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A Facile Method for the Synthesis of Acetylcarbazoles and Carbazole Aldehydes

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ABSTRACT

Acetylation of 9-alkylcarbazoles with acetic anhydride catalyzed by $PPh_3 \cdot HClO_4$ was reported to give acetylcarbazoles. Carbazole aldehydes were easily synthesized by the Vilsmeier reaction of 9-alkylcarbazoles under microwave condition in good yields.

Key Words: Carbazoles; Acetylation; Acetylcarbazoles; Vilsmeier reagent; Carbazole aldehydes.

The synthesis of substituted carbazoles^[1] has attracted considerable attention in recent years as this class of compounds constitutes structural frameworks of several naturally occurring alkaloids which display a wide range

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of biological activities. Acetylcarbazoles were used as the useful synthon for the synthesis of condensed carbazole heterocyles.

The acetylation of 9-ethylcarbazole with acetyl chloride catalyzed by AlCl₃ had been reported to give the mixture of 3- and 3,6-diacetyl derivatives^[2] and large amount of tarry products due to high Lewis acidity of AlCl₃. In continuation of our research on triphenyl phosphonium perchlorate,^[3] it was of our interest to carry out the acetylation of carbazoles catalyzed by PPh₃·HClO₄, since PPh₃·HClO₄ is known to be efficient catalyst for organic reactions.

The reaction was performed by addition of 20 mol% of $PPh_3 \cdot HClO_4$ to a stirred solution of 9-ethylcarbazole in excess acetic anhydride for 2 hr. Examination of the TLC shows only 3-acetylated product and there is no diacetylated carbazole formed during the acetylation. There is not much tarry products formed when $PPh_3 \cdot HClO_4$ was used as a catalyst. $PPh_3 \cdot HClO_4$ is found to be better over other catalysts because it is mild, inexpensive, requires shorter reaction times, and 3-acetylated carbazole was only the product. The results of acetylation of other substituted carbazoles catalyzed by $PPh_3 \cdot HClO_4$ were given in Sch. 1 and Table 1.

To prove the generality of PPh₃·HClO₄, the acylation was carried out with other anhydrides such as benzoic anhydride and propionic anhydride. The reaction of 9-ethylcarbazole with benzoic anhydride in CH₂Cl₂ catalyzed by PPh₃·HClO₄ (20 mol%) for 3 hr yielded the 3-benzoylcarbazole in 34% yield. However, the reaction of 9-ethylcarbazole with propionic anhydride proceeded for 1.5 hr and gave mainly 3,6-propionyl-9-ethylcarbazole (49%) as the major product together with 3-propionylcarbazole (22%). The acylation of carbazoles with acid chlorides results in the formation of large amount of tarry products and lesser yields of the 3-acylcarbazoles due to the formation of HCl as the side product.

Carbazole aldehydes occur in nature as alkaloids, namely, Mukonal, Murrayanine, Heptaphylline, Murrayacine, which exhibit wide range of biological activities.^[1] They also serve as a synthon for the synthesis of pyridocarbazole alkaloids, such as ellipticine, 9-methoxy ellipticine and olivacine,



Scheme 1.

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Synthesis of Acetylcarbazoles and Carbazole Aldehydes

Table 1. Synthesis of acetylcarbazoles with $PPh_3 \cdot HClO_4$ (20 mol%).

	Substituents			
Carbazole	R^1	\mathbb{R}^2	Time (hr)	Yield ^a (%)
1a	CH ₃	Н	2.0	56
1b	C_2H_5	Н	2.0	61
1c	C_2H_5	CH_3	2.5	59

^aThe yield is based on isolation by column chromatography and the products were characterized by IR, NMR, and mass spectra.

which exhibit pronounced anti-cancer activity in several animal and human tumor systems,^[4a] in treatment of myleoblastic leukemia, advanced breast cancer, and other solid tumors.^[4]

In continuation of our research on Vilsmeier reaction,^[5] we herein report the synthesis of carbazole aldehydes through Vilsmeier reaction under microwave irradiation. The procedure offers advantages such as better yields and easier reaction conditions. The reaction is complete within a few minutes.

To a stirred solution of 9-ethylcarbazole in DMF under ice-cold condition, $POCl_3$ was added. When the addition is over, the reaction is brought to room temperature and irradiated in microwave oven with low power (30%) for 1.5 min (with a time intervals of 30 sec). After work up, the crude product is purified by column chromatography and eluted with ethyl acetate– petroleum ether to give 9-ethylcarbazole-3-aldehyde in 89% yield (Sch. 2). The results with other substituted carbazoles are given in Table 2.

In conventional method, *N*-methylformanilide was used instead of DMF and *o*-dichlorobenzene as the solvent in water bath temperature for longer reaction time. Steam distillation is necessary to remove the side product *N*-methylaniline as well as solvent *o*-dichlorobenzene and the product was purified through vacuum distillation. However, the microwave accelerated



Scheme 2.



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Substituents		Time of	
R^1	R^2	(min)	Yield (%)
CH ₃	Н	1.5 (360) ^{a [6]}	82 (61) ^{a [6]}
C_2H_5	Н	1.5 (240) ^{a [7]}	89
C_2H_5	CH_3	2.0	90 (60) ^{a [7]}
C_2H_5	Br	1.8 (240) ^{a [7]}	87
	$\begin{tabular}{c} Substitute & \\ \hline R^1 \\ \hline CH_3 \\ C_2H_5 \\ C_2H_5 \\ C_2H_5 \\ C_2H_5 \\ C_2H_5 \end{tabular}$	$\begin{tabular}{ c c c c c } \hline Substituents \\ \hline \hline R^1 & R^2 \\ \hline CH_3 & H \\ C_2H_5 & H \\ C_2H_5 & CH_3 \\ C_2H_5 & Br \\ \hline \end{tabular}$	$\begin{tabular}{ c c c c c c c c c c c c c c c c c c c$

Table 2. Synthesis of carbazoles aldehydes.

^aYield reported in the literature.

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formylation of 9-alkylcarbazoles with DMF and POCl₃ proceeds nearly giving higher yields of the products in few minutes and pure product was obtained by recrystallization from the crude product (ethyl acetate : petroleum ether mixture).

In conclusion we have shown the efficient method for the synthesis of acetylcarbazoles by acetylation of carbazoles with acetic anhydride catalyzed by $PPh_3 \cdot HClO_4$. Carbazole aldehydes were easily synthesized by the reaction of 9-alkylcarbazoles with Vilsmeier reagent in good yields.

PROCEDURE FOR ACETYLATION

To a stirred mixture of carbazoles (0.5 g, 1 eq.) and acetic anhydride (3 eq.) in CH_2Cl_2 (10 mL), $PPh_3 \cdot HClO_4$ (20 mol%) was added and stirred for appropriate time. Water (50 mL) was added to the reaction mixture, extracted with CH_2Cl_2 (3 × 10 mL), and dried with anhydrous Na_2SO_4 . The solvent was distilled off and the residue was chromatographed over silica gel, eluted with ethyl acetate : petroleum ether mixture (1 : 9) to give the acetyl carbazoles.

3-Acetyl-9-ethylcarbazole (2b). Colorless needles of 0.371 g (61%); m.p. 115–116°C (Lit.^[2] 115); IR: 3046, 2921, 1667, 1593, 1495, 1351, 1170, 838 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 8.75 (d, 1H, J = 1.2 Hz), 8.18 (m, 2H), 7.50 (t, 1H), 7.46–7.26 (m, 3H), 4.42 (q, 2H); 2.73 (s, 3H), 1.46 (t, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 197.2, 142.2, 140.2, 128.3, 126.0, 122.8, 122.2, 121.4, 120.2, 119.5, 108.5, 107.6, 107.4, 37.3, 26.1, 13.3; Mass m/z 237 (M⁺); Anal. calcd for C₁₆H₁₅NO: C, 80.98; H, 6.37; N, 5.90; Found: C, 81.22; H, 6.48; N, 6.76.

3-Methyl-6-acetyl-9-ethylcarbazole (2c). Colorless crystals of 0.354 g (59%); m.p. 90–91°C; IR: 3049, 2976, 2922, 1629, 1667, 1596, 1448, 1353, 1302, 1244, 1161, 804 cm^{-1} ; ¹H NMR (300 MHz, CDCl₃): δ 8.70



Synthesis of Acetylcarbazoles and Carbazole Aldehydes

(d, 1H, J = 1.2 Hz), 8.11 (dd, 1H, $J_1 = 1.5$ Hz, $J_2 = 8.4$ Hz), 7.95 (s, 1H), 7.37 (m, 3H), 4.37 (q, 2H), 2.71 (s, 3H), 2.55 (s, 3H), 1.42 (t, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 198.1, 143.3, 139.3, 129.8, 128.9, 128.1, 126.6, 123.8, 122.9, 122.3, 121.1, 109.1, 108.3, 38.2, 27.1, 21.8, 14.2; Mass m/z 251 (M⁺); Anal. calcd for C₁₇H₁₇NO: C, 81.24; H, 6.82; N, 5.57; Found: C, 81.54; H, 6.79; N, 5.36.

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GENERAL PROCEDURE FOR THE VILSMEIER REACTION

To a stirred mixture of 9-alkyl carbazole (0.5 g, 1 eq.) in DMF (7 mL) under ice-cold condition, POCl₃ (3 eq.) was added and then brought to room temperature. The reaction mixture was then irradiated in MW oven (30% power) for appropriate time. The reaction mixture was then poured onto crushed ice, neutralized with Na₂CO₃ solution (saturated), and extracted with CHCl₃ (3 × 10 mL). The organic layer is separated, dried with anhydrous Na₂SO₄, and distilled under reduced pressure. The residue was recrystallized from ethyl acetate : petroleum ether mixture (2 : 8).

9-Ethylcarbazole-3-aldehyde (3b). Colorless crystalline solid of 0.526 g (89%); m.p. 94–95°C (Lit.^[7] 94); IR: 3051, 2970, 2820, 1674, 1384, 769 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 10.07 (s, 1H, CHO), 8.56 (s, 1H), 8.14 (d, 1H, J = 7.8 Hz), 8.00 (dd, 1H, $J_1 = 1.5$ Hz, $J_2 = 8.6$ Hz), 7.56–7.29 (m, 4H), 4.38 (q, 2H), 1.44 (t, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 191.7, 143.4, 140.5, 128.3, 127.0, 126.6, 123.9, 122.9, 122.8, 120.6, 120.2, 109.0, 108.5, 37.8, 13.7; Mass m/z 223 (M⁺); Anal. calcd for C₁₅H₁₃NO: C, 80.69; H, 5.87; N, 6.27; Found: C, 80.86; H, 5.79; N, 6.36.

3-Methyl-9-ethylcarbazole-6-aldehyde (3c). Colorless crystalline solid of 0.510 g (90%); m.p. 92–93°C (Lit.^[7] 91); IR: 3018, 2973, 1681, 1597, 1484, 1331, 811 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 10.06 (s, 1H, CHO), 8.56 (s, 1H), 7.99 (dd, 1H, $J_1 = 1.5$ Hz, $J_2 = 8.6$ Hz), 7.94 (s, 1H), 7.44 (d, 1H, J = 8.5 Hz), 7.34 (s, 2H), 4.39 (q, 2H), 2.55 (s, 3H), 1.44 (t, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 191.8, 143.6, 138.8, 129.7, 128.2, 127.9, 126.9, 124.0, 123.1, 122.9, 120.7, 108.8, 108.5, 38.9, 21.4, 13.8; Mass m/z 237 (M⁺); Anal. calcd for C₁₆H₁₅NO: C, 80.98; H, 6.37; N, 5.90; Found: C, 80.76; H, 6.42; N, 5.76.

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