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Environmental Friendly Synthesis of Novel Isatin Ketal and Isatin Schiff Base Derivatives Using Michael Addition Reaction under Solvent-Free Conditions

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An efficient and simple procedure for the synthesis of novel isatin derivatives is described. Michael addition of aniline Schiff bases of isatin or *p*-toluidine Schiff bases of isatin to fumaric esters affords the Michael adduct compounds in good to high yields in the presence of K_2CO_3 and tetrabutylammonium bromide (TBAB) under solvent-free conditions. Repeating of this reaction about spiro[1,3-dioxolane-2,3'-indol]-2'(1'*H*)-one, as a Michael donor, in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) gives Michael adducts in remarkable yields under the same conditions.

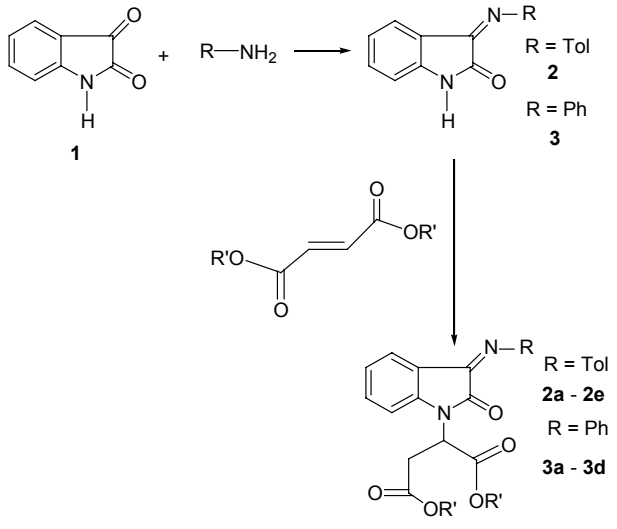
Keywords Michael addition, isatin ketal, isatin Schiff base, fumaric ester, acrylic ester, solvent-free conditions

Introduction

Isatin **1** (1*H*-indol-2,3-diones) is a versatile molecule in the synthesis of many products with pharmacologic activity.[1] In 1841, this compound was obtained by oxidation of Indigo with nitric and chromic acid.[2] In nature, isatin has been identified in blood and urine of mammalian,[3] in rat brain,[4] in plants of genus Isatis[5] and in coal tar.[6] Studies show that isatin readily crosses the blood-brain barrier and acts on the central nervous system (CNS).[7] This compound has been identified as a selective inhibitor of monoamine oxidas B (MAOB)[8] and therefore it has been suggested to be an alternative for the treatment of Parkinson's disease, by increasing dopamine levels in the striatum.[9,10] Numerous investigations show isatin has anxiogenic effects.[11-16] Schiff bases and Mannich bases of isatin are reported to show a variety of biological activities like antibacterial,[17-19] antifungal,[20-22] antiviral,[23-25] anti-HIV,[26-28] antiprotozoal[29,30] and antihelimithic properties.[31,32] Some of Schiff bases of isatin show that they have a potent anticancer activity against human cancer.[33] Isatin ketals have anxiolytic,[34] psychotropic,[35] and anticonvulsant activity.[36] For instance spiro[1,3-dioxolane-2,3'-indol]-2'(1'*H*)-one **4** (as a dioxolane ketal) has sedative, hypnotic and anesthetic properties.[37]

Aza-Micheal addition reaction is one of the most famous methods for forming a carbon-nitrogen bond in organic synthesis.[38] Different Michael donors such as amines,[39] amides,[40] and imides[41] have been used in this reaction. However, to the best of our knowledge, no datum is available on the addition of the Schiff base of isatin **2** or **3** and dioxolane ketal **4** to *α*,*β*-unsaturated esters. Having the above points in mind and also in continuing our previous studies on aza-Michael reaction,[42,43] this work investigates the aza-Michael addition reaction of isatin Schiff bases **2**, **3** and isatin ketal **4** with *α*,*β*-unsaturated esters under solvent-free conditions (Schemes 1 and 2).

Scheme 1 Addition of isatin Schiff bases to *α*,*β*-unsaturated esters



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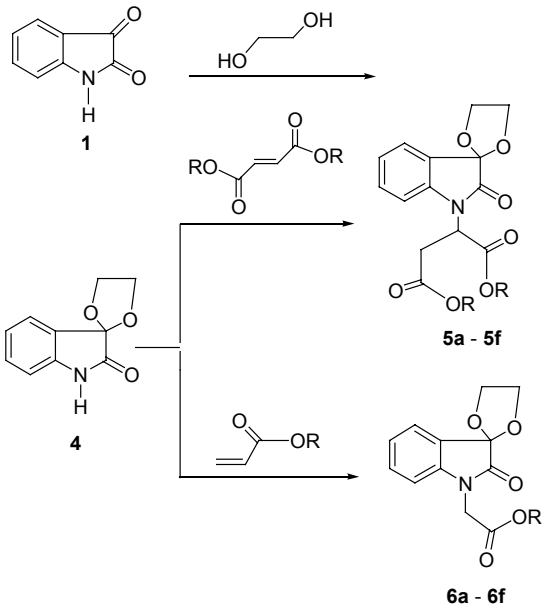
Scheme 2 Addition of isatin ketal to α,β-unsaturated esters



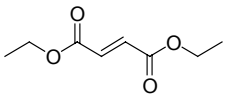
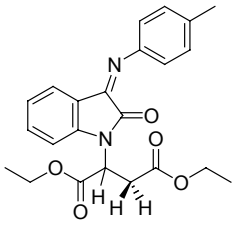
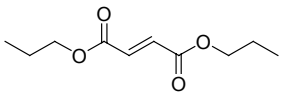
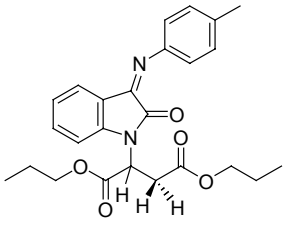
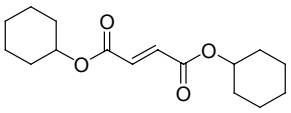
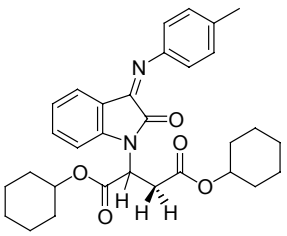
Experimental

Spiro[1,3-dioxolane-2,3'-indol]-2'(1'*H*)-one **4**, and all α,β-unsaturated esters were synthesized in our laboratory according to the literature procedures[37,45] and their structures were confirmed by IR and ^{1}H NMR spectroscopy. The progress of the reactions was followed by TLC using silica gel SILIG/UV 254 plates. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker 300 MHz instrument. FT-IR spectra were recorded on a Perkin-Elmer RX-1 instrument. Mass spectra were recorded on a Shimadzu GC-MS-QP 1000PX. Elemental analysis for C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer. The melting points were determined in open capillaries with a Stuart Melting Point Apparatus and are uncorrected.

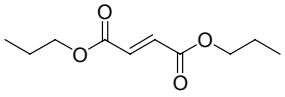
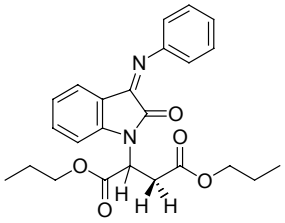
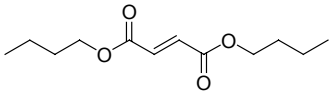
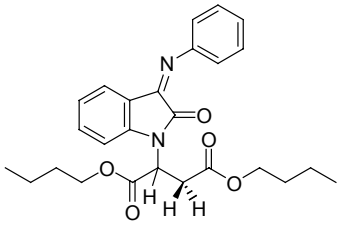
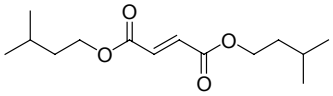
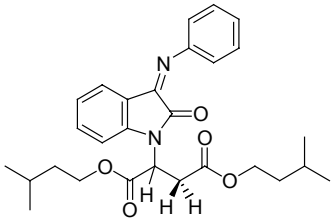
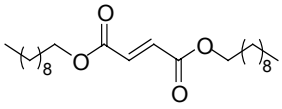
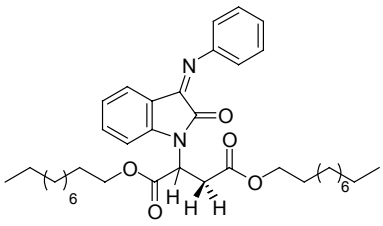
General procedure for addition of isatin Schiff bases 2 or 3 to symmetrical fumaric esters

To a well ground mixture of isatin Schiff base (1.0 mmol), K_2CO_3 (1.0 mmol), and TBAB (0.5 mmol), fumaric ester (1.2 mmol) was added and mixed thoroughly with a glass rod. The resulting mixture was kept in an oil bath at 90—100 ℃ for appropriate time (Table 1). The progress of reaction was monitored by TLC. After the completion of reaction the mixture was suspended in chloroform (30 mL), filtered and the filtrate was washed with water (10 mL×3) and dried with $MgSO_4$. The solvent was removed under reduced pressure and the resulting crude material was purified on short silica-gel column with ethyl acetate∶*n*-hexane (1∶9) as the eluent.

Table 1 Michael addition of isatin Schiff bases **2**, **3** to fumaric esters in the presence of K_2CO_3

Entry	Ester	Product	Time/min	Yield[a]/%
1		 **2a**	40	85
2		 **2b**	60	85
4		 **2d**	300	75

Continued

Entry	Ester	Product	Time/min	Yield[a]/%
5		 **3a**	60	85
6		 **3b**	120	80
7		 **3c**	100	80
8		 **3d**	150	80

[a] Isolated yields.

General procedure for addition isatin ketal 4 to symmetrical fumaric ester and acrylic esters

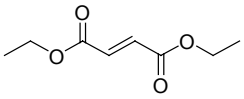
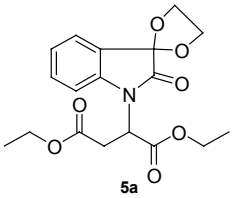
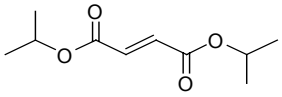
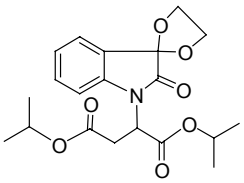
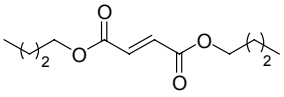
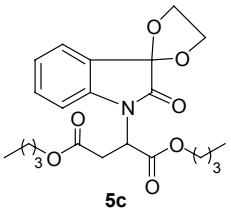
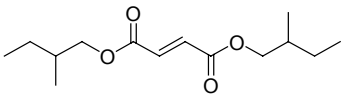
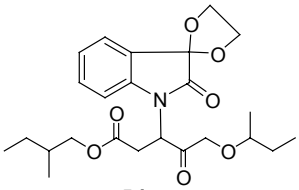
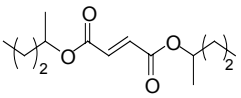
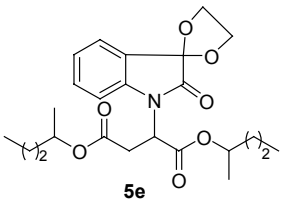
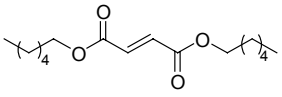
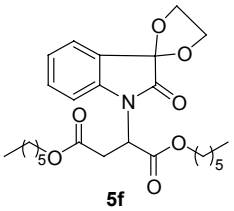
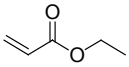
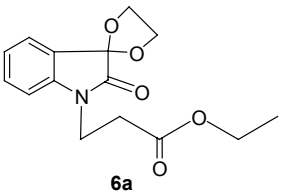
A mixture of isatin ketal **4** (1.0 mmol), DABCO (1.0 mmol), TBAB (0.5 mmol), fumaric esters or acrylic ester (1.2 mmol) was kept in the oil bath for the stipulated time (Table 2) at 80—90 ℃. The progress of the reaction was monitored by TLC. After completion of reaction the reaction mixture was cooled to room temperature and dissolved in chloroform (40 mL). TBAB was recovered by the addition of water (15 mL), then collected and dried under vacuum. The chloroform layer was washed with water (15 mL×3). The organic layer was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the resulting crude material was purified on short silica-gel column with ethyl acetate∶*n*-hexane (2∶8) as the eluent.

Physical and spectroscopic data of isolated products

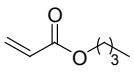
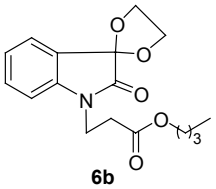
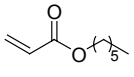
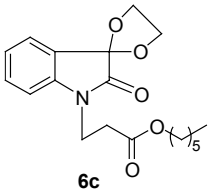
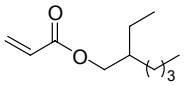
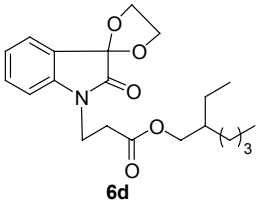
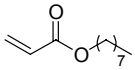
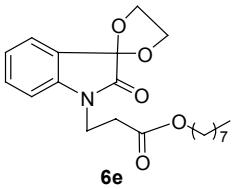
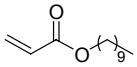
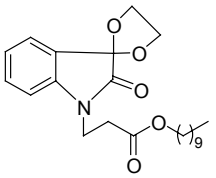
Diethyl 2-(3-(*p*-tolylimino)-2-oxoindolin-1-yl)-succinate (2a) Orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.20—1.26 (m, 6H), 2.39 (s, 3H), 3.20 (dd, J=16.9, 8.0 Hz, 1H), 3.43 (dd, J=16.9, 6.3 Hz, 1H), 4.13—4.25 (m, 4H), 5.41 (dd, J=8.0, 6.3 Hz, 1H), 6.99—7.42 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 12.92, 32.69, 49.62, 60.13, 61.36, 108.92, 114.83, 116.53, 122.21, 124.27, 125.25, 128.30, 132.96, 148.9, 152.27, 161.81, 167.11, 169.08; IR (KBr) v: 2982, 2935, 1735, 1652, 1606, 1466, 1367, 1260, 1096, 1025, 858, 752, 697 cm^{-1}; MS (70 eV) *m/z* (%): 408 (M^+, 32.28). Anal. calcld for $C_{23}H_{24}N_2O_5$: C 67.64, H 5.88, N 6.86; found C 67.48, H 5.90, N 6.64.

Dipropyl 2-(3-(*p*-tolylimino)-2-oxoindolin-1-yl)-succinate (2b) Orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.82—0.93 (m, 6H), 1.58—1.64 (m, 4H),

Table 2 Michael addition of isatin ketal **4** to α,β-unsaturated esters in the presence of DABCO[a]

Entry	Ester	Product	Time/min	Yield[b]/%
1		 **5a**	180	85
2		 **5b**	180	83
3		 **5c**	180	78
4		 **5d**	240	75
5		 **5e**	240	73
6		 **5f**	240	70
7		 **6a**	60	90

Continued

Entry	Ester	Product	Time/min	Yield[b]/%
8		 **6b**	60	89
9		 **6c**	60	89
10		 **6d**	60	87
11		 **6e**	60	88
12		 **6f**	60	87

[a] Ethyl fumarate or acrylic ester, isatin ketal **4**, DABCO and TBAB with molar ratios 1.2∶1.0∶1.0∶0.5 were used respectively. [b] After purification by column chromatography.

2.39 (s, 3H), 3.13 (dd, J=16.8, 7.9 Hz, 1H), 3.45 (dd, J=16.8, 6.4 Hz, 1H), 4.09—4.15 (m, 4H), 5.43 (dd, J=7.9, 6.4 Hz, 1H), 6.80—7.34 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.13, 19.88, 20.66, 32.65, 49.59, 65.66, 108.80, 114.88, 116.74, 121.88, 125.05, 128.79, 132.78, 134.08, 146.31, 151.96, 161.89, 167.19, 169.15; IR (KBr) v: 2969.47, 2939.72, 1739.03, 1654.34, 1606.59, 1468.44, 1364.24, 1269.94, 1179.27, 751.5, 576.08 cm^{-1}; MS (70 eV) m/z (%): 436 (M^+, 18.68). Anal. calcld for $C_{25}H_{28}N_2O_5$: C 68.80, H 6.42, N 6.42; found C 68.62, H 6.55, N 6.81.

Dippentan-2-yl 2-(3-(*p*-tolylimino)-2-oxoindolin-1-yl)succinate (2c) Orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.68—0.80 (m, 6H), 1.05—1.26 (m, 14H), 2.28 (s, 3H), 2.91—3.01 (m, 1H), 3.28—3.32 (m, 1H), 4.85—4.91 (m, 2H), 5.28—5.37 (m, 1H), 6.65—6.83 (m, 5H), 7.10—7.25 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.72, 17.54, 22.45, 21.80, 37.61, 38.10, 39.77, 49.59, 65.66, 108.00, 114.71, 116.43, 121.54, 125.10, 129.02, 132.71, 133.97, 145.33, 151.96, 162.01, 167.41, 169.18; IR (KBr) v: 2961, 2936, 1736, 1654, 1606, 1468, 1364, 1239, 1119, 1057, 750, 653 cm^{-1}; MS (70 eV) m/z (%): 492 (M^+, 21.50). Anal. calcld for $C_{29}H_{36}N_2O_5$: C 70.73, H 7.31, N 5.69; found C 70.55, H 7.38, N 5.82.

Dicyclohexyl 2-(3-(*p*-tolylimino)-2-oxoindolin-1-yl)succinate (2d) Orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.25—1.38 (m, 12H), 1.49—1.75 (m, 8H), 2.39 (s, 3H), 3.06 (dd, J=16.7, 8.1 Hz, 1H), 3.38 (dd, J=16.7, 6.3 Hz, 1H), 4.73—4.76 (m, 2H), 5.43 (dd, J=8.1, 6.3 Hz, 1H), 6.81—7.35 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.97, 22.63, 24.19, 30.37, 33.11, 49.94, 72.69, 109.06, 114.17, 116.86, 121.62, 125.09, 128.86, 132.75, 134.12, 146.43, 152.11, 161.99, 166.62, 168.55; IR (KBr) v: 2937, 2860, 1733, 1651, 1608, 1517, 1468, 1361, 1259, 1188, 1013, 958, 751, 643 cm^{-1}; MS (70 eV) m/z (%): 516 (M^+, 32.63). Anal. calcld for $C_{31}H_{36}N_2O_5$: C 72.09, H 6.97, N 5.42; found C 72.13, H 6.71, N 5.63.

Dipropyl 2-(3-(phenylimino)-2-oxoindolin-1-

yl)succinate (3a) Orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.83—0.95 (m, 6H), 1.58—1.67 (m, 4H), 3.12 (dd, J=16.8, 8.9 Hz, 1H), 3.45 (dd, J=16.8, 6.3 Hz, 1H), 4.05—416 (m, 4H), 5.43 (dd, J=8.9, 6.3 Hz, 1H), 6.76—7.45 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.24, 20.77, 32.76, 49.73, 65.69, 108.95, 114.9, 116.58, 121.81, 124.31, 125.33, 128.38, 133.02, 149.19, 152.33, 161.91, 167.27, 169.28; IR (KBr) v: 2965, 2875, 1736, 1656, 1612, 1468, 1364, 1269, 1180, 1120, 1067, 1022, 752, 697 cm^{-1}; MS (70 eV) *m/z* (%): 422 (M^+, 44.53). Anal. calcld for $C_{24}H_{26}N_2O_5$: C 68.24, H 6.16, N 6.63; found C 68.33, H 6.28, N 6.81.

Dibutyl 2-(3-(phenylimino)-2-oxoindolin-1-yl)-succinate (3b) Orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.84 (t, J=7.8 Hz, 3H), 0.91 (t, J=7.5 Hz, 3H), 1.18—1.24 (m, 2H), 1.26—1.39 (m, 2H), 1.45—1.55 (m, 2H), 1.57—1.66 (m, 2H), 2.92 (dd, J=16.5, 7.5 Hz, 1H), 3.38 (dd, J=16.5, 7.0 Hz, 1H), 4.09—4.16 (m, 4H), 5.27 (dd, J=7.5, 7.0 Hz, 1H), 6.80—7.43 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 12.25, 17.62, 28.93, 32.39, 49.44, 63.65, 108.71, 114.51, 116.19, 121.46, 123.98, 124.91, 128.05, 132.78, 148.82, 152.05, 161.55, 166.87, 168.86; IR (KBr) v: 2961, 2875, 1736, 1656, 1609, 1468, 1364, 1276, 1180, 1116, 1067, 1022, 752, 697 cm^{-1}; MS (70 eV) *m/z* (%): 450 (M^+, 67.14). Anal. calcld for $C_{26}H_{30}N_2O_5$: C 69.33, H 6.66, N 6.22; found C 69.65, H 6.40, N 6.14.

Diisopentyl 2-(3-(phenylimino)-2-oxoindolin-1-yl)succinate (3c) Orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.80—0.90 (m, 12H), 1.47—1.53 (m, 6H), 3.11 (dd, J=16.8, 7.9 Hz, 1H), 3.43 (dd, J=16.8, 6.3 Hz, 1H), 4.08—4.22 (m, 4H), 5.42 (dd, J=7.9, 6.3 Hz, 1H), 6.76—7.42 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.17, 23.72, 32.59, 35.85, 49.58, 62.71, 108.80, 114.71, 116.37, 121.66, 124.16, 125.14, 128.23, 132.90, 148.97, 152.18, 161.72, 161.81, 167.07, 169.08; IR (KBr) v: 2959, 2872, 1740, 1654, 1607, 1468, 1367, 1183, 949, 750, 695 cm^{-1}; MS (70 eV) *m/z* (%): 478 (M^+, 51.27). Anal. calcld for $C_{28}H_{34}N_2O_5$: C 70.29, H 7.11, N 5.85; found C 70.20, H 7.42, N 5.39.

Didecyl 2-(3-(phenylimino)-2-oxoindolin-1-yl)-succinate (3d) Orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.85—0.88 (m, 6H), 1.20—1.26 (m, 28H), 1.57—1.60 (m, 4H), 3.11 (dd, J=16.8, 7.9 Hz, 1H), 3.44 (dd, J=16.8, 6.2 Hz, 1H), 4.07—4.17 (m, 4H), 5.35 (dd, J=7.9, 6.2 Hz, 1H), 6.76—7.45 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 12.95, 21.51, 24.65, 28.06, 28.12, 28.32, 30.71, 32.63, 49.61, 64.28, 108.86, 114.78, 116.48, 121.68, 124.21, 125.21, 128.25, 132.90, 149.02, 152.22, 161.77, 167.15, 169.13; IR (KBr) v: 2926, 2855, 1740, 1653, 1607, 1468, 1362, 1230, 1178, 981, 749, 653 cm^{-1}; MS (70 eV) *m/z* (%): 618 (M^+, 32.63). Anal. calcld for $C_{38}H_{54}N_2O_5$: C 73.79, H 8.74, N 4.53; found C 73.68, H 8.79, N 4.49.

Diethyl 2-(spiro(1,3-dioxolane-2,3'-indolin-2'-one-1'-yl))succinate (5a) Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.18 (t, J=7.1 Hz, 3H), 1.22 (t, J=7.5 Hz, 3H), 2.85 (dd, J=17.0, 7.3 Hz,1H), 3.35 (dd, J=17.0, 7.5 Hz, 1H), 4.14—4.27 (m, 4H), 4.30—4.34 (m, 2H), 4.53—4.59 (m, 2H), 5.26 (dd, J=7.5, 7.3 Hz, 1H), 6.87 (d, J=8.0 Hz, 1H), 7.10 (t, J=7.5 Hz, 1H), 7.34—7.40 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.94, 13.96, 33.70, 50.13, 61.14, 62.20, 65.69, 65.80, 101.54, 109.34, 123.49, 123.83, 125.12, 131.60, 142.81, 168.41, 170.12, 172.99; IR (KBr) v: 2936, 2912, 1732, 1620, 1468, 1420, 1369, 1277, 1187 cm^{-1}; MS (70 eV) *m/z* (%): 363 (M^+, 28.63). Anal. calcld for $C_{18}H_{21}NO_7$: C 59.50, H 5.78, N 3.85; found C 59.53, H 5.41, N 3.91.

Diisopropyl 2-(spiro(1,3-dioxolane-2,3'-indolin-2'-one-1'-yl))succinate (5b) Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.12 (d, J=6.5 Hz, 3H), 1.18 (d, J=6.5 Hz, 3H), 1.22 (d, J=6.5 Hz, 6H), 2.88 (dd, J=17.25, 7.5 Hz, 1H), 3.32 (dd, J=17.25, 7.0 Hz, 1H), 4.31—4.35 (m, 2H), 4.57—4.59 (m, 2H), 5.98—5.10 (m, 2H), 5.23 (t, J=7 Hz, 1H), 6.87 (d, J=8.1 Hz, 1H), 7.10 (t, J=7.40 Hz, 1H), 7.34—7.40 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.42, 21.60, 34.12, 50.40, 65.66, 65.82, 101.23, 109.43, 123.42, 123.88, 125.09, 131.53, 142.98, 167.93, 169.66, 172.99; IR (KBr) v: 2983, 2905, 1735, 1620, 1490, 1470, 1376, 1286, 1188 cm^{-1}; MS (70 eV) *m/z* (%): 391 (M^+, 77.64). Anal. calcld for $C_{20}H_{25}NO_7$: C 61.38, H 6.39, N 3.58; found C 61.41, H 6.22, N 3.79.

Dibutyl 2-(spiro(1,3-dioxolane-2,3'-indolin-2'-one-1'-yl))succinate (5c) Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.83 (t, J=7.5 Hz, 3H), 0.91 (t, J=7.5 Hz, 3H), 1.20—1.37 (m, 4H), 1.50—1.60 (m, 4H), 2.92 (dd, J=7.5, 16.5 Hz, 1H), 3.38 (dd, J=7.2, 16.5 Hz, 1H), 4.07—4.14 (m, 2H), 4.17—4.23 (m, 2H), 4.30—4.34 (m, 2H), 4.54—4.60 (m, 2H), 5.27 (dd, J=7.2, 7.5 Hz, 1H), 6.87 (d, J=8.0 Hz, 1H), 7.10 (t, J=7.5 Hz, 1H), 7.35—7.41 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.33, 13.48, 18.63, 18.85, 30.16, 30.31, 33.60, 50.04, 64.89, 65.56, 65.66, 65.83, 101.45, 109.17, 123.33, 123.80, 125.02, 131.45, 142.77, 168.38, 170.07, 172.90; IR (KBr) v: 2964, 2876, 1738, 1620, 1489, 1470, 1366, 1262, 1187 cm^{-1}; MS (70 eV) *m/z* (%): 419 (M^+, 57.89). Anal. calcld for $C_{22}H_{29}NO_7$: C 63.00, H 6.92, N 3.34; found C 63.19, H 7.15, N 3.54.

Bis(2-methylbutyl) 2-(spiro(1,3-dioxolane-2,3'-indolin-2'-one-1'-yl))succinate (5d) Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.77—0.82 (m, 6H), 0.88—0.91 (m, 6H), 1.00—1.20 (m, 2H), 1.36—1.42 (m, 2H), 1.59—1.63 (m, 1H), 1.64—1.69 (m, 1H), 2.93 (dd, J=17.0, 8.0 Hz, 1H), 3.41 (dd, J=17.0, 7.0 Hz, 1H), 3.87—3.93 (m, 2H), 3.95—4.05 (m, 2H), 4.30—4.36 (m, 2H), 4.54—4.60 (m, 2H), 5.29—5.31 (m, 2H), 6.86 (d, J=7.1 Hz, 1H), 7.10 (t, J=7.5 Hz, 1H), 7.35—7.41 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 10.92, 11.11, 16.11, 16.23, 25.70, 25.90, 33.72, 33.81, 33.88, 50.12, 65.69, 65.77, 69.82, 70.66, 101.59, 109.24, 123.48, 123.90, 125.17, 131.59, 142.91, 168.59, 170.28, 173.05; IR (KBr) v: 2965, 2879, 1736, 1620, 1490, 1469, 1366, 1229,1187 cm^{-1}; MS (70 eV) *m/z* (%): 447 (M^+, 27.14). Anal. calcld for $C_{24}H_{33}NO_7$: C 64.42, H 7.38, N 3.13; found C 64.72, H 7.43, N 3.18.

Di-*sec*-butyl 2-(spiro(1,3-dioxolane-2,3'-indolin-2'-one-1'-yl))succinate (5e) Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.75 (t, J=7.5 Hz, 3H), 0.85 (t, J=7.5 Hz, 3H), 0.92 (m, 4H), 1.08 (d, J=6.5 Hz, 3H), 1.13 (d, J=6.4 Hz, 3H), 1.20—1.26 (m, 4H), 2.86—2.94 (m, 1H), 3.30—3.37 (m, 1H), 4.32—4.38 (m, 2H), 4.53—4.61 (m, 2H), 4.90—4.95 (m, 2H), 5.25—5.29 (m, 1H), 6.86 (d, J=8.0 Hz, 1H), 7.10 (t, J=7.4 Hz, 1H), 7.34—7.40 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.79, 13.86, 18.00, 18.43, 19.48, 19.73, 37.70, 37.83, 37.89, 50.37, 65.66, 65.79, 71.90, 73.27, 101.13, 109.41, 123.41, 123.88, 125.10, 131.52, 142.97, 168.06, 169.79, 172.94; IR (KBr) v: 2962, 2875, 1737, 1621, 1490, 1470, 1387, 1287, 1189 cm^{-1}; MS (70 eV) m/z (%): 447 (M^+, 2.18). Anal. calcld for $C_{24}H_{33}NO_7$: C 64.42, H 7.38, N 3.13; found C 64.39, H 7.72, N 3.51.

Bis(2-methylbutyl) 2-(spiro(1,3-dioxolane-2,3'-indolin-2'-one-1'-yl))succinate (5f) Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.90—1.00 (m, 12H), 1.28—1.70 (m, 12H), 2.68 (dd, J=16.5, 7.5 Hz, 1H), 3.37 (dd, J=16.5, 7.1 Hz, 1H), 4.08—4.15 (m, 4H), 4.30—4.40 (m, 2H), 4.50—4.57 (m, 2H), 5.27 (m, 1H), 6.86 (d, J=7.8 Hz, 1H), 7.09 (t, J=7.5 Hz, 1H), 7.34—7.40 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.43, 13.58, 22.33, 22.44, 25.39, 25.47, 30.41, 30.47, 31.20, 31.32, 33.70, 50.12, 65.34, 65.45, 65.76, 65.96, 101.22, 109.28, 123.44, 123.87, 125.13, 131.55, 142,85, 168.51, 170.21, 173.01; IR (KBr) v: 2962, 2875, 1734, 1621, 1490, 1470, 1369, 1296,1156 cm^{-1}; MS (70 eV) m/z (%): 475 (M^+, 3.75). Anal. calcld for $C_{26}H_{37}NO_7$: C 65.68, H 7.78, N 2.94; found C 65.29, H 7.55, N 2.48.

Ethyl 3-(spiro(1,3-dioxolane-2,3'-indolin-2'-one-1'-yl))propionate (6a) Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.02 (t, J=7.5 Hz, 3H), 2.68 (t, J=7.0 Hz, 2H), 3.93 (t, J=7.0 Hz, 2H), 4.13 (q, J=7.5 Hz, 2H), 4.32—4.38 (m, 2H), 4.53—4.59 (m, 2H), 6.90 (d, J=8.0 Hz, 1H), 7.10 (t, J=7.5 Hz, 1H), 7.36—7.39 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.38, 35.27, 58.62, 60.59, 65.47, 101.58, 108.58, 123.00, 123.65, 124.63, 131.37, 143.16, 170.66, 172.90; IR (KBr) v: 2979, 2904, 1733, 1619, 1491, 1470, 1369, 1292, 1195 cm^{-1}; MS (70 eV) m/z (%): 291 (M^+, 4.37). Anal. calcld for $C_{15}H_{17}NO_5$: C 61.85, H 5.84, N 4.81; found C 61.91, H 5.46, N 4.63.

Butyl 3-(spiro(1,3-dioxolane-2,3'-indolin-2'-one-1'-yl))propionate (6b) Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.9 (t, J=7.5 Hz, 3H), 1.26—1.36 (m, 2H), 1.57—1.69 (m, 2H), 2.70 (t, J=7 Hz, 2H), 3.92 (t, J=7.5 Hz, 2H), 4.07 (t, J=6.5 Hz, 2H), 4.32—4.38 (m, 2H), 4.53—4.59 (m, 2H), 6.90 (d, J=8.0 Hz, 1H), 7.09 (t, J=7.5 Hz, 1H), 7.37—7.39 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.63, 19.01, 32.10, 35.61, 59.13, 64.83, 65.76, 76.75, 101.90, 108.87, 123.29, 123.94, 124.95, 131.66, 143.53, 171.13, 173.24; IR (KBr) v: 2962, 2875, 1733, 1620, 1491, 1469, 1366, 1291, 1193 cm^{-1}; MS (70 eV) m/z (%): 319 (M^+, 37.19). Anal. calcld for $C_{17}H_{21}NO_5$: C 63.94, H 6.58, N 4.38; found C 64.11, H 6.87, N 4.52.

Hexyl 3-(spiro(1,3-dioxolane-2,3'-indolin-2'-one-1'-yl))propionate (6c) Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.88 (t, J=6.5 Hz, 3H), 1.00—1.38 (m, 4H), 1.47—1.50 (m, 2H), 1.57—1.59 (m, 2H), 2.68 (t, J=7.5 Hz, 2H), 3.97 (t, J=7.5 Hz, 2H), 4.05 (t, J=6.5 Hz, 2H), 4.32—4.38 (m, 2H), 4.53—4.59 (m, 2H), 6.90 (d, J=8.0 Hz, 1H), 7.08 (t, J=7.5 Hz, 1H), 7.36—4.39 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.19, 23.33, 24.66, 30.55, 31.33, 34.85, 51.61, 64.29, 65.02, 101.12, 108.15, 123.26, 124.16, 127.55, 130.91, 142.67, 170.24, 172.43; IR (KBr) v: 2958, 2860, 1733, 1620, 1492, 1470, 1293, 1192, 1132 cm^{-1}; MS (70 eV) m/z (%): 347 (M^+, 36.06). Anal. calcld for $C_{19}H_{25}NO_5$: C 65.70, H 7.20, N 4.03; found C 65.49, H 7.32, N 3.89.

2-Ethylhexy-3-(spiro(1,3-dioxolane-2,3'-indolin-2'-one-1'-yl))propionate (6d) Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.85—0.89 (m, 4H), 1.03 (t, J=7.5 Hz, 3H), 1.24 (t, J=7.5 Hz, 3H), 1.46—1.49 (m, 2H), 1.50—1.59 (m, 1H), 1.69—1.71 (m, 2H), 2.70 (t, J=7.5 Hz, 2H), 3.93 (t, J=7.5 Hz, 2H), 4.01 (t, J=7.5 Hz, 2H), 4.32—4.38 (m, 2H), 4.53—4.59 (m, 2H), 6.90 (d, J=7.5 Hz, 1H), 7.09 (t, J=7.5 Hz, 1H), 7.37—7.39 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 10.86, 13.98, 22.85, 24.17, 30.22, 32.06, 35.55, 38.52, 59.04, 65.73, 66.89, 67.37, 101.98, 108.82, 123.28, 123.93, 124.94, 131.64, 143.47, 171.20, 173.23; IR (KBr) v: 2961, 2875, 1732, 1621, 1492, 1469, 1365, 1293, 1193 cm^{-1}; MS (70 eV) m/z (%): 375 (M^+, 32.59). Anal. calcld for $C_{21}H_{29}NO_5$: C 67.20, H 7.73, N 3.73; found C 67.77, H 7.29, N 3.32.

Octyl 3-(spiro(1,3-dioxolane-2,3'-indolin-2'-one-1'-yl))propionate (6e) Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.90 (t, J=7.5 Hz, 3H), 1.25—1.29 (m, 12H), 2.69 (t, J=7.5 Hz, 2H), 3.93 (t, J=7.5 Hz, 2H), 4.07 (t, J=7.5 Hz, 2H), 4.32—4.38 (m, 2H), 4.53—4.59 (m, 2H), 6.90 (d, J=7.5 Hz, 1H), 7.09 (t, J=7.5 Hz, 1H), 7.37—7.39 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.06, 22.60, 25.80, 28.43, 29.10, 29.15, 31.74, 35.65, 65.15, 65.77, 76.73, 101.93, 108.88, 123.28, 124.02, 124.98, 131.65, 143.59, 171.12, 173.27; IR (KBr) v: 2929, 2857, 1734, 1621, 1492, 1469, 1366, 1293, 1193 cm^{-1}; MS (70 eV) m/z (%): 375 (M^+, 62.29). Anal. calcld for $C_{21}H_{29}NO_5$: C 67.20, H 7.73, N 3.73; found C 67.85, H 7.28, N 3.91.

Decyl 3-(spiro(1,3-dioxolane-2,3'-indolin-2'-one-1'-yl))propionate (6f) Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.89 (t, J=7.5 Hz, 3H), 1.27 (m, 14H), 1.55—1.59 (m, 2H), 2.69 (t, J=7.3 Hz, 2H), 3.92 (t, J=7.3 Hz, 2H), 4.06 (t, J=7.5 Hz, 2H), 4.32—4.38 (m, 2H), 4.53—4.59 (m, 2H), 6.90 (d, J=8.0 Hz, 1H), 7.09 (t, J=7.5 Hz, 1H), 7.37—7.39 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.06, 22.63, 25.88, 28.58, 29.18, 29.25, 29.44, 29.47, 31.84, 35.63, 62.98, 64.68, 65.14, 65.76, 101.92, 108.86, 123.27, 124.00, 124.96, 131.63, 143.57, 171.11, 173.25; IR (KBr) v: 2927, 2856, 1734, 1621, 1492, 1469, 1366, 1262, 1192 cm^{-1}; MS (70 eV) m/z (%): 403 (M^+, 82.00). Anal. calcld for $C_{23}H_{33}NO_5$:

C 68.48, H 8.18, N 3.47; found C 68.52, H 8.43, N 3.21.

Results and Discussion

As a first step, we decided to extend our previous work[44] concerning the synthesis of novel derivatives of isatin Schiff bases by applying the solvent-free system conditions. Therefore, aza-Michael addition of *p*-toluidine Schiff base of isatin **2** to ethyl fumarate, as a model reaction, was investigated in the presence of tetrabutylammonium bromide TBAB and various organic and inorganic bases to evaluate their capabilities and selectivities. This study showed that the best results were obtained when K_2CO_3 was applied as a base at 100 ℃ under solvent-free conditions. In the absence of TBAB, in the reaction media, no progressing was observed for model reaction at all. It was also observed that using ethyl fumarate, *p*-toluidine Schiff base of isatin, K_2CO_3 and TBAB with molar ratios 1.2∶1.0∶1.0∶0.5, respectively, gives the desired product in high yield and in short reaction time. We varied the amount of K_2CO_3 and TBAB loading in the reaction and there was no improvement in yield with the decrease or increase of loading. Using this method, *p*-toluidine Schiff base of isatin **2** was added to four different fumaric esters (Table 1, Entries 1—4), and aniline Schiff base of isatin **3** was also added to four different fumaric esters under model reaction conditions (Table 1, Entries 5—8). According to these results the method is applicable to primary fumaric esters (Table 1, Entries 1, 2, 5, 6, 8) as well as to secondary fumaric esters (Table 1, Entries 3, 4, 7). All reactions were very clean and the products were obtained in very good to excellent yields within 40 to 300 min. It is important to note that, when the fumaric esters containing sterically hindered alkoxy groups were used, the reaction proceeded slowly (Table 1, Entries 8, 9). Since a large variety of primary amines can be coupled to isatin, this method is suitable for various scaffolds.

In another study, we extended this reaction to spiro[1,3-dioxolane-2,3'-indol]-2'(1'*H*)-one **4** as Michael donor. But when **4** was treated with ethyl fumarate, in the presence of potassium carbonate and TBAB, we faced the problem of getting product in low yield. Therefore we decided to try the reaction in the presence of various organic and inorganic bases as well as in the presence of various solvents. The obtained results from this test indicated that DABCO is the reasonable base for catalysis of the reaction in the presence of TBAB under solvent-free conditions at 100 ℃. Using solvents such as DMSO, DMF, EtOH and H_2O, in the reflux conditions, the product was isolated in very low yields. Therefore, the solvent-free reaction in the presence of TBAB is more efficient.

Having this model reaction in hand, we examined the reaction of **4** with different types of α,β-unsaturated esters, and the results are summarized in Table 2. These results were quite surprising, since the best results were achieved by carrying out the reaction with acrylic esters, despite containing only one carbonyl electron-withdrawing group, as Michael acceptor. The results allow the conclusion that the steric effects of substitutes on β-carbon atom are more important than their electronic effects. These effects caused that fumaric esters were more sensitive to the size of alkoxy groups than acrylic esters. We see that the bulkiness of alkoxy group, when the Michael acceptors are acrylic esters, has no significant effect on the yields and the reaction times (Table 2, Entries 7—12). But, in contrast to these results, when fumaric esters are used as Michael acceptor, the sterical hindrance of alkoxy groups influence the yields and reaction times under the same conditions (Table 2, Entries 1—6).

Conclusions

In summary, we developed a new, effective and environment friendly procedure for the Michael addition of aniline Schiff bases of isatin, *p*-toluidine Schiff bases of isatin, as well as spiro[1,3-dioxolane-2,3'-indol]-2'(1'*H*)-one to α,β-unsaturated esters in the presence of TBAB under solvent-free conditions. It was found that among the various organic and inorganic bases, K_2CO_3 is a more suitable base for former reactions, while DBCO effectively catalyzes the latter reaction. We, also, observed that in both reactions, when Michael acceptor is fumaric ester, the structure of alkoxy group has significant effect on the yield and reaction time. Lower yields of products and longer reaction times were obtained when sterically hindered fumaric esters were used as α,β-unsaturated systems.

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