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One-pot three-component synthesis of chromeno[4,3-d]pyrimidinone derivatives

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ABSTRACT

A simple, efficient, and general methods has been developed for the One-pot three-component reaction of salicylaldehyde 1,3-dicarbonyl compounds and 2-Aminobenzimidazole in the presence of catalytic amounts of piperidine in acetic acid led to a chemo selective synthesis of chromeno[4,3-d]pyrimidine-6-one derivatives, in good yields.

Keywords: Chromeno [4,3-d]pyrimidine-6-one, Multi component reactions, 2-Aminobenzimidazole, 1,3-Dicarbonyl compounds.

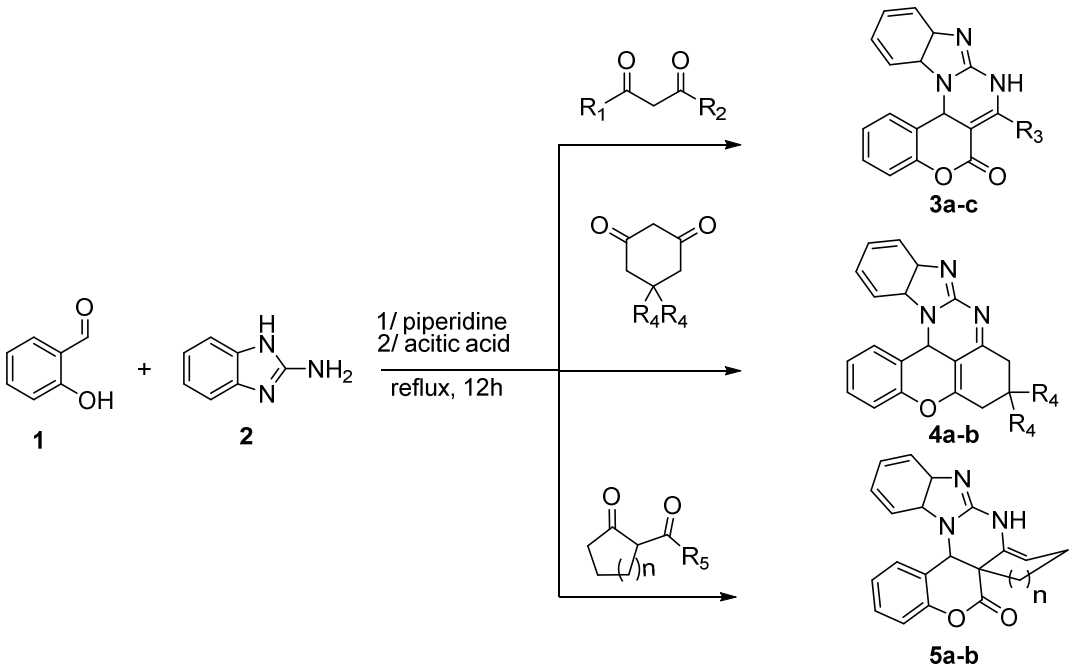
INTRODUCTION

In multi component reactions (MCRs), three or more reactants come together in a single reaction vessel to form new products that contain structural units of all the components. This type of reaction becomes increasingly important in organic and medicinal chemistry because it allows the chemist to obtain highly sophisticated polyfunctional molecules through simple one-pot procedures.

The use of three or more building blocks in a one-pot, high-yield multicomponent reaction leads to a wide structural and functional diversity combined with excellent combinatorial efficiency. Over the past decade, industrial and academic research has made powerful MCR strategies into one of the most efficient and cost-effective tools for combinatorial synthesis. The development of new MCR is an intellectual challenge because we have to consider not only the game of the reactivity of the starting materials but also the reactivity of intermediate molecules generated in situ, their mutual compatibility and compartmentalization [1-7].

Chromene derivatives represent an important class of compounds. They are often present as structural unit in many natural products [8] and have been reported to possess various pharmacological activities such as antimicrobial [9], anti-tumor [10], anti-aggregating [11], anti-depressant [12] and anti-proliferative activities [13]. It is well known that pyrimidine and coumarin derivatives were also found to possess anti-allergic [14], anti-microbial [15-16], anti-oxidant [17], anti-inflammatory [18] and anti-cancer activities [19].

As part of our continuing efforts on the development of new routes for the synthesis of heterocyclic compounds [20-22], herein, we wish to report an one-pot chemo-selective synthesis of some new chromeno [4,3-d] pyrimidinone derivatives via reaction of salicyl aldehyde (1) with 1, 3-dicarbonyl compounds (3) and 2-aminobenzimidazole (2), in the presence of catalytic amounts of piperidine in acetic acid.



Scheme 1: One pot reaction of three components

MATERIALS AND METHODS

Melting points were measured using Kofler bench method. All reactions were followed by TLC (E. Merck Kieselgel 60 F-254), with detection by UV light at 254 nm. IR spectra were recorded on a Perkin-Elmer spectrometer.1H and 13C NMR spectra were recorded on a Bruker AQS-AVANCE spectrometer at 300 and 75 MHz, respectively, in DMSO-d_6 and $CDCl_3$ Chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane (0 ppm) as an internal reference and the following multiplicity abbreviations were used: s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet. All chemicals were obtained from Merck and were used without further purification.

General procedure for Synthesis of chromeno [4,3-d] pyrimidinone derivatives

To a mixture of salicyl aldehyde **(1)** (1 mmol), 1,3-dicarbonyl compounds **(3)** (1 mmol) and 2-amino-benzimidazole **(2)** (1 mmol), in acetic acid is added two drops of piperidine , the mixture was heated at reflux for 12 Hours. Upon completion of the reaction, [monitored by TLC (eluent system – petroleum ether/ethyl acetate, 98:2)], the mixture was cooled to room temperature , the precipitated product was filtered, washed three times with Ethanol, and dried at 60-70°C. The corresponding products were analytically pure without recrystallization.

7-Méthyle-8,14a-dihydro-6H-benzo[4,5]imidazo[1,2-a] chromeno [3,4-e]pyrimidin-6-one (3a): Light yellow; Mp 226-228°C. IR (KBr) : υ (cm-1) 3,294 (NH stretching), 1,674 (C=O), 1,620 (C=N); ^{1}HNMR (DMSO-d6 , 300 MHz) δ: 8,76 (1H, s, NH); 7,91-7,70(2H, m, Ar-H); 7,43-7,36(2H, m, Ar-H); 7,13-7,11(4H, m, Ar-H); 2,28 (3H, s, O-Me). ^{13}CNMR spectrum δ, ppm:163,65; 155,15; 154,80; 149,26; 137,45; 134,80; 130,55; 125,08; 121,15; 119,84; 118,03; 117,59; 116,37; 111,65; 17,65.

8,14a-dihydro-6H-benzo[4, 5]imidazo[1, 2-a]chromeno [3,4-e]pyrimidin-6-one (3b): Yellow-green powder; Mp 187-189°C. IR (KBr) : υ (cm-1) 3,290 (NH stretching), 1,679 (C=O), 1,624 (C=N); 1HNMR (DMSO-d6 , 300 MHz) δ: 8,76(1H, s, NH); 7,91-7,70(2H, m, H Ar); 7,43-7,36(2H, m, H-Ar); 7,13-7,11(4H, m, H Ar), 7,08(1H, t, H vinylyque); 13CNMR (DMSO-d6 , 75 MHz) 163,65; 155,15; 154,80; 149,26; 137,45; 134,80; 130,55; 125,08; 121,15; 119,84; 118,03; 117,59; 116,37; 111,65.

7-Méthoxy-8,14a-dihydro-6H-benzo[4,5]imidazo[1,2-a]chromeno[3,4-e]pyrimidin-6-one (3c): Yellow-green powder; Mp 186-188°C. ^{1}HNMR (DMSO-d6 , 300 MHz) δ: 8,76(1H, s, NH); 7,91-7,70(2H, m, H Ar); 7,43-7,36(2H, m, H-Ar); 7,13-7,11(4H, m, H Ar); 3,83(3H, s, O-Me). ^{13}CNMR (DMSO-d6 , 75 MHz) 163,65; 155,15; 154,80; 149,26; 137,45; 134,80; 130,55; 125,08; 121,15;119,84; 118,03; 117,59; 116,37; 111,65; 52,65.

6,7,8,15a-tétrahydrobenzo[4,5]imidazo[2,1-b]chromeno[4,3,2-e]quinazoline (4a): Brown powder; Mp 186-190°C. IR (KBr) : υ (cm-1) 1,562 (C=C), 1,609 (C=N); ^{1}HNMR ($CDCl_3$, 300 MHz) δ: 9,9(1H, s, NH), 7,61-7,55(4H, m, Ar-H), 7,53-7,42(2H, m, Ar- H); 7,19-7,21(2H, m, H Ar); 7,05-7(1H, m, H vinylique), 6,91(1H, s,

CH); 2,57-2,11(2H, m, CH_2); 1,12-0,99(2H, t, CH_2).^{13}CNMR ($CDCl_3$, 75 MHz) 136,92; 133,65; 127,93; 124,50; 119,77; 118,24; 117,55; 115,87; 111,60; 110,99; 49,88; 41,47; 32,21; 30,90; 27,67; 21,88.

7,7-diméthyle-6,7,8,15a-tétrahydro-benzo[4,5]imidazo[2,1-b]chromeno[4,3,2-e]-quinazoline (4b): Yellow powder; Mp 216-218°C. ^{1}HNMR ($CDCl_3$, 300 MHz) δ: 9,9(1H, s, NH); 7,61-7,55(4H, m, Ar-H); 7,53- 7,42(2H, m, Ar-H); 7,20-7,14(2H, m, Ar-H); 7,05-7.02(1H, m, H vinylique); 6.91(1H, s, CH); 2,17(2H, s, CH_2); 2,09(6H, s, CH_3).^{13}HNMR ($CDCl_3$, 75 MHz) 137,01; 133,73; 129,90; 127,83; 122,87; 119,85; 117,63; 116,28; 111,35; 36,92; 30,91; 28,10; 27,11; 21,39; 20,27.

7,8,9,16a-téraehydro-6H-benzo[4,5]imidazo[1,2-a]chromeno[3,4]cyclopenta[d]- pyrimidine-6-one (5a): Yellow powder; Mp 226-230°C. ^{1}HNMR ($CDCl_3$, 300 MHz) δ: 8,57(1H, s, NH); 7,5-7,4(4H, m, Ar-H); 7,61-7,56(2H, m, Ar-H); 7,25-7,29(2H,m, Ar-H), 7,07(1H, t, H vinylique); 6,91(1H, s, CH); 2,63-2,62 (2H, m, CH_2); 2,2-1,91(2H, m, CH_2).^{13}HNMR ($CDCl_3$, 75 MHz) δ:160,17; 148,78; 127,55; 125,74; 122,47; 121,85; 116,16; 113,55; 108,02; 62,36; 38,15; 31,23; 29,42; 24,48; 16,56.

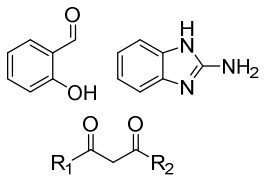
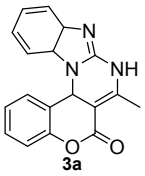
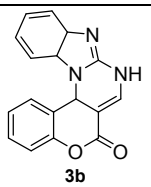
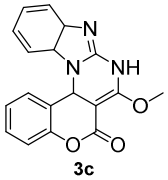
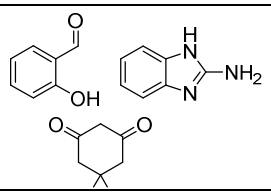
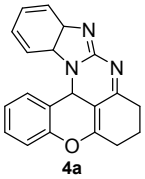
7,8,9,16a-téraehydro-6H-benzo[4,5]imidazo[1,2-a]chromeno[3,4]cyclohexa-[d]-pyrimidine-6-one (5b): Yellow powder; Mp 210-216°C. ^{1}HNMR ($CDCl_3$, 300 MHz) δ:8,57(1H, s, NH); 7,5-7,4(4H, m, Ar-H); 7,61-7,56(2H, m, Ar-H); 7,25-7,29(2H,m, Ar-H), 7,07(1H, t, H vinylyque); 6,91(1H, s, CH); 2,86-2,82(2H, t, CH_2); 2,67-2,61(2H, m, CH2); 1,91-1,84(2H, m, CH_2).^{13}HNMR ($CDCl_3$, 75 MHz) δ:160,17; 148,78; 127,55; 125,74; 122,47; 121,85; 116,16; 113,55; 108,02; 62,36; 38,15; 31,23; 29,42; 21,98; 21,48; 17,56.

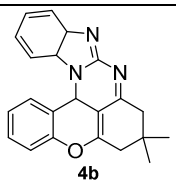
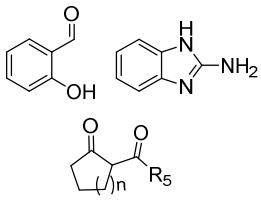
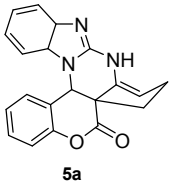
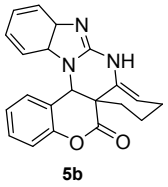
RESULTS AND DISCUSSION

We found that combining salicylaldehyde **(1)** with 1, 3-dicarbonyl compounds **(3)** and 2-aminobenzimidazole **(2)** leads to the formation of chromeno [4,3-d] benzoimidazole [3,4-b] pyrimidines deriatives **3a–c**, **4a–b** and **5a–b** (Scheme 1).

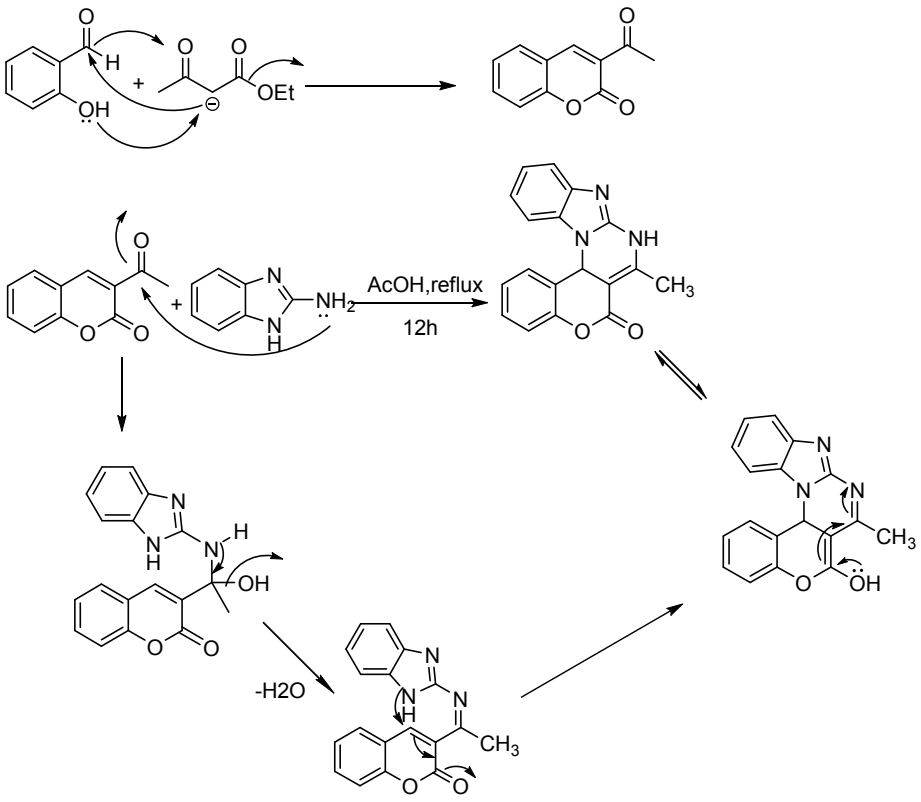
Generally, the polyheterocyclic compounds were obtained with good yields when mixtures of three starting components and two drops of piperidine are refluxed in acetic acid for 12 h (*Table 1*). The desired products precipitate upon cooling of the reaction mixture and a filtration provides analytically pure material (>95%).

Table 1: One-pot synthesis of chromeno [4, 3-d] pyrimidinone derivatives

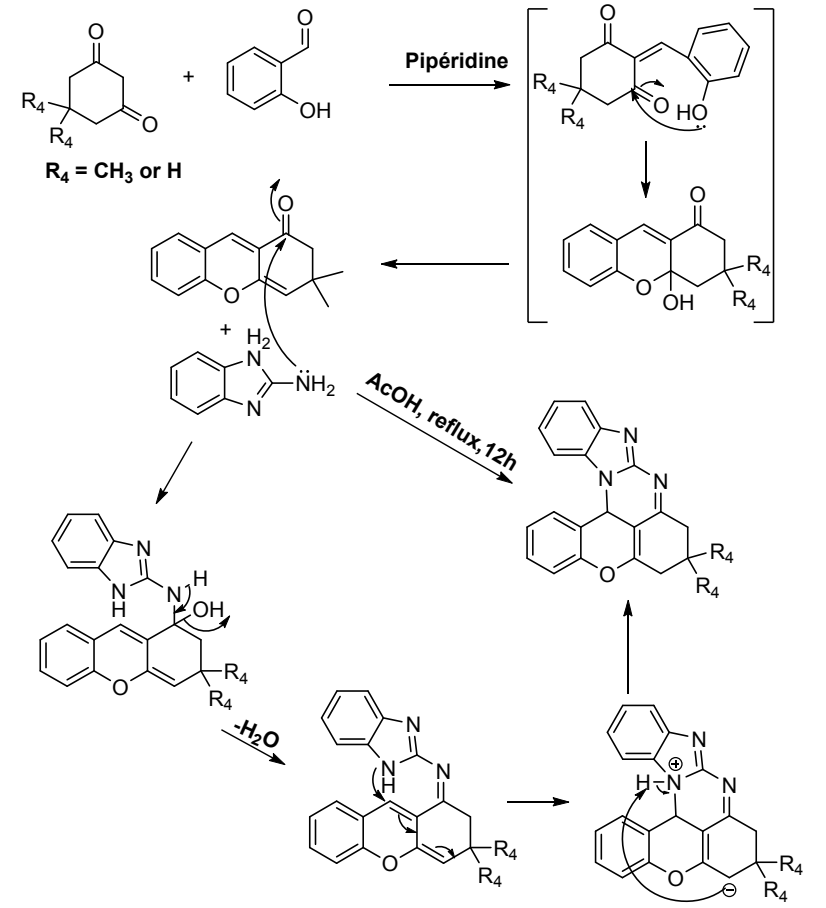
Entry	Reactants		Products	Reaction time (h)	Yield (%)
1		$R_1 = CH_3$ $R_2 = OCH_2CH_3$	 **3a**	12h	67%
2		$R_1 = OCH_3$ $R_2 = CH_2CO_2CH_3$	 **3b**	12h	40%
3		$R_1 = R_2 = OCH_3$	 **3c**	12h	69%
4		$R_1 = H$	 **4a**	12h	70%

5		R_4= CH_3	 **4b**	12h	61%
6		n =1 R_5 = OCH_3	 **5a**	12h	65%
7		n = 2 R_5 = OCH_3	 **5b**	12h	63%

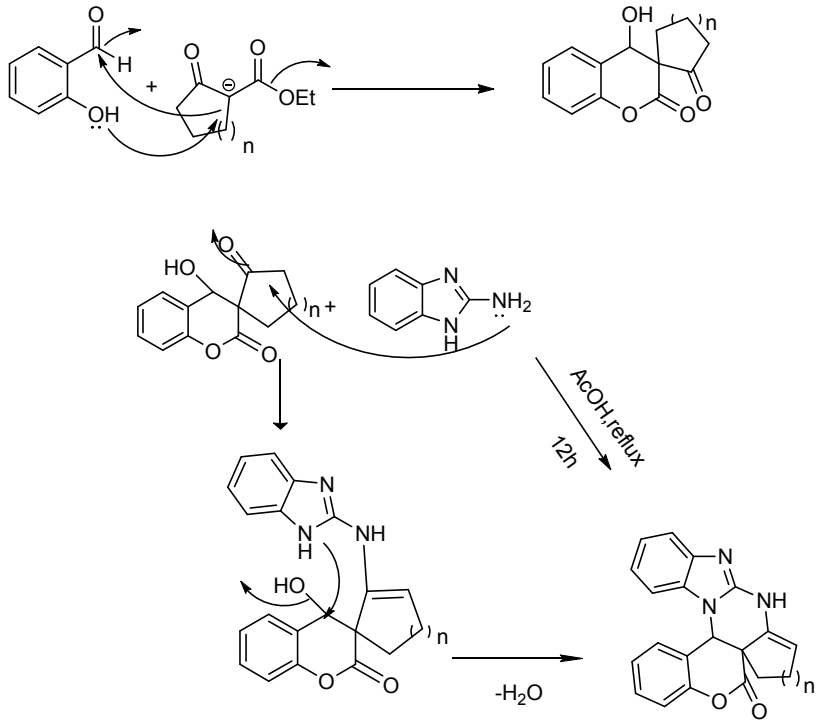
The proposed mechanism for the synthesis of chromeno[4,3-d] pyrimidinone derivatives 3a–c is presented in (Scheme 2), 4a–c is presented in (Scheme 3) and 5a–b is presented in (Scheme 4). The mechanistic path which we propose for this transformation is based on the in situ formation of 3-alkyl coumarin derivative and subsequent condensation with 2-amino-benzimidazole.



Scheme 2: Mechanism for the synthesis of chromeno[4,3-d]pyrimidinone derivatives 3a-c



Scheme 3: Mechanism for the synthesis of chromeno [4,3-d] pyrimidinone derivatives 4a-b



Scheme 4: Mechanism for the synthesis of chromeno [4, 3-d] pyrimidinone derivatives 5a-b.

CONCLUSION

In conclusion, the described one-pot three-component reaction of salicylic aldehyde with 1,3-dicarbonyl derivatives compounds and 2-aminobenzimidazole the presence of catalytic amounts of piperidine in acetic acid is

an extremely efficient and chemo selective method for the synthesis of chromeno[4,3-d]pyrimidinone, derivatives. The products were obtained in good yield without further purification.

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