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A new method for synthesis of 3,6-diacetyl-9-ethylcarbazole and its oxidation to the corresponding diglyoxal using several oxidizing agents

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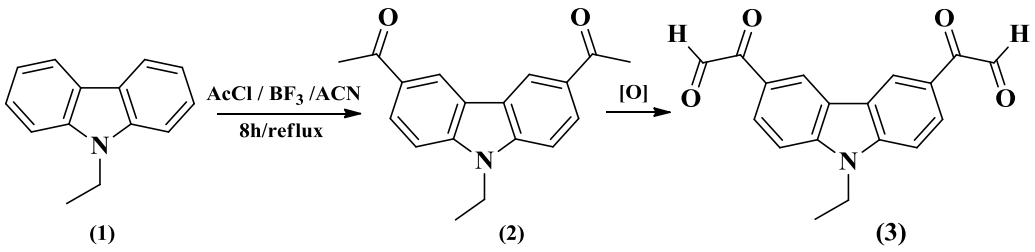
Abstract: The reaction of 9-ethylcarbazole with AcCl/BF_3 in acetonitrile under reflux gave 3,6-diacetyl-9-ethylcarbazole in high yield. The oxidation of this product using several oxidizing agents gave the corresponding diglyoxal in 23-89% yield.

Keywords: 3,6-Diacetyl-9-ethylcarbazole; Oxidation, Diglyoxal; Selenium dioxide; I_2/Metal catalyst/DMSO.

Introduction

Aryl diketones and aryl glyoxals are important building blocks in organic synthesis, particularly in the synthesis of biologically active imidazoles, oxazoles and quinolines[1-4]. Aryl glyoxals (ArCOCHO) are aromatic α-keto aldehydes containing both aldehyde and ketone functional groups with different reactivity, and play an important role in synthesis of heterocyclic compounds. A variety of methods have been reported for the oxidative conversion of aryl methyl ketones to glyoxals. This oxidation is usually carried out with selenium dioxide to provide the glyoxal in good yield and selenium dioxide is readily reduced to selenium[5]. The oxidation of α-bromo ketones into α-ketoaldehydes using DMSO was first reported by Kornblum and co-workers in 1957[6].

The synthesis of aryl glyoxals using milder oxidants such as selenium dioxide[5,7], DMSO/I_2/CuO[9], HBr/DMSO[8,10] and DMSO/$CuCl_2$[11] has been reported. We have previously reported AcCl/BF_3/ACN as a convenient reagent system for the formation of the indanone ring by cyclization of 3-(2-chlorophenyl)propanoic acid in high yield[12]. As part of our studies on the synthesis of heterocyclic compounds via one-pot multicomponent reactions of arylglyoxals[13-18], herein we report a new method for the preparation of 3,6-diacetyl-9-ethylcarbazole (**2**) by reaction of 9-ethylcarbazole (**1**) with AcCl/BF_3 and its oxidation to the corresponding new diglyoxal (**3**) using different oxidizing agents (Scheme 1).



Scheme 1. The synthesis of diglyoxal.

Results and Discussion

In comparison with the Friedel-Craft acetylation of carbazole using AcCl/$AlCl_3$, which gives 3,6-diacetylcarbazole in unknown yield[19], the reaction of 3,6-dilithio-9-ethylcarbazole with *N*-methoxy-*N*-methylacetamide provides 3,6-diacetyl-9-ethylcarbazole **(2)** in 64% yield[20]. While the acetylation of *N*-methylcarbazole using AcCl/$AlCl_3$ occurs in 83% yield[21], we obtained the desired product in high yield (87%) by refluxing 9-ethylcarbazole in AcCl/BF_3 in acetonitrile for 6 hours. Although our yield of 87% for compound **(2)** using AcCl/BF_3 in acetonitrile is close to the literature yield using AcCl/$AlCl_3$[21], this new acetylation has the advantage of being simpler to work up, homogenous, and ecofriendly. The

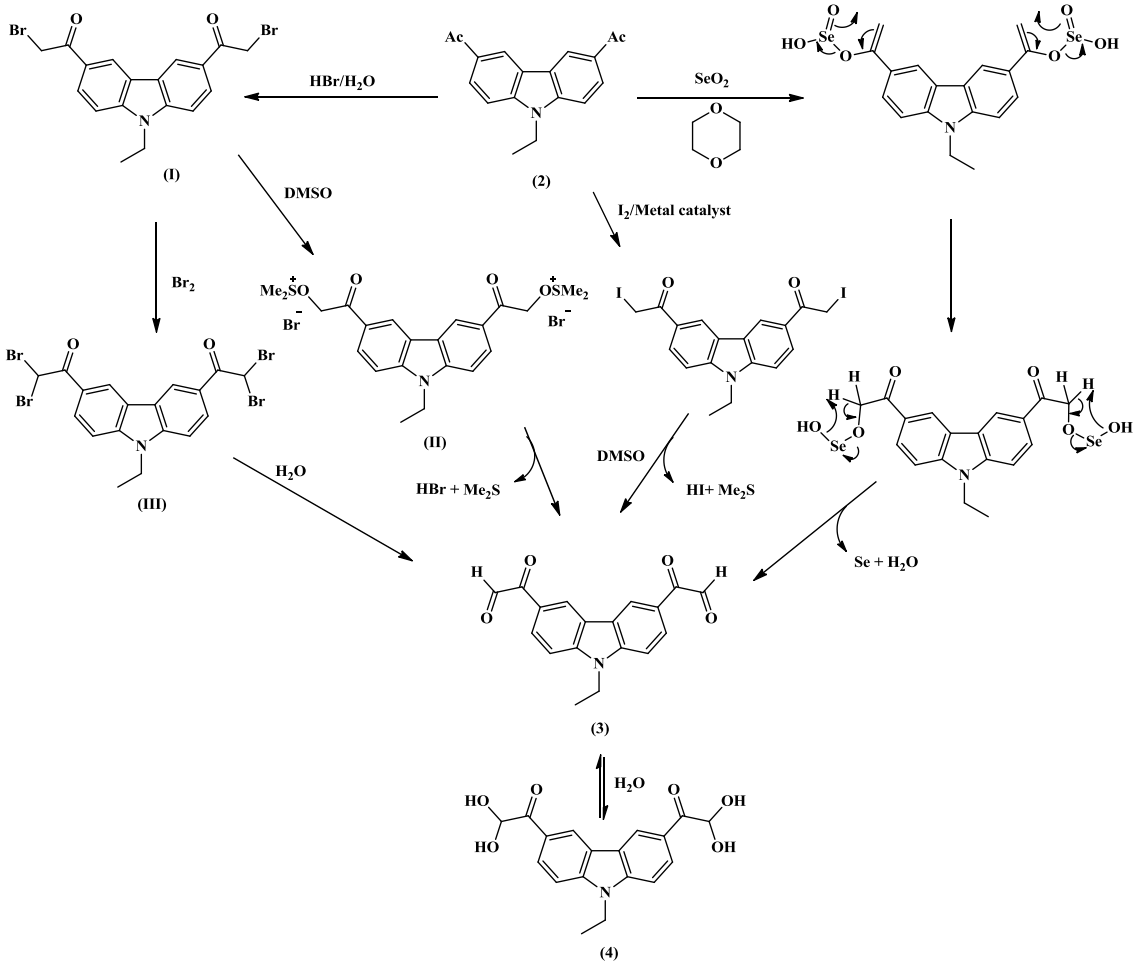
structure of the product was confirmed by ^{1}H-NMR, ^{13}C-NMR and FT-IR spectral data. The oxidation of 3,6-diacetyl-9-ethylcarbazole **(2)** to give the corresponding 2,2'-(9-ethyl-9*H*-carbazole-3,6-diyl)bis(2-oxoacetaldehyde) **(3)** is possible using SeO_2/dioxane/H_2O[5,7], HBr/DMSO/H_2O[8,10] and $CuCl_2$/ DMSO/H_2O[9], and reagent combinations including iodine such as I_2/CuO/DMSO, I_2/Al_2O_3/DMSO, I_2/NaI/DMSO, I_2/KI/DMSO, I_2/$FeCl_3$/DMSO, I_2/$SbCl_3$/DMSO, and I_2/As_2O_3/DMSO. Iodine was preferred to bromine because of the milder reaction conditions, easy use of solid iodine in comparison with liquid bromine, less toxicity and a cleaner conversion to the desired glyoxal[10]. Examples of the conversion of 3,6-diacetyl-9-ethylcarbazole **(2)** into the corresponding diglyoxal **(3)** along with reaction condition, reaction times, type of oxidant and yields are listed in the following Table.

Table. Oxidation of 3,6-diacetyl-9-ethylcarbazole **(2)** to the corresponding diglyoxal (**3**) with different oxidizing agents.

Entry	Reagent	Reaction condition	Yield (%)
1	SeO_2 /Dioxane/H_2O	70°C/6hr	71
2	HBr/DMSO/H_2O	55°C/12hr	79
3	$CuCl_2$/H_2O/DMSO	80°C/8hr	81
4	I_2/CuO/DMSO	65°C/8hr	75
5	I_2/Al_2O_3/DMSO	65°C/8hr	89
6	I_2/NaI/DMSO	65°C/8hr	32
7	I_2/KI/DMSO	65°C/8hr	23
8	I_2/$FeCl_3$/DMSO	65°C/8hr	74
9	I_2/$SbCl_3$/DMSO	65°C/8hr	63
10	I_2/As_2O_3/DMSO	65°C/8hr	83

The structure of new diglyoxal **(3)** was confirmed from its ^{1}H-NMR, ^{13}C-NMR, FT-IR and mass spectral data.

Two mechanisms for the oxidation of aryl methyl ketones with DMSO have been reported. According to the first mechanism, α-bromoketone (**I**) formed by bromination of aryl methyl ketone is rapidly converted into arylglyoxal through an alkoxydimethylsolfonium intermediate (**II**)[21]. The second mechanism suggests that the bromination of



Scheme 2. The proposed mechanisms for the formation of diglyoxal

α-bromoketone followed by hydrolysis gives an α-hydroxy-α-bromo intermediate (**III**), which is finally hydrolyzed to the glyoxal[10].

The proposed mechanisms for the formation of diglyoxal **(3)** using the conditions reported in the above Table are shown in Scheme 2.

Conclusion

In summary we have provided a convenient and facile synthesis of 3,6-diacetyl-9-ethylcarbazole by treatment of 9-ethylcarbazole with AcCl/BF_3 in acetonitrile under reflux and the oxidation of this product to the corresponding diglyoxal using ten different oxidizing systems, which was successful in most cases. The diglyoxal may be employed for the synthesis of a variety of the bis-heterocyclic compounds.

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Experimental Section

Melting points were recorded on a Philips Harris C4954718 apparatus and are not corrected. Infrared-spectra were measured with a Bruker FT-IR spectrometer using KBr disks. ^{1}H-NMR spectra were recorded on a Bruker spectrometer (300 MHz). ^{13}C-NMR spectra were recorded on a 75 MHz spectrometer from Bruker. All measurements were made in deuterated chloroform and dimethyl sulfoxide. Analytical thin layer chromatography (TLC) was carried out on pre-coated aluminum sheet with silica gel 60 F254 obtained from Merck and detection was made with the help of a UV lamp (λ 254 nm). Mass analysis was performed on a Shimadzu GC-MS 2010 Plus apparatus.

General procedure for the preparation of 3,6-diacetyl-9-ethylcarbazole (2):

9-Ethylcarbazole (1.95 g, 10 mmol) was dissolved in the solution of boron trifluoride in acetonitrile (12%, 10 mL) and acetyl chloride (1.72 g, 22 mmol) was added slowly. The reaction mixture was refluxed for 6 hours. After cooling to room temperature, the excess boron trifluoride was decomposed with crushed ice (5 g). The mixture was extracted with dichloromethane (5 mL) and dried over anhydrous sodium sulfate. Removal of the solvent and recrystallization from ethyl acetate gave the desired product as light yellow needles (2.43 g, 87%), m.p. 180-181 °C (lit.[20] m.p. 179-180 °C). ^{1}H NMR (DMSO-d_6) δ (ppm) 1.47 (t, J = 7.2 Hz, 3H, CH_3), 2.74 (s, 6H, 2×CH_3), 4.42 (q, J = 7.2 Hz, 2H, CH_2), 7.45-8.79 (m, 6H). ^{13}C NMR (DMSO-d_6) δ (ppm) 197.46, 143.43, 129.76, 127.06, 123.01, 122.06, 108.73, 38.19, 26.68, 13.85. FT-IR ν_{max} (KBr disk): 3450, 2970, 1670, 1249 cm^{-1}.

General procedure for the synthesis of 2, 2'-(9-ethyl-9*H*-carbazole-3,6-diyl) bis (2-oxoacetaldehyde)hydrate (4):

Using SeO_2/Dioxane/H_2O: A solution selenium dioxide (1.55 g, 14 mmol) in 90% aqueous dioxane (10 mL) was warmed to 70 °C and a solution of 3,6-diacetyl-9-ethylcarbazole (2.79 g, 10 mmol) in dioxane (12 mL) was added. The mixture was refluxed for 6 hours. The precipitated selenium was filtered off hot. The solution was cooled and the precipitate was collected and recrystallized from dioxane: water (1:9) to give 2,2'-(9-ethyl-9*H*-carbazole-3,6-diyl)bis(2-oxoacetaldehyde)hydrate (**4**) as yellow needles (2.43 g, 71%), m.p: 120-122 °C. ^{1}H NMR (DMSO-d_6) δ (ppm): 1.35 (t, J = 7.2 Hz, 3H, CH_3), 4.53 (q, J = 7.2 Hz, 2H, CH_2), 5.87 (s, 2H, 2×CH), 6.72 (s, 4H, 4×OH, exchanged by D_2O addition), 7.71-9.03 (m, 6H). ^{13}C NMR (DMSO-d_6) δ (ppm) 195.93, 143.58, 128.39, 126.20, 123.72, 122.55, 110.11, 89.52, 38.10, 14.19. FT-IR ν_{max} (KBr disk): 3383, 1675, 1588, 1402, 1226, 1087 cm^{-1}. MS: m/z: 307 (M^+, 6), 278 (100), 250 (7), 221 (54), 193 (8), 178 (11), 164 (14).

Using HBr/DMSO/H_2O: To a stirred solution of 3,6- diacetyl-9-ethylcarbazole (1.39 g, 5 mmol) in DMSO (16 mL) was added slowly 48% aqueous HBr (8.8 M) (3.4 mL, 30 mmol). The solution was stirred in an open flask at 55 °C and the reaction was followed by TLC using butanol and acetic acid (1:1) as eluent. After 12 hours the starting material was consumed and the solution was poured onto ice. The solid product was filtered, washed with water, recrystallized from dioxane: water (1:9) to give 2, 2'-(9-ethyl-9*H*-carbazole-3,6-diyl)bis (2-oxoacetaldehyde) hydrate (1.35 g, 79%).

Using $CuCl_2$/DMSO/H_2O: A mixture of 3, 6-diacetyl-9-ethylcarbazole (1 eq), $CuCl_2$ (3 eq) in freshly distilled dimethyl sulfoxide (4 mL) was stirred at 80 °C for 8 hours. Then it was diluted with water, acidified with dil HCl and extracted with ethyl acetate. Removal of the solvent and recrystallization from H_2O and dioxane gave the desired product (1.38 g, 81% yield)

Using I_2/Metal catalysts/DMSO: Iodine (2.6 mmol) and metal catalysts (CuO, Al_2O_3, NaI, KI, $FeCl_3$, $SbCl_3$, As_2O_3) (3 mmol) was added to a solution of 3,6-diacetyl-9-ethylcarbazole (1 mmol) in dry DMSO (4 mL) at room temperature under a dry nitrogen atmosphere and the mixture was heated to 65 °C for 8 hours. After completion of the reaction, the mixture was diluted with water, extracted with ethyl acetate, washed with water and dried over anhydrous sodium sulfate. Removal of the solvent and recrystallization from dioxane:water (1:9) gave the corresponding product as hydrate form (**4**).

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