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Three-component coupling reactions of isoquinolines, dimethyl acetylenedicarboxylate and indoles: a facile synthesis of 3-indolyl-1,2-dihydro-2-isoquinolinyl-2-butenedioate

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Abstract

A three-component coupling of isoquinolines, dimethyl acetylenedicarboxylate (DMAD) and indoles is achieved for the first time to produce dimethyl (*E*)-2-[1-(1*H*-3-indolyl)-1,2-dihydro-2-isoquinolinyl]-2-butenedioates in excellent yields and with high selectivity. The reaction proceeds smoothly at room temperature without a catalyst. Quinoline, DMAD and indole also undergo smooth coupling to furnish dimethyl (*E*)-2-[2-(1*H*-3-indolyl)-1,2-dihydro-1-quinolinyl]-2-butenedioate under similar conditions. This method is very useful to functionalize both indoles and aza-aromatic compounds in a one-pot operation.

Keywords: Isoquinoline/quinoline; Indole; Dimethyl acetylenedicarboxylate; 3-Indolyl-dihydroisoquinolines

Indole nucleus is frequently found in medicinal chemistry and is considered as 'privileged scaffolds'.[1] SUGEN found an indolin-2-one as a pharmacophore for potent KDR kinase inhibitors,[2] and Merck recently reported a class of potent KDR kinase inhibitors containing the indol-2-yl quinolin-2-one structure (Fig. 1).[3]

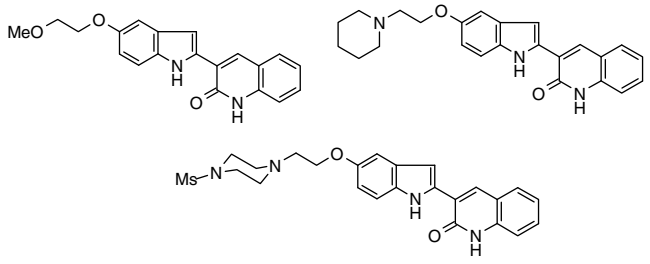

Fig. 1. Merck KDR inhibitors.

Isoquinoline is also present in various natural products such as cryptaustoline (i) and cryptowoline (ii) (Fig. 2).[4] They are known to exhibit various biological activities such as antileukaemic,[5] tubulin polymerization inhibitory[6] and anti-tumour activities.[7,8] Related synthetic acetoxy-substituted 5,6-dihydro[2,1-*a*]isoquinolines (iii) also exhibit strong binding affinities for the oestrogen receptor of

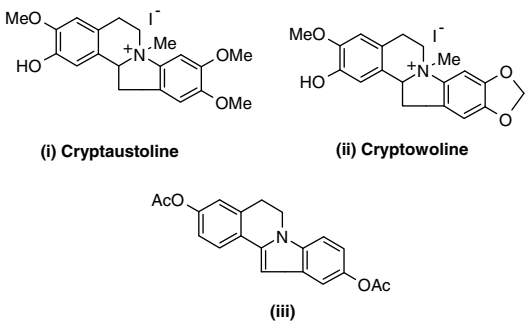

Fig. 2. Biologically active indolo[2,1-1]isoquinolines.

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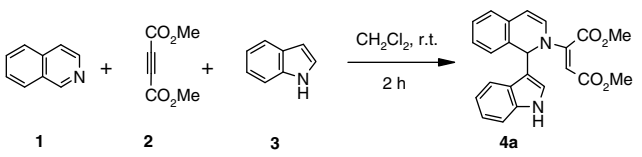


Scheme 1. Preparation of product **4a**.

MDA-MB 231 and MCF-7 mammary tumour cell lines.[9] It has also been reported that hydroxy-substituted indolo-[2,1-*a*]isoquinolines bind to the colchicine binding site and inhibit the polymerization of tubulin.[9]

Given this proven utility, it seems reasonable that the synthesis of a novel series of indol-3-yl-1,2-dihydro quino-

Table 1
Three-component coupling reactions of isoluinolines, DMAD and indoles

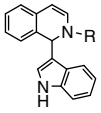
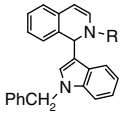
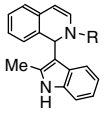
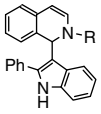
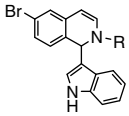
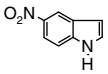
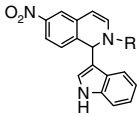
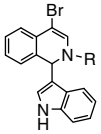
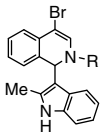
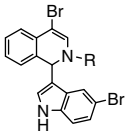
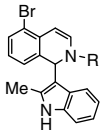
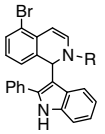
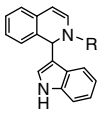
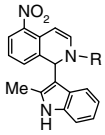
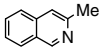
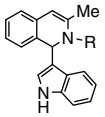
Entry	Isoquinoline **1**	DMAD **2**	Indole **3**	Produce[a] **4**	Time (h)	Yield[b] (%)
a					2.0	90
b					4.0	78
c					2.0	92
d					1.5	85
e					2.5	70
f					4.0	60
g					2.5	75
h					1.0	88
i					2.5	90

Table 1 (*continued*)

Entry	Isoquinoline **1**	DMAD **2**	Indole **3**	Produce[a] **4**	Time (h)	Yield[b] (%)
j					3.0	82
k					2.0	90
l					3.5	70
m					3.5	73
n					2.0	82

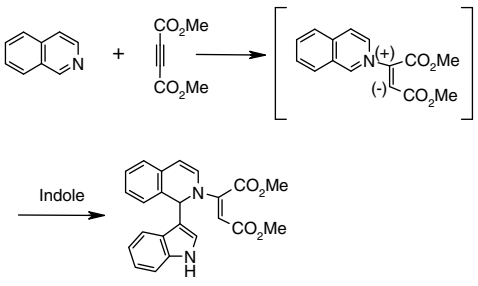
[a] All products were characterized by NMR, IR and spectrometry. R=  .
[b] Isolated yields after purification.

line derivatives would provide additional lead molecules for use in drug discovery. Aza-aromatic compounds activated by acyl chlorides or DMAD are important intermediates for the synthesis of a variety of biologically active nitrogen containing alkaloids.[10–12] Knowing the importance of isoquinoline/quinoline and indole derivatives, the preparation of their new analogs is of prime importance in both synthetic and medicinal chemistry.

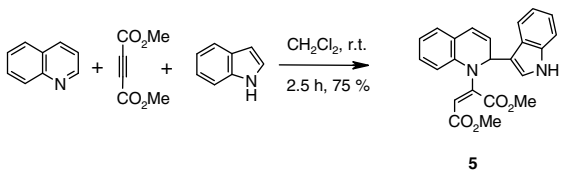
In continuation of our interest on the functionalization of aza-aromatic systems activated by acyl chlorides,[13] we herein report a simple and catalyst free method for the direct coupling of indoles with quinoline and isoquinolines activated by dimethyl acetylenedicarboxylate via a three-component reaction. Accordingly, treatment of isoquinoline (**1**) with dimethyl acetylenedicarboxylate (**2**) and indole (**3**) in dichloromethane at room temperature for 2 h gave the product, dimethyl 2-(1-(indolin-3-yl)isoquinolin-2(1*H*)-yl)but-2-enedioate **4a** in 90% yield (Scheme 1).

Similarly, various indoles such as *N*-benzyl-, 2-methyl-, 2-phenyl-, 5-bromo- and 5-nitro-indole underwent smooth coupling with activated isoquinolines to produce the corresponding products in good to excellent yields (Table 1, entries b–f). The geometry of alkene in product **4a** was found to be *E*, which was confirmed by comparison of NMR data with authentic sample.[14] In all the cases, the nucleophilic addition took place selectively at the 1-position of isoquinoline, showing high regioselectivity. No 1,4-addition products were observed under these reaction conditions. Like indoles, 4-bromo-, 5-bromo-, 5-nitro- and 3-methyl-isoquinolines also reacted readily with DMAD and indoles to afford the corresponding 1-substituted isoquinolines (Table 1, entries g–n). Mechanistically, the reaction may proceed via the formation of a zwitterionic intermediate,[15] which reacts simultaneously with indole to furnish the desired product (Scheme 2).

Like isoquinolines, the quinoline also coupled readily with indole under identical conditions. The reaction went to completion in 2.5 h and the product, dimethyl

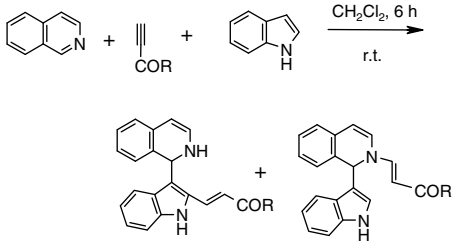


Scheme 2. A plausible reaction mechanism.



5

Scheme 3. Preparation of product **5**.



R = OMe; Yield = 85%; Ratio of 6 and 7 = 7:3
R = Ph; Yield = 80%; Ratio of 8 and 9 = 7:3

Scheme 4. Preparation of products **6**–**9**.

2-(2-(1*H*-indol-3-yl)quinolin-1(2*H*)-yl)but-2-enedioate **5**, was obtained in 75% yield (Scheme 3).[16]

This method worked well for both electron rich and electron deficient substrates. Various functional groups such as halides, esters and nitro derivatives are well tolerated under the reaction conditions (Table 1). This method offers several advantages such as high yields of products, mild reaction conditions, greater selectivity, cleaner reaction profiles and operational simplicity. No additives or catalysts were required to effect the reaction. It should be noted that isoquinolines gave higher yields of products when compared to quinolines. The scope and generality of this process is illustrated with respect to various isoquinolines and indoles and the results are presented in Table 1.[17] It is noteworthy to mention that isoquinoline was also activated by methyl propiolate and 1-ethynylphenyl ketone (Scheme 4). However, the products were obtained as mixtures in each reaction, the structures of which were established by NMR, IR and mass spectrometry.[18] A similar method has been reported using chlorovinyl phenyl ketone instead of 1-ethynylphenyl ketone for the preparation of **9**.[19]

In summary, we have developed a novel multi-component reaction capable of coupling of indoles with quinoline and isoquinolines activated by dimethyl acetylenedicarboxylate at room temperature without a catalyst to produce indolyl-dihydroquinoline and isoquinolines. In addition to its simplicity and mild reaction conditions, this method provides high yields of products with high selectivity, which makes it a useful and attractive process for the synthesis of indolyl quinoline and isoquinolines in a single step operation.

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16. Compound **5**: Dark yellow solid, mp 114–116 °C, IR (KBr): *v* 3410, 2924, 2853, 1741, 1603, 1494, 1453, 1288, 1159, 745 cm^{-1}. ^1H NMR

(200 MHz, $CDCl_3$): δ 7.55–7.51 (m, 1H), 7.32–7.00 (m, 7H), 6.75 (d, $J = 9.4$ Hz, 1H), 6.66 (d, $J = 3.3$ Hz, 1H), 6.50 (d, $J = 5.4$ Hz, 1H), 6.37–6.34 (m, 1H), 6.05 (dd, $J = 9.4$, 5.6 Hz, 1H), 5.58, 3.68 (s, 3H), 3.65 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ: 51.6, 52.9, 68.5, 103.8, 106.2, 109.1, 119.3, 120.1, 121.3, 122.3, 122.4, 123.9, 124.6, 125.9, 127.6, 129.1, 133.6, 136.5, 150.2, 164.9, 166.0; LCMS: *m/z*: 411.0 (M^++Na), 304.1, 272.0; HRMS (ESI) calcd for $C_{23}H_{20}N_2O_4$: 411.1320. Found: 411.1324.

17. *General procedure*: To a stirred solution of indole (1 mmol) and DMAD (1 mmol) in 5 mL dichloromethane was added isoquinoline. The mixture was stirred at the room temperature for appropriate time (see Table 1). After complete conversion as indicated by TLC, the reaction mixture was quenched with water (10 mL) and extracted with dichloromethane (2 × 15 mL). The combined extracts were dried over anhydrous Na_2SO_4, and concentrated in vacuo. The resulting product was purified by column chromatography on silica gel (Merck, 60–120 mesh, ethyl acetate–hexane, 1:9) to afford pure products as a yellow solid. Spectroscopic data for selected compound: Compound (**4a**): Pale yellow solid, mp 145–147 °C, IR (KBr): *v* 3445, 3046, 2948, 2850, 1736, 1601, 1458, 1430, 1283, 1212, 1171, 1035, 922, 767, 714 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.66 (d, $J = 7.4$ Hz, 1H), 7.51 (d, $J = 7.4$ Hz, 1H), 7.32–7.03 (m, 8H), 6.60 (d, $J = 7.4$ Hz, 1H), 6.38 (d, $J = 3.3$ Hz, 1H), 6.07 (d, $J = 8.3$ Hz, 1H), 5.31 (s, 1H), 3.70 (s, 3H), 3.59 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 51.4, 53.3, 66.3, 95.4, 104.3, 107.5, 109.0, 120.1, 121.4, 122.6, 124.6, 125.3, 125.7, 126.0, 127.6, 128.0, 128.4, 129.2, 134.3, 149.3, 164.8, 166.4; LCMS: *m/z*: 411.1 (M^++Na), 387.1, 290.1, 245.1. HRMS (ESI) calcd for $C_{23}H_{20}N_2O_4$Na: 411.1320. Found: 411.1315. Compound (**4b**): Yellow solid, mp 167–169 °C, IR (KBr): *v* 3385, 2923, 2852, 1742, 1701, 1587, 1563, 1459, 1208, 1158, 743 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.74–7.70 (m, 1H), 7.30–6.89 (m, 13H), 6.41 (d, $J = 8.0$ Hz, 1H), 6.19 (s, 1H), 5.93 (d, $J = 8.0$ Hz, 1H), 5.23 (s, 1H), 5.19 (s, 2H), 3.86 (s, 3H), 3.59 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 50.0, 51.1, 53.1, 56.0, 90.8, 109.3, 110.0, 115.3, 119.5, 119.9, 122.0, 124.9, 125.4, 125.9, 126.1, 126.3, 126.4, 127.2, 127.5, 127.6, 128.6, 131.8, 136.5, 136.9, 150.2, 165.3, 167.3; LCMS: *m/z*: 501.2 (M^++Na), 477.2, 335.1; HRMS (ESI) calcd for $C_{30}H_{26}N_2O_4$Na: 501.1790. Found: 501.1785. Compound (**4d**): Orange solid, mp 182–184 °C, IR (KBr): *v* 3313, 2923, 2852, 1742, 1671, 1565, 1457, 1207, 1168, 904, 743, 697 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.06 (s, 1H), 7.75 (d, $J = 7.8$ Hz, 1H), 7.57–7.39 (m, 5H), 7.30–6.89 (m, 7H), 6.46 (s, 1H), 6.03 (d, $J = 7.8$ Hz, 1H), 5.58 (d, $J = 7.8$ Hz, 1H), 4.76 (s, 1H), 3.73 (s, 3H), 3.46 (s, 3H);^{13}C NMR (75 MHz, $CDCl_3$): δ 50.8, 52.9, 54.9, 91.6, 106.8, 110.9, 114.5, 120.1, 120.4, 122.5, 124.8, 126.5, 126.7, 127.0, 127.4, 128.8, 129.2, 132.2, 132.4, 135.1, 135.3, 149.8, 165.1, 167.3; LCMS: *m/z*: 487.1 (M^++Na), 463.1, 335.1, 279.1; HRMS (ESI) calcd for $C_{29}H_{23}N_2O_4$: 463.1657. Found: 463.1640.
18. Compound **6** (major): light yellow solid, mp 88–90 °C; IR (KBr): *v* 3319, 2924, 2854, 1681, 1606, 1568, 1457, 1425, 1264, 1162, 1109, 748 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.19 (br s, 1H), 7.62 (d, $J = 8.3$ Hz, 1H), 7.50 (d, $J = 13.5$ Hz, 1H), 7.25 (d, $J = 7.5$ Hz, 1H), 7.13–7.02 (m, 6H), 6.93 (br s, 1H), 6.45 (d, $J = 7.5$ Hz, 1H), 6.14 (d, $J = 1.5$ Hz, 1H), 5.90 (d, $J = 7.5$ Hz, 1H), 5.13 (d, $J = 13.5$ Hz, 1H), 3.62 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 50.8, 67.4, 90.4, 106.9, 111.4, 116.8, 119.2, 119.7, 121.9, 122.6, 124.6, 126.6, 126.8, 127.4, 129.2, 131.4, 136.3, 147.5, 169.5; LCMS: *m/z*: 353.1 (M^++Na), 329.1. HRMS (ESI) calcd for $C_{21}H_{18}N_2O_2$Na: 353.1265. Found: 353.1264. Compound **7** (minor): orange solid, mp 65–68 °C; IR (KBr): *v* 3415, 2924, 2854, 1696, 1618, 1570, 1456, 1268, 1163, 768, 746 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58 (d, $J = 8.3$ Hz, 1H), 7.53 (d, $J = 13.5$ Hz, 1H), 7.51 (br s, 1H), 7.27–7.15 (m, 2H), 7.15–7.05 (m, 5H), 6.96 (d, $J = 3.0$ Hz, 1H), 6.63 (d, $J = 7.5$ Hz, 1H), 6.38 (d, $J = 3.0$ Hz, 1H), 6.01 (d, $J = 7.5$ Hz, 1H), 5.15 (d, $J = 13.5$ Hz, 1H), 3.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 51.1, 67.2, 94.2, 103.7, 105.8, 109.2, 120.1, 121.3, 122.5, 125.2, 125.3, 126.6, 127.4, 127.6, 128.4, 128.6, 129.2, 134.6, 146.5, 168.0; LCMS: *m/z*: 353.1 (M^++Na), 329.1. HRMS (ESI) calcd for $C_{21}H_{18}N_2O_2$Na: 353.1265. Found: 353.1280. Compound **8** (major): dark yellow solid, mp 202–204 °C; IR (KBr): *v* 3216, 2923, 1638, 1581, 1532, 1455, 1383, 1346, 1267, 1208, 1110, 1045, 911, 769, 745, 701, 658, 569 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 10.79–10.65 (br s, 1H), 7.88–7.66 (m, 3H), 7.75 (d, $J = 13.2$ Hz, 1H), 7.49–7.21 (m, 4H), 7.19–6.92 (m, 6H), 6.79 (d, $J = 7.8$ Hz, 1H), 6.50 (br s, 1H), 6.42 (d, $J = 2.3$ Hz, 1H), 6.41 (d, $J = 13.2$ Hz, 1H), 6.01 (d, $J = 7.8$ Hz, 1H); ^{13}C NMR (75 MHz, DMSO): δ 96.7, 111.6, 115.5, 116.6, 118.9, 119.2, 121.1, 122.6, 123.0, 123.5, 124.5, 126.7, 126.8, 127.3, 127.4, 128.2, 131.6, 136.2, 139.0, 148.3, 186.8; LCMS: *m/z*: 377.1 (M^++H), 260.1, 245.1; HRMS (ESI) calcd for $C_{26}H_{20}N_2O$Na: 399.1473. Found: 399.1470.
19. For compound **9** (minor), see reference: Sheinkman, A. K.; Prilepskaya, A. N.; Ginzburg, A. O.; Tokarev, A. K.; Deikalo, A. A. *Khim. Geterotsiklich. Soedin.* **1971**, 421 [*Chem. Heterocycl. Compd.* (Engl. Transl.) **1971**, *7*, 389].