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Research Article

An Efficient, One-Pot and New Synthesis of 2-amino-12H-spiro[indolo[1,2-b]quinazoline]pyrano-3-carbonitril

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ABSTRACT

An efficient synthesis of spiroindolopyranoquinazolines has been achieved in good yields by using one-pot, three-component condensation of alkyl malonates, tryptanthrin, and active methylene compounds in the presence of DABCO as organocatalyst in CH_3CN at reflux

Keywords: Tryptanthrin; One-pot; Spiropyran; Alkyl malonates; Spiroindoloquinazoline

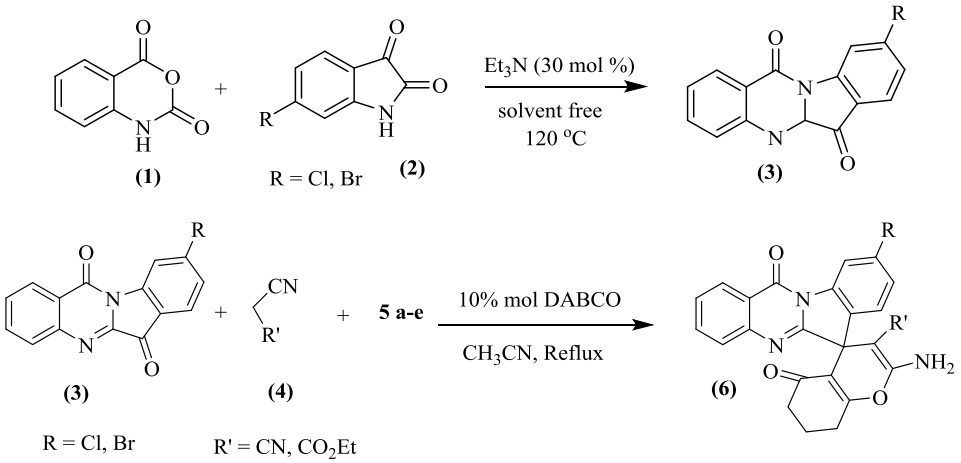
1. Introduction

Multi-component reactions (MCRs) present reactions, in which are formed multiple chemical bonds during one step, is one of the biggest research and investigation basis to introduction of synthetic methods with less number of steps. Nowadays, these categories of reactions attract special attention. [1-10] The most important quality which cause multi-component reactions be in a group of reactions accordance with green chemistry, is avoiding complicated purification operations and allowing saves both solvents and reagents. [11, 12]

Tryptanthrin (indolo[2,1-*b*]quinazoline-6,12-dione) (3) (Scheme 1) is a weakly basic alkaloid which is qualified of binding at numerous sites with high affiliation and simplify

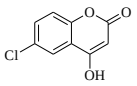
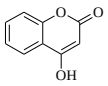
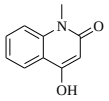
synthesis of more useful compounds with medicinally activities.[13-16] On the basis of biological researches, the entity of two or more diverse heterocyclic moieties in a single molecule enhances the biocidal activity remarkably. [17] This natural compound contains a quinazoline ring fused to an indole moiety with carbonyl group of tryptanthrin and its derivatives are of huge interest due to their biological activities, such as antibacterial, [18] antiparasitic, [19] and antineoplastic [20] properties. And also there are many witnesses to explain the application of tryptanthrin derivatives as dyes and pigments and as photoelectric materials. [21]

Compounds containing heterocyclic spiro ring molecules are target system for almost all chemists, because of their pharmaceutical and biological properties. [22-24] On the other hand, as these complex compounds have cyclic structures fused at a central carbon, and their useful conformational features and structural implications on biological systems, [25] herein we report a three-component reaction between indolo[2,1-*b*]quinazoline-6,12-dione (3), alkyl malonates (4) and active methylene reagents (**5a-e**) in CH_3CN as solvent and catalytic DABCO, leading to synthesize several 2-amino-spiropyrano carbonitril (carboxylate) derivatives (**6a-i**)(Scheme 1,Table 3).



Scheme 1

Table 1. Compound (5a-e)

5a	5b	5c	5d	5e
				

2. Experimental

All melting points were determined by using an electro thermal 9200 apparatus. IR spectra were recorded (in KBr discs) on Jasco FT-IR 6300 spectrophotometer. The ^{1}H NMR, and ^{13}C NMR were measured on a Brucker Avance III 400 MHz in DMSO-d_6. Chemical shifts are reported relative to tetramethylsilane.

Synthesis of 2-amino spiropyrano carbonitrile (carboxylate) derivatives (6a-k): General procedure

A mixture of respective tryptanthrin[26] (3) (1mmol), malononitrile or ethylcyanoacetate (4) (1mmol), active methylene reagents (**5a-e**) (1mmol), and DABCO (20 mol%) in CH_3CN (10 ml) was stirred at reflux for the time period as shown in table 1. After completion of the reaction (monitored by TLC, n-Hexane/ ethylacetate, 20/8), the residue was cooled and the resulting crystal product was collected by filtration and crystallized from the CH_3CN.

The spectroscopic data of some compounds are presented below:

2-amino-7,7-dimethyl-5,12'-dioxo-5,6,7,8-tetrahydro-12'*H*-spiro[chromene-4,6'-indolo[2,1-*b*]quinazoline]-3-carbonitrile (6a): (mp: 297-299 ºC) IR (KBr): υ_{max} 3403, 3166, 3074, 2964, 2196, 1662, 1639, 1599, 1463, 1422, 1355, 1321, 1052, 773;^{1}H NMR (400 MHz, DMSO-d_6): δ= 1.02 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 2.11 (ABq, 2H, CH_2, *J*=16.4 Hz), 2.68 (ABq, 2H, CH_2, *J*= 16.8 Hz), 7.37 (td, 1H, *J*= 7.6 Hz, *J*= 0.8 Hz, ArH), 7.43 (dd, 1H, *J*= 6.8Hz, *J*= 1.2 Hz, ArH), 7.48 (td, 1H, *J*= 8.0 Hz, *J*=1.2 Hz, ArH), 7.54 (s, 2H, NH_2), 7.64 (td, 1H, *J*= 7.6 Hz, *J*= 0.8 Hz, ArH), 7.74 (d, 1H, *J*= 8.0 Hz, ArH), 7.88 (td, 1H, *J*= 7.2 Hz, *J*= 1.6 Hz, ArH),

8.33 (dd, 1H, *J*= 8.0 Hz, *J*= 1.2 Hz, ArH), 8.44 (d, 1H, *J*= 8.0 Hz, ArH); ^{13}C NMR (100MHz, DMSO-d_6): 18.52, 27.01, 27.44, 32.11, 49.78, 55.99, 111.18, 115.75, 117.28, 120.60, 123.77, 126.40, 127.04, 127.29, 127.33, 129.08, 134.88, 135.58, 138.53, 147.11, 158.31, 158.91, 162.64, 164.42, 195.39.

2-amino-5,12'-dioxo-5,6,7,8-tetrahydro-12'*H*-spiro[chromene-4,6'-indolo[2,1-*b*]quinazoline]-3-carbonitrile (6b): (mp: 282-284 ºC) IR (KBr): υ_{max} 3362, 3079, 2250, 2196, 1675, 1640, 1598, 1463, 1351, 1215, 754; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.94-1.98 (m, 2H, CH_2), 2.18-2.23 (m, 2H, CH_2), 2.72-2.84 (m, 2H, CH_2), 7.36 (td, 1H, *J*= 7.5 Hz, *J*= 0.8 Hz, ArH), 7.46 (d, 1H, *J*= 7.0 Hz, ArH), 7.50 (dd, 1H, *J*= 7.7 Hz, *J*= 1.2 Hz, ArH), 7.53 (s, 2H, NH_2), 7.64 (td, 1H, *J*= 7.5 Hz, *J*= 1.0 Hz, ArH), 7.77 (d, 1H, *J*= 7.8 Hz, ArH), 7.89 (td, 1H, *J*= 7.6 Hz, *J*= 1.5 Hz, ArH), 8.33 (dd, 1H, *J*= 8.0 Hz, *J*= 1.4 Hz, ArH), 8.44 (d, 1H, *J*= 7.9 Hz, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 19.67, 26.77, 36.25, 47.95, 58.05, 112.28, 115.65, 117.26, 120.61, 123.94, 126.39, 127.00, 127.31, 129.02, 134.83, 135.76, 138.45, 147.10, 158.15, 158.94, 162.72, 166.30, 195.46.

2'-amino-9'-chloro-5',12-dioxo-5'*H*,12*H*-spiro[indolo[2,1-*b*]quinazoline-6,4'-pyrano[3,2-*c*]chromene]-3'-carbonitrile(6c) : (mp: 289-291 ºC) IR (KBr): υ_{max} 3456, 3232, 3073, 2194, 1739, 1679, 1603, 1602, 1462, 1355, 1327, 973, 766; ^{1}H NMR (400MHz, DMSO-d_6): δ = 7.43 (td, 1H, *J*= 7.5 Hz, *J*= 0.6 Hz, ArH), 7.55-7.59 (m, 2H, ArH), 7.65-7.69 (m, 2H, ArH), 7.77 (d, 1H, *J*= 8.0 Hz, ArH), 7.85-7.93 (m, 2H, ArH), 7.96 (s, 2H, NH_2), 8.08 (d, 1H, *J*= 2.6 Hz, ArH), 8.36 (dd, 1H, *J*= 8.4 Hz, *J*= 1.4 Hz, ArH), 8.48 (d, 1H, *J*= 8.0 Hz, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 48.51, 57.62, 102.31, 114.02, 115.76, 116.77, 118.08, 118.97, 120.70, 122.33, 125.00, 126.52,127.23, 127.46, 127.83, 129.24, 129.90, 133.56, 133.90, 135.10, 138.76, 146.84, 150.82, 153.99, 157.88, 158.18, 158.76, 161.46.

2'-amino-5',12-dioxo-5'*H*,12*H*-spiro[indolo[2,1-*b*]quinazoline-6,4'-pyrano[3,2-*c*]chromene]-3'-carbonitrile(6d): (mp: 330-335 ºC) ^{1}H NMR (400MHz, DMSO-d_6): δ= 7.41 (t, 1H, *J*= 7.6

Hz, ArH), 7.52 (d, 1H, *J*= 8.4 Hz, ArH), 7.55-7.69 (m, 5H, NH_2 and ArH), 7.77 (d, 1H, *J*= 8.1 Hz, ArH), 7.82 (t, 1H, *J*=

8.3 Hz, ArH), 7.90 (t, 1H, *J*=7.2 Hz, ArH), 7.92 (s, 1H, ArH), 8.04 (d, 1H, *J*=7.9 Hz, ArH), 8.36 (d, 1H, *J*=7.9 Hz, ArH), 8.48 (d, 1H, *J*=8.0 Hz, ArH); ^{13}C NMR (100MHz, DMSO-d_6): 48.53, 57.67, 101.58, 112.46, 115.76, 116.81, 116.92, 120.71, 122.95, 124.90, 125.22, 126.51, 127.22, 127.44 127.76, 129.80, 133.99, 134.14, 135.06, 138.82, 146.89, 152.14, 154.94, 158.03, 158.56, 158.79, 161.73.

2'-amino-6'-methyl-5',12-dioxo-5',6'-dihydro-12*H*-spiro[indolo[2,1-*b*]quinazoline-6,4'-pyrano[3,2-*c*]quinoline]- 3'-carbonitrile (6e): (mp: 292-297 ºC) ^{1}H NMR (400MHz, DMSO-d_6): δ = 2.07 (s, 3H, CH_3), 7.32 (t, 1H, *J*=8.0 Hz, ArH), 7.44-7.52 (m, 3H, ArH), 7.58-7.64 (m, 2H, ArH), 7.68-7.73 (m, 3H, NH_2, ArH), 7.78 (t, 1H, *J*=8.0 Hz, ArH), 7.85 (t, 1H, *J*=8.0 Hz, ArH), 8.16 (d, 1H, *J*=8.0 Hz, ArH), 8.34 (d, 1H, *J*=8.0 Hz, ArH), 8.47 (d, 1H, *J*=8.0 Hz, ArH); ^{13}C NMR (100MHz, DMSO-d_6): 29.82, 49.66, 58.27, 107.10, 112.76, 115.77, 116.18, 117.89, 121.25, 123.14, 123.24, 124.70, 126.93, 127.52, 127.83, 127.88, 129.71, 133.10, 135.36, 135.89, 139.26, 139.60, 147.59, 151.77, 158.95, 159.28, 159.47, 163.27.

ethyl 2'-amino-6'-methyl-5',12-dioxo-5',6'-dihydro-12*H*-spiro[indolo[2,1-*b*]quinazoline-6,4'-pyrano[3,2-*c*]quinoline]-3'-carboxylate(6f): (mp: 262-266 ºC) ^{1}H NMR (400MHz, DMSO-d_6): δ = 0.69-0.98 (3H, CH_3), 2.32 (3H, CH_3-N), 4.21 (2H, OCH_2), 7.16 (1H, ArH), 7.32 (1H, ArH), 7.46-7.50 (t, 2H, ArH), 7.57-7.58(4H, ArH), 7.78-7.79 (2H, NH_2, ArH), 8.24 (1H, ArH), 8.37 (1H, ArH), 8.48 (1H, ArH), 8.62 (1H, ArH);

2'-amino-3-bromo-5',12-dioxo-5'*H*,12*H*-spiro[indolo[2,1-*b*]quinazoline-6,4'-pyrano[3,2-*c*]chromene]-3'-carbonitrile(6g): (mp: 335-337 ºC) ^{1}H NMR (400MHz, DMSO-d_6): δ = 7.44-7.93 (8H, ArH), 7.94-8.1 (4H, ArH), 8.26-8.48 (2H, ArH); ^{13}C NMR (100MHz, DMSO-d_6): 47.76, 66.98, 101.36, 113.13, 117.35, 117.98, 120.01, 123.52, 125.71, 127.02, 128.01,

128.61, 133.22, 134.51, 135.76, 137.06, 138.46, 147.35, 152.70, 155.83, 158.62, 159.22, 161.63, 162.32, 163.13, 192.87, 194.96.

2-amino-3'-chloro-5,12'-dioxo-5,6,7,8-tetrahydro-12'*H*-spiro[chromene-4,6'-indolo[2,1-*b*]quinazoline]-3-carbonitrile(6h): (mp: 272-274 ºC) ^{1}H NMR (400MHz, DMSO-d_6): δ =0.28-2.29 (7H, 3CH_2), 7.49-7.93 (m, 7H, ArH), 8.24 (2H, ArH);

ethyl 2'-amino-3-chloro-5',12-dioxo-5'*H*,12*H*-spiro[indolo[2,1-*b*]quinazoline-6,4'-pyrano[3,2-*c*]chromene]-3'-carboxylate(6i): (mp: 330-335 ºC) IR (KBr): υ_{max} 3375, 3090, 2983, 2196, 1686, 1472, 1349, 1108, 1024, 755; ^{1}H NMR (400MHz, DMSO-d_6): δ = 0.55 (s, 3H, CH_3), 4.19 (2H, OCH_2), 7.42-7.85 (m, 9H, ArH), 8.07-8.46 (m, 4H, ArH);

3. Result and discussion

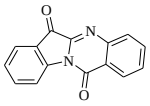
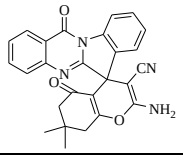
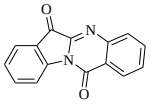
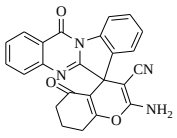
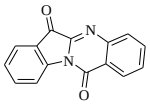
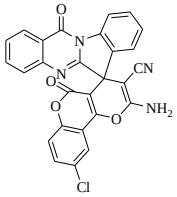
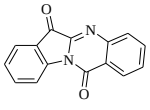
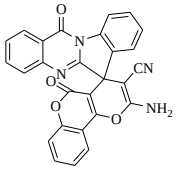
In an initial effort, we examined 1 equiv each of indolo[2,1-*b*]quinazoline-6,12-dione (3a), dimedone (5a), and malononitrile (4a) in different solvents with or without the presence of diverse catalysts (Table 2). As shown in Table 2, the best result was obtained with 10 mol% of DABCO as the catalyst in refluxing acetonitrile (entry 3). Using less catalyst produced lower yields, while higher amounts of catalyst did not change reaction times and yields considerably (Table 2). When this reaction was accomplished without DABCO or with other catalysts like NH_4Cl, *p*-TSA, Et_3N, and CAN , the yield of the product was low (Table 2). In the presence of L-proline as catalyst the product was achieved in moderate yield. To recognize the best solvent, the reaction was tested in various solvents such as, acetic acid, EtOH, CH_3CN. The low yield was achieved, when we use acetic acid as solvent (Table 2). CH_3CN was the best choice of solvent and the use of DABCO (10 mol%) in refluxing CH_3CN decrease the reaction time and increase the product yield.

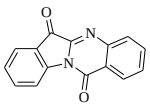
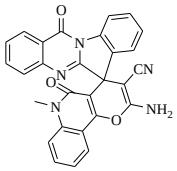
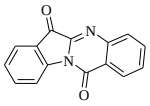
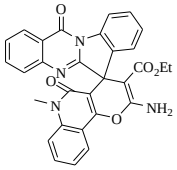
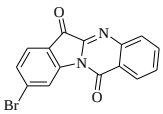
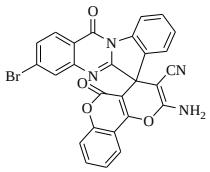
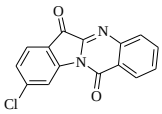
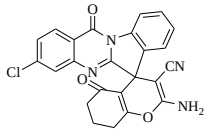
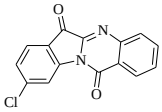
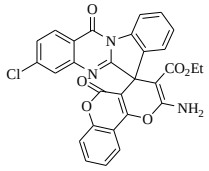
Table 2. Effect of reaction condition.

Entry	Solvent	Catalyst(mol%)	Time(min)	[a]Yield(%)
1	CH_3CN	DABCO (25)	10	99
2	CH_3CN	DABCO (20)	20	97
3	CH_3CN	DABCO (10)	20	95
4	CH_3CN	DABCO (5)	45	83
5	CH_3CN	None	3 h	Trace
6	CH_3CN	L-proline (25)	25	40
7	CH_3CN	NH_4Cl (25)	25	Trace
8	CH_3CN	*p*-TSA (25)	25	Trace
9	CH_3CN	Et_3N (25)	25	Trace
10	CH_3CN	CAN (25)	25	Trace
11	EtOH	DABCO (25)	25	50
12	H_2O	DABCO (25)	25	Trace
13	Acetic acid	–	25	35
14	–	L-proline (25)	12	15

[a] Isolated yields

Table 3. Prepration of 2-amino-12*H*-spiro[indolo[1,2-*b*]quinazoline]pyrano-3-carbonitril (carboxylate) catalyzed by DABCO at reflux in CH_3CN.

Entry	Related tryptanthrin	5	R'	Time(min)	Product	[a]Yield(%)	MP (°C)
1		5a	CN	20		95	297-299
2		5b	CN	20		90	282-284
3		5c	CN	25		96	289-291
4		5d	CN	30		92	331-333

5		5e	CN	25		84	292-297
6		5e	CO_2Et	30		80	262-266
7		5d	CN	25		88	335-337
8		5b	CN	20		92	272-274
9		5d	CO_2Et	25		89	325-327

[a] Isolated yields

Obtained results indicate the effectiveness of this provided method for synthesis of 2-amino-spiropyrano carbonitril (carboxylate) derivatives. On the basis of experimental results, the rate and yield of reaction used malononitrile was increased in comparison with ethylacetate under constant conditions. The structures of products were characterized by IR, ^{1}H NMR, ^{13}C NMR.

4. Conclusion

In summary, the reaction described herein provides a simple and efficient into numerous novel spiropyranoquinazoline derivatives via one-pot, three-component reaction of tryptanthrin, alkyl malonates, and active methylene reagents in the presence of DABCO as catalyst, in CH_3CN at reflux in very good yields (80-96%). This method proffers advantages such as, easy workup, short reaction time, and simple procedure.

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