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Three-component, simple and one-pot reaction between 4-hydroxy coumarin with aromatic aldehydes and 1-ethyl-5-amino-pyrazole in the presence of iodine

Safiyeh Miri and Alireza Hassanabadi*

Department of Chemistry, Zahedan Branch, Islamic Azad University, Zahedan, Iran

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Abstract: We reported a three-component, simple, one-pot and efficient method for the synthesis of pyrazolopyridocoumarin derivatives from the condensation of 4-hydroxycoumarin, aryl aldehydes and 1-ethyl-5-amino-pyrazole in the presence of iodine (I2) as catalyst under reflux. The structure of compounds 4a-f is deduced from their IR, 1H, and 13C NMR spectra. This new protocol offers advantages such as simply available starting materials, easy and clean work-up, and use of an inexpensive and non-toxic catalyst, high yields of biological active products and does not involve any hazardous solvent. Therefore, this procedure could be classified as green chemistry. Fused polyheterocycles are an important class of organic molecule because of their wide spread applications as pharmaceutical candidates, optical materials, florescence dyes and sensors. In recent times, the use of molecular iodine has received considerable attention as an inexpensive, nontoxic, readily available catalyst for various organic transformations to afford the corresponding products in excellent yields with high selectivity.

Keywords: 4-Hydroxycoumarin, 1-Ethyl-5-amino-pyrazole, iodine, Aryl aldehydes, Pyrazolopyridocoumarin derivatives.

Introduction

Multi-component reactions (MCRs) efficiently combine three or more reactants simultaneously in one pot that does not need the isolation, purification and characterization of intermediate products. The MCRs have additional benefits of being selective, time saving, convergent, atom economy and playing an important role in modern synthetic methodology [1-5]. Fused polyheterocycles are an important class of organic molecule because of their wide spread applications as pharmaceutical candidates, optical materials, florescence dyes and sensors [6].

Fused polyheterocycles have received increasing attention due to their potential biological activities [7] such as antimicrobial, antitumor [8], antibiotic, antidiabetic [9] and analgesic [10] properties.

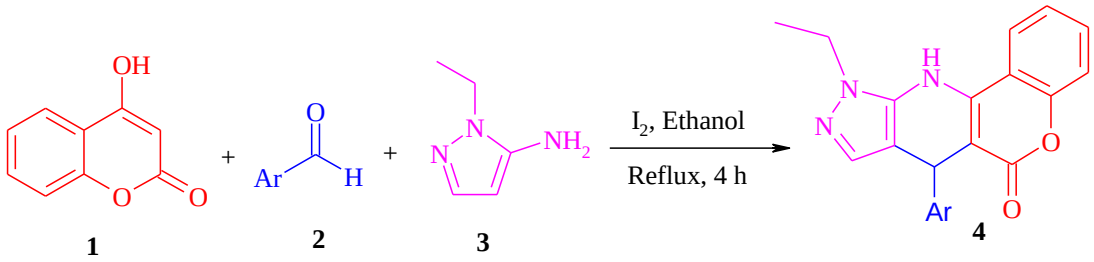
The synthesis of fused polyheterocycles has evoked much attention as a result of which a variety of synthetic methodologies have been reported. The most important approaches are: For example: (i) two step synthesis of pyrazolo[3,4-b]pyridine-based coumarin from salicylaldehyde [11] (ii) one-pot three-component tandem Knoevenagel–Michael reaction catalysed by n-tetrabutylammonium tribromide (TBATB)[12] (iii) one-pot three component-AcOH catalysed reaction of 5-amino-3-methyl-1-phenypyrazole with aromatic aldehydes and 4-hydroxycoumarin [13]. However, these methodologies suffer from one or more short coming such as long reaction time, use of excess amounts of expensive, metal, moisture sensitive catalysts and low yields. Therefore, the development of an efficient, eco-friendly and a metal free method for the synthesis of fused polyheterocycles is still in great damand. In recent times, the use of molecular

*Corresponding author. E-mail: ar_hasanabadi@yahoo.com

iodine has received considerable attention as an inexpensive, nontoxic, readily available catalyst for various organic transformations to afford the corresponding products in excellent yields with high selectivity. A large number of heterocycles such as benzofurans, furans, benzothiophenes, thiophenes, benzopyrans, selenophenes, α-pyrones, isocoumarins, isoxazoles, chromones, β-lactams, 2,3-dihydropyrroles, pyrroles, furopyridines, furanones and isochromenes have been prepared by iodine-mediated domino or one-pot multicomponent reactions. It has also high tolerance to air as well as moisture and can be easily removed from reaction systems by washing with reducing agents [14-17].

Results and discussion

Reaction between 4-hydroxycoumarin **1**, aryl aldehydes **2** and 1-ethyl-5-amino-pyrazole **3** in the presence of iodine (I_2) as catalyst affords pyrazolopyridocoumarin derivatives **4** in excellent yields (Scheme **1**).



1 **2** **3** **4**

Scheme 1: Synthesis of pyrazolopyridocoumarin derivatives

To study the scope of the reaction, a series of aryl aldehydes were applied. The results are shown in Table **1**. In all cases, aryl aldehyde substituted with either electron-donating or electron-withdrawing groups underwent the reaction smoothly and gave products in excellent yields.

Table 1: Yields of a series of pyrazolopyridocoumarin derivatives (**4**)

Entry	Ar	Product	Yield%[a]	m.p./°C
1	C_6H_5	**4a**	87	302-304
2	4-Br C_6H_4	**4b**	91	312-314
3	2-OH C_6H_4	**4c**	89	307-309
4	4-OCH_3 C_6H_4	**4d**	94	272-274
5	2,3-$(OCH_3)_2$ C_6H_3	**4e**	96	295-297

To find out the optimum quantity of iodine, the reaction of 1-ethyl-5-amino-pyrazole and 4-methoxybenzaldehyde with 4-hydroxycoumarin was carried out under reflux using different quantities of iodine (Table **2**). Iodine of 10% gave excellent yield in 4 h (Table **2**, entry 5).

Table 2: Optimisation amount of piperidine on the reaction

Entry	Catalyst/mol%	Time/h	Yield/%[a]
1	0	6	20
2	3	5	50
3	5	5	60
4	8	4	70
5	10	4	94
6	10	3	90
7	12	4	95

[a]Isolated yield.

The structures of compounds **4a-e** were deduced from their high-field ^{1}H NMR, ^{13}C NMR and IR spectral data. The ^{1}H NMR spectrum of 4a exhibited a triplet (δ = 1.45 ppm, $^3J_{HH}$ = 7.6Hz) and a quartet (δ = 4.19 ppm, $^3J_{HH}$ = 7.6Hz) for ethyl protons and exhibits a sharp line at δ = 3.54 ppm for the proton of methine group. A single signal is observed at 10.67 ppm that disappeared after addition of a few drops of D_2O to DMSO-d_6 solution of compound **4a**. These signal is related to NH proton. Aromatic protons resonate as multiples at δ = 6.88-8.74 ppm. The ^{13}C NMR spectrum of compound 4a shows 19 distinct signals in consistent with the proposed structure. The IR spectrum showed an absorption bond at 3310 cm^{-1} for NH group. The carbonyl stretching vibration observed as strong absorption bond at 1670 cm^{-1}. Although we didn't study the mechanism of the reaction, but a reasonable possibility is presented in Scheme **2**. Iodine can serve as a mild lewis acid catalyst for the reaction of 4-hydroxycoumarin and aryl aldehydes to give the corresponding intermediate. The michael addition of 1-ethyl-5-amino-pyrazole on the intermediate, followed by intramolecular cyclisation would eventually afford the final fused polyheterocycles. Iodine is likely to enhance the rate of this multicomponent reaction.

Conclusion

In conclusion, here we reported a green and efficient method for the synthesis of pyrazolopyridocoumarin derivatives from the condensation of 4-hydroxycoumarin, aryl aldehydes and 1-ethyl-5-amino-pyrazole in the presence of iodine (I_2) as catalyst under reflux. This new protocol offers advantages such as simply available starting materials, easy and clean work-up, and use of an inexpensive and non-toxic catalyst, high yields of biological active products and does not involve any hazardous solvent. Therefore, this procedure could be classified as green chemistry.

Experimental

Melting points were determined with an Electrothermal 9100 apparatus. IR spectra of selected compounds were recorded on a Shimadzu IR-470 spectrometer in KBr discs. ^{1}H and ^{13}CNMR spectra were obtained on a Bruker DRX-400 Avance spectrometer in DMSO-d_6 using TMS as internal standard. The chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification.

General procedure for preparation of compounds 4a-e:

To a stirring solution of 4-hydroxycoumarin (2 mmol), aryl aldehyde (2 mmol) and 1-ethyl-5-amino-pyrazole (2 mmol) in ethanol (15 mL) was added iodine (10 mol %). The reaction flask was heated at 70°C in an oil bath for 4 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure. The resulting precipitate was filtered off, washed with cold diethyl ether (10 mL) to give a pure product.

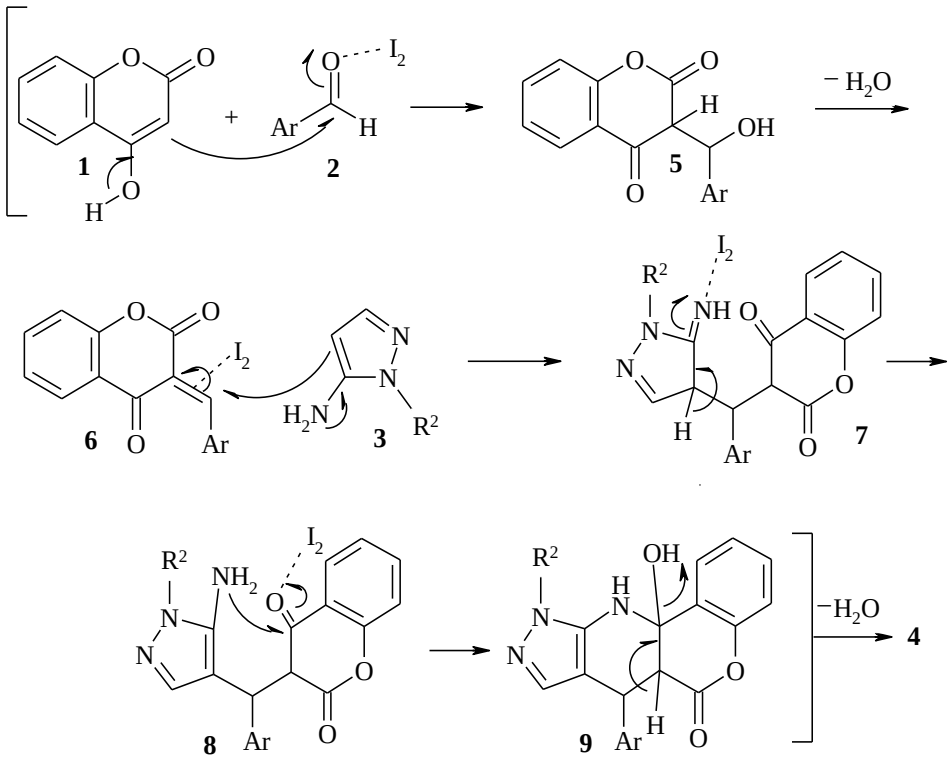
10-Ethyl-7-phenyl-10,11-dihydro-7H-5-oxa-9,10,11-triaza-cyclo-penta[b]phenanthren-6-one (4a):

Colorless solid; m.p. 301-303 °C; IR (KBr, ν_{max} cm^{-1}): 1670 (C=O), 3310 (NH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.45 (t, 3H, CH_3 of C_2H_5 group, $J_{1,2}$ = 7.6 Hz), 3.54 (s, 1H, methine proton), 4.19 (q, 2H, CH_2 of C_2H_5 group, $J_{1,2}$ = 7.6 Hz), 6.88-8.74 (m, 10H, Ar-H), 10.67 (s, 1H, NH)ppm.; ^{13}C NMR (100 MHz, DMSO-*d*6): δ 14.0, 45.9, 48.1, 101.1, 104.5, 108.0, 114.5, 120.9, 121.8, 127.5, 127.7, 128.3, 137.0, 137.2, 147.9, 152.0, 157.4, 159.9ppm.

7-(4-Bromo-phenyl)-10-ethyl-10,11-dihydro-7H-5-oxa-9,10,11-triaza-cyclopenta[b]phenanthren-6-one (4b):

Brown solid; m.p. 311-313 °C; IR (KBr, ν_{max} cm^{-1}): 1696 (C=O), 3270 (NH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.44 (t, 3H, CH_3 of C_2H_5 group, $J_{1,2}$ = 7.6 Hz), 3.47 (s, 1H, methine proton), 4.44 (q, 2H, CH_2 of C_2H_5 group, $J_{1,2}$ = 7.6 Hz), 7.15-8.92 (m, 9H, Ar-H), 10.50 (s, 1H, NH)ppm.; ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.0, 45.3, 49.8, 102.8, 103.7, 113.0, 115.9, 119.9, 124.0, 125.5, 132.9, 133.1, 142.1, 148.2, 149.2, 151.3, 152.0, 160.15ppm.

10-Ethyl-7-(2-hydroxy-phenyl)-10,11-dihydro-7H-5-oxa-9,10,11-triaza-cyclopenta[b]phenanthren-6-one (4c):



Scheme 2: Suggested mechanism for formation of compound **4**.

Colorless solid; m.p. 309-311 °C; IR (KBr, ν_{max} cm^{-1}): 1674 (C=O), 3065 (OH), 3230 (NH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.53 (t, 3H, CH_3 of C_2H_5 group, $J_{1,2}$ = 7.6 Hz), 3.61 (s, 1H, methine proton), 4.45 (q, 2H, CH_2 of C_2H_5 group, $J_{1,2}$ = 7.6 Hz), 7.09-8.33 (m, 9H, Ar-H), 9.85 (s, 1H, OH), 10.70 (s, 1H, NH)ppm.; ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.1, 45.9, 48.0, 102.4, 107.6, 108.3, 112.9, 114.7, 122.2, 123.9, 127.8, 129.7, 133.9, 139.1, 141.7, 148.3, 150.9, 152.0, 152.9, 160.4ppm.

10-Ethyl-7-(4-methoxy-phenyl)-10,11-dihydro-7H-5-oxa-9,10,11-triaza-cyclopenta[b]phenanthren-6-one (4d):

Colorless solid; m.p. 274-276 °C; IR (KBr, ν_{max} cm^{-1}): 1672 (C=O), 3345 (NH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.44 (t, 3H, CH_3 of C_2H_5 group, $J_{1,2}$ = 7.6 Hz), 3.41 (s, 1H, methine proton), 3.61 (s, 3H, OCH_3), 4.45 (q, 2H, CH_2 of C_2H_5 group, $J_{1,2}$ = 7.6 Hz), 7.16-8.45 (m, 9H, Ar-H), 10.32 (s, 1H, NH)ppm.; ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.7, 44.6, 48.8, 58.8, 102.1, 106.0, 114.7, 114.9, 125.6, 128.1, 129.3, 129.4, 130.5, 133.5, 133.6, 142.6, 149.4, 150.7, 160.4ppm.

10-Ethyl-7-(2,3-dimethoxy-phenyl)-10,11-dihydro-7H-5-oxa-9,10,11-triazacyclopenta[b]phenanthren-6-one (4e):

Colorless solid; m.p. 297-299 °C; IR (KBr, ν_{max} cm^{-1}): 1676 (C=O), 3255 (NH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.48 (t, 3H, CH_3 of C_2H_5 group, $J_{1,2}$ = 8.0 Hz), 3.40 (s, 3H, OCH_3), 3.44 (s, 1H, methine proton), 3.61 (s, 3H, OCH_3), 4.62 (q, 2H, CH_2 of C_2H_5 group, $J_{1,2}$ = 8.0 Hz), 6.81-8.73 (m, 8H, Ar-H), 10.23 (s, 1H, NH)ppm.; ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.5, 24.8, 40.1, 55.6, 60.0, 109.6, 113.3, 116.6, 119.2, 120.3, 123.8, 124.5, 125.1, 130.6, 132.7, 134.0, 144.8, 147.9, 149.7, 150.6, 151.9, 152.0, 158.7ppm.

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