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SYNTHESIS OF BIPHENYL COMPOUNDS FROM AROMATIC ENAMINO KETONES

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ABSTRACT

A Nobel method for the synthesis of substituted biphenyls from aromatic ketones having active methylene groups via the corresponding hydroxymethylene ketones and enamino-ketones has been developed. Formylation of these aromatic ketones having active methylene groups with ethyl formate followed by enamine reaction with pyrrolidine produces enamino – ketones which on reaction with six fold excess of malononitrile in boiling toluene in the presence of ammonium acetate in acetic acid with continuous separation of water gives the substituted biphenyles in good yields. The reaction may be extended to other aliphatic and heterocyclic ketones to give the respective substituted benzenes.

KEYWORDS: Synthesis, Biphenyl Derivatives.

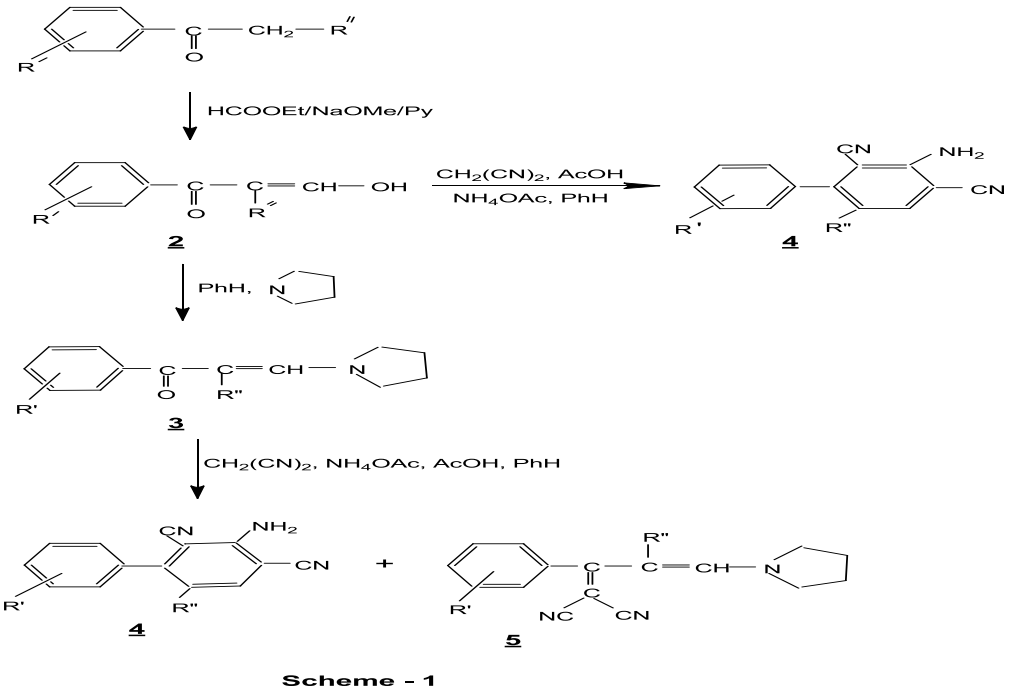
INTRODUCTION

With an aim at studying the feasibility of the scheme adopted by Khaidem et al[1] and Green et al[2] as a means of a facile and smooth synthesis of substituted biphenyles from aromatic ketones having α – methylene groups, a scheme was drawn under which Claisen condensation of these aromatic ketones 1a-e with ethyl formate in pyridine in the presence of dry sodium methoxide under nitrogen atmosphere gave the hydroxymethylene ketones 2a-e respectively. Following the methods adopted by Stork et al[3] the hydroxymethylene ketones on enamine reaction with pyrrolidine gave the enamino ketones 3a-e. These enamino ketones were cyclized with malononitrile under Knoevenagel conditions to give the biphenyl derivatives 4a-e (Scheme – 1). This scheme may find additional advantages over other

schemes as the biphenyl derivatives so obtained contain active functional groups at specific positions in the nucleus.

Because of the extreme ease of preparation from hydroxyl methylene keto aromatic compounds and reactivity, pyrrolidine has been used in the enamine reaction. Also because of the small size, malononitrile has been found to be used more conveniently as the active methylene component.[4,5]

	R’	R”
a	H	H
b	H	CH_3
c	*m*- (CH_3O)	H
d	*p*- (C_2H_5O)	H
e	*p*- (CH_3)	H



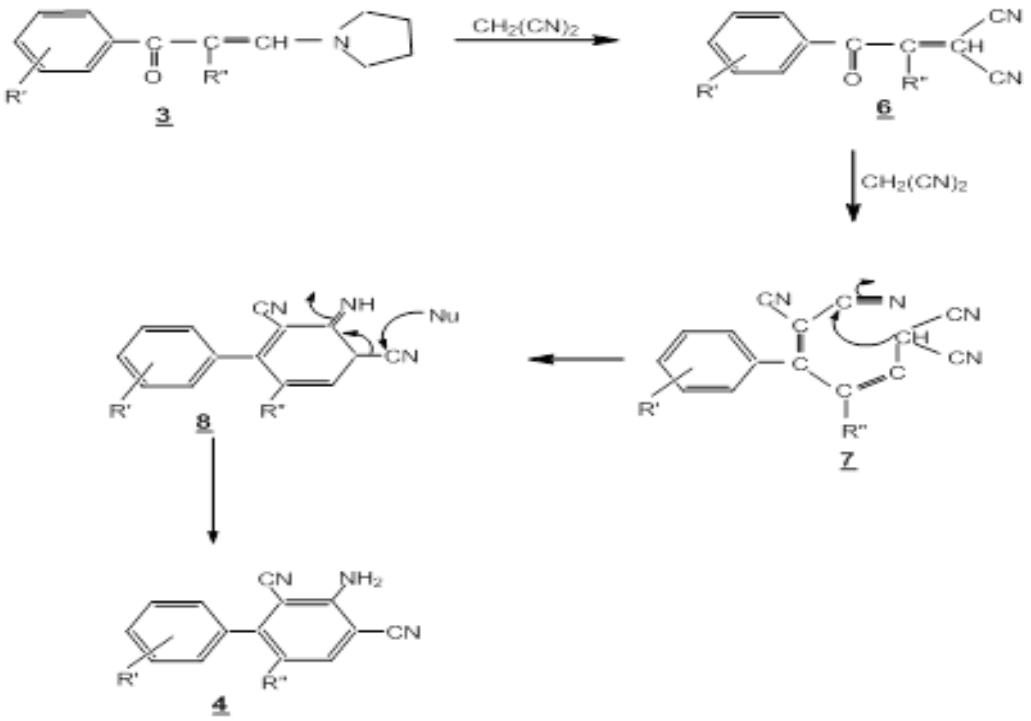
Scheme - 1

RESULT AND DISCUSSION

The reaction of 3a-e with three fold malononitrile was carried out under Knoevenagel condensation conditions in the presence of ammonium acetate glacial acetic acid in toluene by refluxing for three hours with continuous separation of water (Dean and Stark) to give substituted biphenyls 4 a-e as major products in about 40 % yield along with simple Knoevenagel products 5a-e as minor products. The structures of these products were

established on the basis of ir, ^{1}H nmr spectral data and elemental analyses. The ir (KBr) peaks of 4 at about 3475, 3350 and 1600 cm^{-1} were attributed to an amino group and the peak at about 2200 cm^{-1}was assigned to a conjugated nitrile group. The ^{1}H nmr spectra of 4 gave a broad peak at around ∂5 (2H) exchangeable with deuterium oxide confirmed the presence of an amino group. Attempts for acylation of the amino group in these substituted biphenyls were unsuccessful. This failure may be expected due to the presence of substituents in both the o-positions with respect to the amino group.[4]

A suggested mechanism for the formation of 4 is given in Scheme II. An addition/elimination reaction of the activated form of malononitrile at the carbon atom where pyrrolidinyl group is attached can lead to the formation of the intermediate 6 which on Knoevenagel condensation with the second molecule of malononitrile at the carbonyl carbon would yield the intermediate 7. Intramolecular attack leading to the imine intermediate 8 which aromatizes by nucleophilic attack on one of the nitrile groups. It is supposed that a third molecule of malononitrile acts as the nucleophile in this step. An alternate route that comprises an initial Knoevenagel condensation at the carbonyl carbon to yield 5 followed by addition/elimination at the carbon where pyrrolidinyl group is attached to give 8 is ruled out by the fact that 5 is fairly stable under the conditions of Knovenagel condensation.



Scheme - II

R' and R" are same as in Scheme - I

Table 1: physical and Spectral data of Compounds 4a-e.

Compound	m.p. ^{0}C	Yield %	Mol. Formula	Elemental Analysis			^{1}Hnmr ($CDCl_3$, ∂, ppm)
				Element	Calculated	Found	
4a	141-2	34	$C_{14}H_{19}N_3$	C H N	76.96 4.67 20.00	76.71 4.10 18.80	7.97(m,2H,ar,C-2',6'), 7.48(q,3H,ar,C-3',4',5'; 7.76(d,1H,ar,C-6; 7.17(d,1H,ar,C-5); 5.27(s,br,2H,exchangeable with D_2O, NH_2
4b	150-2	36	$C_{15}H_{11}N_3$	C H N	77.25 4.64 18.00	77.20 4.70 18.02	7.56(unresolved,4H,ar,C-3'-6');7.31(m,2H,ar,C-5,2');5.1(s,br,2H, exchangeable with D_2O, NH_2); 2.06(s,3H,CH_3)
4c	120	40	$C_{15}H_{11}N_3O$	C H N	72.39 4.17 17.00	72.28 4.41 16.84	7.65(d,1H,ar,C-6);7.45(unresolved,,3H,ar,C-2',4',6');7.39s,1H,ar,C-5');2.02(d,1H,ar,C-5); 5.3(s,br,2H,exchangeable with D_2O, NH_2); 3.85(s,3H, CH_3)
4d	198	40	$C_{16}H_{13}N_3O$	C H N	75.79 5.56 17.00	75.88 5.13 16.80	7.94(d,2H,ar,C-3',5'); 7.71(d,1H,ar,C-6); 7.11(d,1H,ar,C-5);7.04(d,2H,ar,C-2',6); 5.2 (s,br,2H,exchangeable with D_2O, NH_2); 4.1(q,2H, CH_2);1.45(t,3H,CH_3)
4e	178	17	$C_{15}H_{11}N_3$	C H N	77.00 4.96 18.00	77.25 4.72 18.02	7.85(d,1H,ar,C-6); 7.7(d,2H,ar,C-3',5'); 7.26 (d,1H, ar,C-5);7.09(d,2H,ar,C-2',6'); 5.31(s,br, 2H, exchangeable with D_2O, NH_2);2.35(s,3H,CH_3 at C-4')

Experimental

Melting points were taken in open capillaries in an electrically heated silicone oil bath and are uncorrected; ir(KBr) spectra were recorded on a Perkin-Elmer 577 spectrophotometer and ^{1}H nmr spectra in $CDCl_3$ on a Varian EM 360 L (60 MHz or 90 MHz) spectrometer using TMS as internal standard (chemical shifts in ∂ scale). Microanlyses were performed on a Carlo-Erba 106 instrument. Organic solvent extracts were dried over anhydrous Na_2SO_4. Column chromatography was carried over silica gel (100-200 mesh), unless otherwise mentioned and tlc on glass plates by pouring method after activation at 120^{o}C for 30 minutes using silica gel G. Spots were visualized either by oxidizing in iodine chamber or by spraying either with 5% $KMnO_4$ or methanolic $FeCl_3$ solution. Pet. Ether refers to light petroleum b.p. 60-80^{0}C.

Preparation of Hydroxymethylene ketones 2: (General Method)

A mixture of the aromatic ketones having active methylene groups (1a-e) and ethyl formate in pyridine was stirred at 0^{0}C under nitrogen atmosphere in the presence of dry sodium methoxide (freshly prepared by making molecular sodium by shaking sodium metal in boiling xylene, decanted, washed in dry ether and dissolving in methanol and then removing excess methanol) to get a gel which was kept overnight (ratio of aromatic ketone, ethyl formate and sodium was 1:3:2). The gel was precipitated with diethyl ether (100 mL X 4), air dried and the precipitate was dissolved in water (300-2000mL) and acidified with HCl (50%).

The products aromatic hydroxymethylene ketones (2a-c) were obtained as oils which were extracted with diethyl ether from the aqueous solution, dried and distilled under reduced pressure. The hydroxymethylene ketones (2d-e) were converted into crystalline solids by acidification which were filtered, washed with cold water and air dried.

Preparation of Enamino ketones 3: (General Method)

A mixture of 2 and pyrrolidine (1:1.5 to 2) in dry benzene (150 mL) was refluxed with continuous separation of water (Dean & Stark, 30 Mins. To 4 Hrs.) The reaction mixture was concentrated by evaporation in vacuo at room temperature, washed with cold water, dried and kept overnight. The enaminoketones 3a,d,e were separated out as fine yellow crystals which were filtered and recrystallized from benzene while 3b.c were collected as brown oils by distilling off the solvent under reduced pressure. No attempt was made to isolate these oily enamino ketones because of their high unstability and Knoevenagel condensation for such

enamino ketones were performed in situ by condensation of the corresponding enamino ketones with Malononitrile using excess quantity of acetic acid.

Reaction of Enamino-ketones with Malononitrile: (General Method)

A mixture of 3 (14mmoles) and malononitrile (42 mmoles) in dry benzene (175 mL) was refluxed for 1½ hrs. to 6½ hrs. with continuous separation of water (Dean & Stark) in the presence of ammonium acetate (1 g) in glacial acetic acid (15 mL). The cold mixture was diluted with diethyl ether (200 mL), washed with water (100 mL X 4), the organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated to yield a brown gummy material which was column chromatographed over silica gel (100 g) using ethyl acetate in pet. ether. Compound 5 was eluted as first fraction followed by compound 4.

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