrano[2,3-*a*]carbazoles (**2**).

Preparation of 2-Oxopyrido[2,3-*a*]carbazoles (3).- To a solution of the 2-oxopyrano[2,3-*a*]carbazole **2** (0.001 mole) in absolute methanol (20 mL), ammonia gas was passed for about 5 hrs until saturation. After that time period, the excess of methanol was removed by distillation to give a crude product which was extracted with chloroform. The organic layer was washed thoroughly with water and dried over anhydrous sodium sulfate. The excess of solvent was removed by distillation to yield the corresponding 2-oxopyrido[2,3-*a*]carbazole (**3**) which was recrystallized from petroleum ether.

Acknowledgements.- The authors are grateful to RSIC, CDRI, Lucknow for providing elemental analysis, mass spectral data and SIF, IISc, Bangalore for ^{1}H NMR, respectively.

REFERENCES

1. V. K. Kansal and P. Potier, *Tetrahedron*, **42**, 2389 (1986).

2. L. K. Dalton, S. Demarac, T. Teitei, *Australian J. Chem.*, **22**, 185 (1969).

3. C. B. de Koning, J. P. Michael and A. L. Rosseau, *J. Chem. Soc. Perkin Trans. 1*, 1705 (**2000**).

4. K. Hirata, C. Ito, H. Furukawa, M. Itogiawa, L. M. Cosentino and K. H. Lee, *Bioorg. Med. Chem. Lett.*, **9**, 119 (1999).

5. N. Haider, *J. Heterocyclic Chem.*, **39**, 511 (2002).

6. V. M. Hedin, T. Tabka, L. Poulain, T. Godard, M. Lachevrel, C. Saturnino, J. C. Lancelot, J. Y. Le Talaer and P. Gauduchon, *Anti-Cancer Drug Design*, **15**, 109 (2000).

7. F. Le Goffic, A. Gouyette and A. Ahond, *Tetrahedron*, **29**, 2264 (1973).

8. T. Kametani, Y. Ichikawa, T. Suzuki and K. Fukumoto, *Heterocycles*, **3**, 40 (1975).

9. Y. Langlois, N. Langlois and P. Potier, *Tetrahedron Lett.*, 955 (**1975**).

10. J. C. Perche, G. Saint-Ruf, *J. Heterocyclic Chem.*, **11**, 93 (1974).

11. J. C. Lancelot, S. Rault, M. Robba and N. Huy Dung, *Chem. Pharm. Bull.*, **35**, 425 (1987).

12. B. Danieli and G. Palmisano, *J. Heterocyclic Chem.*, **14**, 839 (1977).

13. D. Sowmithran and K. J. Rajendra Prasad, *Heterocycles*, **24**, 2195 (1986).

14. M. Sekar and K. J. Rajendra Prasad, *Indian J. Chem.*, **33B**, 479 (1994).

15. D. Sowmithran and K. J. Rajendra Prasad, *Heterocycles*, **24**, 711 (1986).

16. M. Sekar and K. J. Rajendra Prasad, *J. Chem. Technol. Biotechnol.*, **72**, 50 (1998).

****