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DABCO Catalyzed Synthesis of Pyrano(*c*)Chromene Derivatives

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Abstract

Multicomponent one-pot cyclocondensation of heteroaromatic aldehyde 1, malononitrile 2, 5,5-dimethyl-cyclohexane-1,3-dione (dimedone) 3 in presence of 1,4-diazabicyclo [2.2.2] octane in aqueous-ethanol. Reaction proceeds via initial Knoevenagel condensation, subsequent Michael addition and final heterocyclization reactions to give substituted and functionalized pyrano(c)chromene derivatives 4. These pyrano(c)chromenes on reaction with acetyl acetone as an active methylene compounds result in the formation of differently functionalized and diversely substituted linear tricyclic chromenopyridine 5 via cyclocondensation followed by heterocyclization.

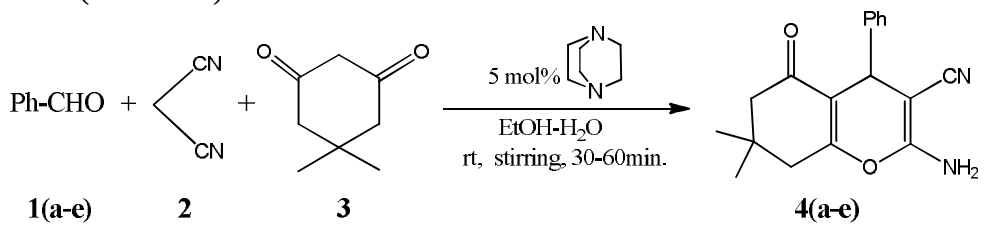
Keywords: Mulicomponent reactions, Dihydropyrano(c)chromenes, Fused heterocycles, DABCO.

1. Introduction

Multi-component reactions (MCRs) have attracted considerable interest because of their exceptional synthetic and practical efficiency.[1,2] Polyfuctionalized pyran derivatives are some examples of multi-component synthesis and are found in variety of important natural products including alkaloids, pheromones, carbohydrates and antibiotics.[3,4] Dihydropyrano(*c*)chromene structures are of considerable interest as they possess a wide range of biological properties such as spasmolytic, diuretic,

anticoagulant, antitumor, antiallergic cognitive enhancers and potassium channel activators.[5-8]

Because of long standing interest in the condensation reactions of active methylene compounds and generation of new fused, bridged, spiro, ring assembly and cyclophane heterocyclic compounds the synthetic activity has been extended along these lines for the synthesis of some chromeno[2,3-*b*]quinoline, tetrahydrobenzo-[*b*]pyran, chromeno[2,3-*b*]pyridine and chromene [3',2': 5,6]pyrido[2,3-*d*]pyrimidine systems using different catalyst and hazardous solvents.[9-15] 1,4-Diazabicyclo [2.2.2] octane (DABCO) is an inexpensive, non toxic and commercially available catalyst and can be used in laboratory without special precautions.[16-18] But, it has not been used much as a catalyst in fused heterocyclic synthesis in the condensation reaction of barbituric acid, dimedone and other active methylene compounds, only a few reports are there in the literature.[16] Therefore in the present work the use of DABCO as catalyst for the synthesis of these heterocyclic compounds has been explored.To prepare these novel classes of compounds, 2-amino-3-cyano-4(heteroaryl)-7,7-dimethyl-5-oxo-4*H*-5,6,7,8-tetrahydro benzo[*b*]pyran **4** was synthesized and used as the key intermediate synthon.[17] (Scheme **1**)



Scheme- 1

1a = Furan-2-aldehyde, 1b = 5-methyl, furfural, 1c = Thiophene-2-aldehyde, 1d = 3-methyl, thienaldehyde, 1e = 5-methyl, thienaldehyde

2. Experimental

Unless otherwise noted, materials were obtained from commercial suppliers (Aldrich Chemical Co. and CDH Chemical Co.) and used without further purification. All reactions were monitored by thin-layer chromatography (TLC) on 0.25 mm silica gel (60GF-254, Merck) plates and visualized with UV light. ^{1}H and ^{13}C spectra were recorded on a BRUKER instrument 300 MHz and 75 MHz NMR spectrophotometer respectively on δ scale (ppm). LCMS analysis (EI, 70V) were performed on a Hewlett-Packard HP 5971 instrument. IR spectra were recorded on a Perkin-Elmer 298 spectrophotometer. Melting points were determined on electro thermal apparatus by open capillary method and were uncorrected.

2.1. General procedure for the synthesis of heteroaryl substituted dihydropyrano(c)chromenes 4(a-e)

5-membered heteroaryl aldehyde **1** (10 mmol), malononitrile **2** (10 mmol), dimedone (10mmol) **3** and 5mol% DABCO were added to a R.B. flask containing 20mL EtOH: H2O (1:1). The reaction mixture was stirred for appropriate time at room temperature (Table **1**). The completion of the reaction was monitored by TLC. The solid obtained was washed with distilled water (3x10ml) for removal of the catalyst. The product was

extracted with dichloromethane and filtered. The solvent was evaporated under reduced pressure and the pure product **4** was obtained by recrystallization from ethanol: water (4:1).

2.2. General procedure for the synthesis of 3-acetyl-4-amino-5-(2-heteroaryl)-2,8,8-trimethyl-8,9-dihydro-5H-chromeno[2,3-b]pyridine-6(7H)-one 6(a-e)

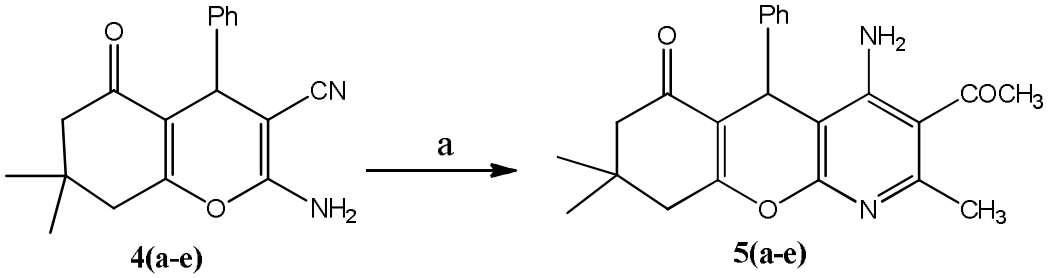
A mixture of **4** (2 mmol) and acetyl acetone (2 mmol) in ethanol containing DABCO (5 mol%) was refluxed for 8-10 hr. The reaction was left to cool at room temperature and then poured into ice-cold water with stirring. The solid product so formed was collected by filtration and purified by recrystallization from ethanol in each case.

2.3. Spectral data

2-Amino-7,7-dimethyl-4-(furan-2-yl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile **(4a):** White solid, m.p. 216-218°C (lit. m.p. 217-219°C). IR (KBr): 3355, 3208 (NH2), 2941 (C-H), 2202 (CN), 1680 (C=O), 1652 (C=C) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) : δ 0.99 (s, 3H, CH3), 1.05 (s, 3H, CH3), 2.17 (m, 2H, CH2), 2.48 (m, 2H, CH2), 4.33 (s, 1H, chiral-CH), 6.05 (d, 1H, Ar-H), 6.32 (d, 1H, Ar-H), 7.07 (s, 2H), 7.48 (dd, 1H, Ar-H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 186.3, 159.4, 155.8, 147.5, 142.5, 118.4, 114.6, 112.2, 63.2, 32.1, 28.5; EI-MS (*m/z*): 284 (M^+).

3-acetyl-4-amino-5-(furan-2-yl)-2,8,8-trimethyl-8,9-dihydro-5H-chromeno [2,3-b] pyridine-6(7H)-one **(5a):** IR (KBr): 3280cm^{-1} (NH2), 3040 (C-H, Aromatic), 2948 (C-H, Aliphatic), 1675, 1715 (C=O), 1664 (C=C); ^{1}HNMR (DMSO-d_6): δ 4.31 (s, 1H, chiral CH), 2.48 (s, 2H, CH2), 2.14 (s, 2H, CH2), 1.15 (s, 3H, CH3), 0.99 (s, 3H, CH3), 1.50 (s, 3H, OC=CH3), 0.94 (s, 3H, N=C-CH3), 6.15 (d, 1H, Ar-H), 7.54 (dd, 1H, Ar-H), 6.51 (d, 1H, Ar-H), 7.25 (s, 2H, NH2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 198.2, 191.4, 169.7, 165.0, 154.8, 152.5, 146.5, 126.1, 113.8, 111.3, 27.6, 14.0; EI-MS (*m/z*): 366(M^+).

3. Results & Discussion



4(a-e) **5(a-e)**

Scheme- 2

Reaction conditions: **a** = acetyl acetone, DABCO 5mol%, EtOH- H2O, reflux 8-10 hr; Ph = 1a, 1b, 1c, 1d, 1e.

The key intermediates **4(a-e)** used as starting materials in the synthetic scheme **2** have been prepared in excellent yields by stirring heteroaryl aldehydes **1**, malononiterile **2**, dimedone **3** and catalytic amount of DABCO in ethanol-water solvent mixture (1:1) (Scheme **1**) and the products are listed in Table **1.**

The structure of 2-amino-3-cyano-4-(furan-2-yl)-7,7-dimethyl-5-oxo-4*H*-5,6,7,8-tetra hydro benzo-[*b*]pyran **4a** was established on the basis of spectral data. The IR spectrum of compound **4a** showed strong absorption bands at 2202, 3355, 3442 cm^{-1} corresponding to nitrile and amino group respectively and a sharp singlet at δ 4.33 due to the presence of chiral CH in ^1H NMR. The reactivity of this compound towards different active methylene compounds was investigated. The structures of the latter products have been established on the basis of their spectral data and elemental analysis.

The treatment of **4(a-e)** with acetyl acetone under typical condition for enamine formation (refluxing ethanol-water in presence of catalytic amount of DABCO) gave the **5(a-e)** in moderate to good yields. The structures of these products have been established on the basis of their spectral data and elemental analysis. The ^1H spectrum of the reaction product 5a showed singlet peak at δ 7.25 due to NH2 group. A singlet at δ 4.31 indicated the presence of CH proton of the pyran ring. In the IR spectrum, absence of absorption peak at 2190-2240cm^{-1} clearly indicates that CN group consumed in the reaction. Compounds **5(a-e)** have the tricyclic chromeno[2,3-*b*]pyridine skeleton with different functional groups. All the other products were also characterized by IR, ^1H, ^{13}C NMR and elemental analysis and the results were in agreement with the assigned structures.

Table 1: Synthesized compounds with m.p., yield, mol. formulae and elemental analysis.

Product	Ar	Yield (%)	M.P0C [Ref]	Mol. Formula (Mol. Wt.)	Calculated % (found %)
4a	1a	95	216-218 [204-205]	C16H16N2O3 (284)	C67.59(67.88),H5.67(5.56), N 9.85(9.63)
4b	1b	94	205-207 [204-205]	C17H18N2O3 (298)	C68.44(68.40),H6.08(6.10), N9.39(9.41)
4c	1c	95	208-210 [209-211]	C16H16N2O2S (300)	C63.98(63.92),H5.37(5.34), N9.33(9.34), S10.67(10.69)
4d	1d	95	214-215	C17H18N2O2S (314)	C64.94(64.91),H5.77(5.74), N8.91(8.89),S10.20(10.24)
4e	1e	97	217-219	C17H18N2O2S (314)	C64.94(64.92),H5.77(5.75), N8.91(8.86),S10.20(10.26)
5a	1a	54	130-132	C21H22N2O4 (366)	C68.84(68.80),H6.05(6.01), N7.65(7.68)

5b	1b	58	145-147	C22H24N2O 4 (380)	C69.46(69.41),H3.36(3.34), N7.36(7.40)
5c	1c	67	137-139	C21H22N2O 3S (382)	C65.95(65.99),H5.80(5.77), N7.32(7.29),S8.38(8.33)
5d	1d	61	159-160	C22H24N2O 3S (396)	C66.64(66.61),H6.10(6.07), N7.07(7.09),S8.09(8.06)
5e	1e	64	154-156	C22H24N2O 3S (396)	C66.64(66.59),H6.10(6.07), N7.07(7.03),S8.09(8.06)

4. Conclusion

In conclusion, we have developed a simple, efficient and improved protocol for the synthesis of biologically active fused heterocycles in presence of DABCO as the catalyst with excellent yields. The simplicity of the system, excellent yields of the products and ease of work-up fulfill the triple bottom line philosophy of green chemistry.

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