DOI: 10.1002/cjoc.201300094

Diastereoselective Synthesis of Arylidene Bis(3-arylamino-acrylates) *via* One-pot Domino Reactions

Zhenming Liu,[a] Lili Zhang,[b] Jing Sun,[b] and Chaoguo Yan*,[b]

[a] *Analysis and Test Center, Yangzhou University, Yangzhou, Jiangsu 225002, China*
[b] *College of Chemistry & Chemical Engineering, Yangzhou University, Yangzhou, Jiangsu 225002, China*

The functionalized arylidene bis(3-arylaminoacrylates) were efficiently prepared by $FeCl_3$ catalyzed one-pot domino reactions of primary amines, methyl propiolate and aromatic aldehydes. When isatins were utilized under similar conditions, only 2-oxoindolinyl 3-arylaminoacrylates were obtained in moderate yields. ^1H NMR data and single crystal structures indicated that this reaction has high diastereoselectivity.

Keywords domino reaction, electron-deficient alkyne, acrylate, isatin, stereoselectivity

Introduction

During these years the versatile reactivity of Huisgen's 1,4-dipoles, which were easily generated from the addition reaction of nitrogen-containing aromatic heterocycles to electron-deficient alkynes have been widely recognized as practical synthons to develop versatile carbon-carbon bond formation reactions and heterocyclic constructions.[1-3] On the other hand the addition of aliphatic or aromatic primary amine to the activated alkynes results in an active intermediate β-enamino esters, which are also useful synthetic building blocks for the synthesis of a wide variety of heterocycles and pharmaceutical compounds.[4,5] Many domino reactions have been developed by trapping this kind of *in situ* generated β-enamino esters with sequential adding nucleophilic or electrophilic reagents to give versatile nitrogen-containing compounds and *N*,*O*-heterocycles.[6-14] We also successfully reported several new domino reactions by using the *in situ* formed β-enamino esters derived from the reactions of arylamines with electron-deficient alkynes such as dimethyl acetylenedicarboxylate and methyl propiolate.[15-18] It is very interesting to find that the β-enamino esters derived from the addition of primary amines to methyl propiolate usually showed very different reactivity and therefore different reaction patterns to the β-enamino esters generated from the addition of the corresponding amines to dimethyl acetylenedicarboxylates.[19-22] Recently we found that the three-component reactions of aromatic aldehydes, aryl amines and acetylenedicarboxylates could give 2-hydroxyhydropyridines, 1,4-dihydropyridines or 2-pyrrolidinones under different conditions.[23] Encouraged by these results and in order to hunt for new domino reactions, we investigated the one-pot domino reactions of arylamines, methyl propiolate and aromatic aldehydes and successfully developed a facile synthetic procedure for the functionalized arylidene bis(3-arylaminoacrylates).

Experimental

Reagents and apparatus

All reagents and solvents were commercial available with analytical grade and used as received. Evaporation removal of organic solvents was carried out with a rotary evaporator in conjunction with a aspirator. Melting points were taken on a hot-plate microscope apparatus and uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker AV-600 instrument. IR spectra were obtained on a Bruker Tensor27 spectrometer (KBr disc). HRMS were measured at Bruker UHR-TOF maXis spectrometer. X-ray data were collected on a Bruker Smart APEX-2 diffractometer.

General procedure for the preparation of compounds 1a—1q from one-pot domino reactions of arylamines, methyl propiolate and aromatic aldehydes

In a round bottom flask, a mixture of arylamine (2.0 mmol) and methyl propiolate (2.0 mmol, 0.168 g) in 5.0 mL ethanol was stirred at room temperature for 8—12 h. Then aromatic aldehyde (1.0 mmol) and $FeCl_3$ (0.2 mmol, 0.032 g) were added to it. The solution was stirred at room temperature for an additional 24 h. The resulting precipitates were collected by filtration and washed with cold alcohol to give the pure product.

* E-mail: cgyan@yzu.edu.cn
Received February 2, 2013; accepted March 5, 2013; published online April 3, 2013.
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/cjoc.201300094 or from the author.

(2*Z*,4*Z*)-Dimethyl 2,4-bis((4-methoxyphenyl-amino)-methylene)-3-(4-methoxyphenyl)pentanedioate (1a) White solid, 45%. m.p. 122—125 ℃; ^{1}H NMR (600 MHz, DMSO-d_6) δ: 9.78 (d, J=12.6 Hz, 2H, NH), 7.14 (d, J=9.0 Hz, 2H, ArH), 6.92 (brs, 1H, ArH), 6.90—6.88 (m, 6H, ArH, CH), 6.87—6.85 (m, 5H, ArH), 5.12 (s, 1H, CH), 3.74 (s, 3H, OCH_3), 3.68 (s, 6H, OCH_3), 3.61 (s, 6H, OCH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 168.9, 157.4, 154.8, 143.3, 135.3, 134.6, 129.5, 116.8, 114.9, 113.5, 100.7, 56.0, 55.2, 54.9, 50.8, 42.7, 18.5; IR (KBr) v: 3385, 3002, 2946, 2834, 2060, 1619, 1514, 1438, 1360, 1325, 1286, 1213, 1171, 1101, 1033, 948, 823, 769 cm^{-1}; HRMS (ESI) calcd for $C_{30}H_{31}N_2O_7$ ([M–H]$^-$): 531.2137, found 531.2127.

(2*Z*,4*Z*)-Dimethyl 2,4-bis((4-methoxyphenylamino)-methylene)-3-(4-methylphenyl)pentanedioate (1b) White solid, 68%. m.p. 144—147 ℃; ^{1}H NMR (600 MHz, DMSO-d_6) δ: 9.80 (d, J=12.6 Hz, 2H, NH), 7.12 (brs, 4H, ArH), 6.92—6.86 (m, 10H, ArH, CH), 5.13 (brs, 1H, CH), 3.68 (s, 6H, OCH_3), 3.60 (s, 6H, OCH_3), 2.28 (s, 3H, CH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 168.9, 154.8, 143.5, 140.5, 134.8, 134.6, 128.8, 128.4, 116.8, 114.9, 100.5, 55.2, 50.8, 43.1, 20.6; IR (KBr) v: 3450, 2998, 2949, 2837, 2063, 1667, 1619, 1514, 1443, 1400, 1356, 1322, 1216, 1177, 1103, 1035, 998, 947, 825, 770 cm^{-1}; HRMS (ESI) calcd for $C_{30}H_{31}N_2O_6$ ([M–H]$^-$): 515.2188, found 515.2182.

(2*Z*,4*Z*)-Dimethyl 2,4-bis((4-methoxyphenylamino)-methylene)-3-(4-chlorophenyl)pentanedioate (1c) White solid, 69%. m.p. 120—122 ℃; ^{1}H NMR (600 MHz, DMSO-d_6) δ: 9.83 (d, J=12.6 Hz, 2H, NH), 7.35 (d, J=8.4 Hz, 2H, ArH), 7.27 (d, J=7.8 Hz, 2H, ArH), 6.97—6.92 (m, 6H, ArH, CH), 6.86 (d, J=9.0 Hz, 4H, ArH), 5.15 (brs, 1H, CH), 3.68 (s, 6H, OCH_3), 3.60 (s, 6H, OCH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 168.8, 154.9, 143.8, 142.9, 134.5, 130.3, 128.0, 116.9, 114,9, 99.8, 55.2, 50.8, 43.2; IR (KBr) v: 3322, 3285, 3010, 2951, 2834, 2061, 1868, 1671, 1615, 1514, 1442, 1403, 1354, 1285, 1205, 1169, 1099, 1031, 951, 864, 822, 770 cm^{-1}; HRMS (ESI) calcd for $C_{29}H_{28}ClN_2O_6$ ([M-H]$^-$): 535.1641, found 535.1632.

(2*Z*,4*Z*)-Dimethyl 2,4-bis((4-methylphenylamino)-methylene)-3-(4-methoxyphenyl)pentanedioate (1d) White solid, 46%. m.p. 132—135 ℃; ^{1}H NMR (600 MHz, DMSO-d_6) δ: 9.82 (d, J=12.6 Hz, 2H, NH), 7.14 (d, J=8.4 Hz, 2H, ArH), 7.06 (d, J=7.8 Hz, 4H, ArH), 6.97 (d, J=12.6 Hz, 2H, CH), 6.88 (d, J=8.4 Hz, 2H, ArH), 6.83 (d, J=8.4 Hz, 4H, ArH), 5.13 (brs, 1H, CH), 3.74 (s, 3H, OCH_3), 3.61 (s, 6H, OCH_3), 2.20 (s, 6H, CH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 168.9, 157.5, 142.7, 138.6, 135.1, 131.0, 130.0, 129.5, 115.3, 113.6, 101.3, 54.9, 50.9, 42.8, 20.1; IR (KBr) v: 3449, 3014, 2951, 1699, 1614, 1516, 1439, 1357, 1298, 1220, 1183, 1100, 1034, 994, 808, 676 cm^{-1}; HRMS (ESI) calcd for $C_{30}H_{31}N_2O_5$ ([M–H]$^-$): 499.2238, found 499.2230.

(2*Z*,4*Z*)-Dimethyl-2,4-bis((4-methylphenylamino)-methylene)-3-(4-*tert*-butylphenyl)pentanedioate (1e) White solid, 66%. m.p. 157—160 ℃; ^{1}H NMR (600 MHz, DMSO-d_6) δ: 9.80 (d, J=12.2 Hz, 2H, NH), 7.35 (d, J=6.6 Hz, 2H, ArH), 7.15 (d, J=6.6 Hz, 2H, ArH), 7.04 (d, J=6.6 Hz, 4H, ArH), 6.89 (d, J=12.2 Hz, 2H, CH), 6.80 (d, J=7.2 Hz, 4H, ArH), 5.17 (brs, 1H, CH), 3.62 (s, 6H, OCH_3), 2.19 (s, 6H, CH_3), 1.28 (s, 9H, CH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 168.8, 142.8, 138.7, 131.0, 129.9, 128.2, 124.9, 115.4, 115.3, 101.2, 50.9, 43.1, 34.1, 31.2, 31.1, 20.1; IR (KBr) v: 3449, 3023, 2915, 2865, 1885, 1671, 1615, 1517, 1440, 1360, 1280, 1222, 1187, 1108, 1002, 946, 865, 810 cm^{-1}; HRMS (ESI) calcd for $C_{33}H_{37}N_2O_4$ ([M–H]$^-$): 525.2759, found 525.2755.

(2*Z*,4*Z*)-Dimethyl 2,4-bis((3-nitrophenylamino)-methylene)-3-(4-methylphenyl)pentanedioate (1f) Yellow solid, 73%. m.p. 170—172 ℃; ^{1}H NMR (600 MHz, DMSO-d_6) δ: 9.92 (d, J=12.6 Hz, 2H, NH), 8.06 (brs, 2H, ArH), 7.76 (d, J=7.2 Hz, 1H, ArH), 7.59 (t, J=8.4 Hz, 1H, ArH), 7.15 (d, J=12.6 Hz, 2H, CH), 7.07 (d, J=7.2 Hz, 4H, ArH), 6.92 (d, J=7.8 Hz, 4H, ArH), 5.29 (brs, 1H, CH), 3.61 (s, 6H, OCH_3), 2.20 (s, 6H, CH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 168.7, 147.7, 146.5, 143.9, 138.4, 135.4, 131.2, 129.9, 129.4, 122.8, 121.1, 115.6, 99.5, 50.9, 43.8, 20.1; IR (KBr) v: 3281, 2918, 1677, 1611, 1528, 1524, 1352, 1220, 1104, 1000, 949, 817 cm^{-1}; HRMS (ESI) calcd for $C_{29}H_{28}N_3O_6$ ([M–H]$^-$): 514.1984, found 514.1974.

(2*Z*,4*Z*)-Dimethyl 2,4-bis((4-methylphenylamino)-methylene)-3-(4-bromohenyl)pentanedioate (1g) White solid, 61%. m.p. 146—148 ℃; ^{1}H NMR (600 MHz, DMSO-d_6) δ: 9.87 (d, J=10.2 Hz, 2H, NH), 7.48 (brs, 2H, ArH), 7.22 (brs, 2H, ArH), 7.07 (brs, 6H, ArH, CH), 6.88 (brs, 4H, ArH), 5.14(s, 1H, CH), 3.61 (s, 6H, OCH_3), 2.20 (s, 6H, CH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 168.8, 143.2, 138.5, 131.1 130.9, 130.8, 129.9, 118.9, 115.4, 100.3, 50.9, 43.3, 20.1; IR (KBr) v: 3277, 2950, 1671, 1608, 1519, 1437, 1302, 1263, 1192, 1074, 993, 945, 864, 814, 793 cm^{-1}; HRMS (ESI) calcd for $C_{29}H_{28}BrN_2O_4$ ([M–H]$^-$): 547.1238, found 547.1231.

(2*Z*,4*Z*)-Dimethyl 2,4-bis(phenylamino)methylene)-3-(4-chlorophenyl)pentanedioate (1h) White solid, 75%. m.p. 142—144 ℃; ^{1}H NMR (600 MHz, DMSO-d_6) δ: 9.92 (d, J=12.7 Hz, 2H, NH), 7.37 (d, J=8.4 Hz, 2H, ArH), 7.30—7.25 (m, 6H, ArH), 7.09 (d, J=12.7 Hz, 2H, CH), 6.98 (d, J=8.4 Hz, 4H, ArH), 6.94 (t, J=7.2 Hz, 2H, ArH), 5.19 (brs, 1H, CH), 3.63 (s, 6H, OCH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 168.8, 142.8, 142.5, 140.9, 130.5, 130.4, 129.5, 128.1, 122.1, 115.4, 101.1, 51.0, 43.3; IR (KBr) v: 3390, 3337, 2948, 1669, 1594, 1498, 1438, 1359, 1307, 1190, 1085, 1002, 947, 854, 748 cm^{-1}; HRMS (ESI) calcd for $C_{28}H_{24}ClN_2O_4$ ([M–H]$^-$): 475.1430, found 475.1419.

(2*Z*,4*Z*)-Dimethyl-2,4-bis((4-chlorophenylamino)-methylene)-3-(4-methoxyphenyl)pentanedioate (1i) White solid, 76%. m.p. 156—159 ℃; ^{1}H NMR (600 MHz, DMSO-d_6) δ: 9.90 (d, J=12.6 Hz, 2H, NH), 7.30 (d, J=9.0 Hz, 4H, ArH), 7.16 (d, J=8.4 Hz, 2H, ArH), 7.00—6.98 (m, 5H, ArH, CH), 6.97 (brs, 1H, ArH), 6.88

(d, J=8.4 Hz, 2H, ArH), 5.14 (brs, 1H, CH), 3.74 (s, 3H, OCH_3), 3.62 (s, 6H, OCH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 168.8, 157.5, 142.0, 140.0, 134.5, 129.6, 129.3, 125.5, 116.9, 113.6, 102.7, 54.9, 51.0, 42.9; IR (KBr) v: 3393, 2949, 2836, 2069, 1880, 1668, 1624, 1502, 1438, 1358, 1317, 1257, 1221, 1188, 1097, 1037, 1001, 942, 818, 744, 710, 663, 506 cm^{-1}; HRMS (ESI) calcd for $C_{28}H_{25}Cl_2N_2O_5$ ($[M-H]^-$) 539.1146, found 539.1139.

(2*Z*,4*Z*)-Dimethyl-2,4-bis((benzylamino)methylene)-3-(4-methoxyphenyl)pentanedioate (1j) White solid, 60%. m.p. 136－139 ℃; ^1H NMR (600 MHz, DMSO-d_6) δ: 8.14 (brs, 2H, NH), 7.31－7.24 (m, 6H, ArH), 7.15 (brs, 4H, ArH), 6.95－6.94 (m, 2H, ArH), 6.78 (brs, 2H, ArH), 6.36 (d, J=12.6 Hz, 2H, CH), 4.93 (s, 1H, CH), 4.23 (brs, 4H, CH_2), 3.70 (s, 3H, OCH_3), 3.47 (s, 6H, OCH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 169.1, 157.0, 152.2, 140.0, 136.7, 129.1, 128.4, 127.0, 126.8, 113.3, 96.9, 54.8, 51.2, 50.1, 42.0; IR (KBr) v: 3333, 3027, 2950, 2915, 1663, 1608, 1509, 1443, 1363, 1318, 1177, 974 cm^{-1}; HRMS (ESI) calcd for $C_{30}H_{31}N_2O_5$ ($[M-H]^-$): 499.2238, found 499.2231.

(2*Z*,4*Z*)-Dimethyl-2,4-bis((benzylamino)methylene)-3-(4-methylphenyl)pentanedioate (1k) White solid, 63%. m.p. 146－149 ℃; ^1H NMR (600 MHz, DMSO-d_6) δ: 8.16－8.14 (m, 2H, NH), 7.31－7.29 (m, 4H, ArH), 7.25－7.24 (m, 2H, ArH), 7.15－7.14 (m, 4H, ArH), 7.02－7.01 (m, 2H, ArH), 6.93－6.92 (m, 2H, ArH), 6.37 (d, J=12.6 Hz, 2H, CH), 4.94 (s, 1H, CH), 4.23 (brs, 4H, CH_2), 3.47 (s, 6H, OCH_3), 2.24 (s, 3H, CH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 169.1, 152.3, 141.9, 140.0, 134.1, 128.4, 128.1, 127.0, 126.8, 96.7, 51.2, 50.2, 42.4, 20.5; IR (KBr) v: 3363, 3025, 2944, 1937, 1666, 1609, 1511, 1442, 1358, 1207, 1178, 1121, 1068, 964, 853, 794 cm^{-1}; HRMS (ESI) calcd for $C_{30}H_{31}N_2O_4$ ($[M-H]^-$): 483.2289, found 483.2288.

(2*Z*,4*Z*)-Dimethyl-2,4-bis((benzylamino)methylene)-3-(4-chlorophenyl)pentanedioate (1l) White solid, 68%. m.p. 144－147 ℃; ^1H NMR (600 MHz, DMSO-d_6) δ: 8.20－8.17 (m, 2H, NH), 7.31 (t, J=7.2 Hz, 4H, ArH), 7.26－7.25 (m, 4H, ArH), 7.15 (d, J=7.2 Hz, 4H, ArH), 7.06 (d, J=8.4 Hz, 2H, ArH), 6.39 (d, J=13.2Hz, 2H, CH), 4.94 (s, 1H, CH), 4.25 (d, J=6.0 Hz, 4H, CH_2), 3.47 (s, 6H, OCH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 168.9, 152.5, 144.3, 139.9, 129.9, 129.8, 128.6, 128.5, 128.4, 128.3, 128.2, 127.8, 127.0, 126.9, 96.0, 51.2, 50.2, 42.5; IR (KBr) v: 3728, 3361, 3311, 3025, 2948, 1668, 1610, 1490, 1443, 1359, 1315, 1208, 1179, 1123, 1007, 965, 856, 794 cm^{-1}; HRMS (ESI) calcd for $C_{29}H_{28}ClN_2O_4$ ($[M-H]^-$): 503.1743, found 503.1737.

(2*Z*,4*Z*)-Dimethyl-2,4-bis((benzylamino)methylene)-3-(4-bromophenyl)pentanedioate (1m) White solid, 62%. m.p. 147－150 ℃; ^1H NMR (600 MHz, DMSO-d_6) δ: 8.19 (brs, 2H, NH), 7.39－7.38 (m, 2H, ArH), 7.31－7.25 (m, 6H, ArH), 7.15 (brs, 4H, ArH), 7.01－7.00 (m, 2H, ArH), 6.40 (d, J=12.6 Hz, 2H, CH), 4.93 (s, 1H, CH), 4.25 (brs, 4H, CH_2), 3.47 (s, 6H, OCH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 168.9, 152.5, 139.9, 130.7, 130.6, 130.5, 130.4, 130.3, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 127.2, 127.1, 127.0, 126.9, 95.9, 51.2, 51.1, 50.2; IR (KBr) v: 3363, 3026, 2947, 1668, 1488, 1441, 1354, 1207, 1123, 1070, 1030, 964, 793 cm^{-1}; HRMS (ESI) calcd for $C_{29}H_{28}BrN_2O_4$ ($[M-H]^-$): 547.1238, found 547.1230.

(2*Z*,4*Z*)-Dimethyl 3-phenyl-2,4-bis((phenethylamino)-methylene)pentanedioate (1n) White solid, 65%. m.p. 128－130 ℃; ^1H NMR (600 MHz, DMSO-d_6) δ: 8.17－8.15 (m, 2H, NH), 7.32－7.29 (m, 4H, ArH), 7.25－7.20 (m, 4H, ArH), 7.15－7.11 (m, 5H, ArH), 7.05 (d, J=7.2 Hz, 2H, ArH), 6.37 (d, J=13.2 Hz, 2H, CH), 4.99 (s, 1H, CH), 4.23－4.22 (m, 4H, CH_2), 3.47 (s, 6H, OCH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 169.1, 152.4, 145.0, 140.0, 128.4, 128.2, 127.8, 127.0, 126.9, 125.4, 96.6, 51.2, 50.1, 42.9; IR (KBr) v: 3343, 3057, 3023, 2948, 1946, 1665, 1609, 1492, 1442, 1362, 1326, 1210, 1179, 1121, 1071, 1032, 1000, 966, 793 cm^{-1}; HRMS (ESI) calcd for $C_{29}H_{29}N_2O_4$ ($[M-H]^-$): 469.2133, found 469.2130.

(2*Z*,4*Z*)-Dimethyl 3-(4-methoxyphenyl)-2,4-bis((phenethylamino)methylene)pentanedioate (1o) White solid, 60%. m.p. 102－105 ℃; ^1H NMR (600 MHz, DMSO-d_6) δ: 7.84－7.81 (m, 2H, NH), 7.28 (t, J=7.2 Hz, 4H, ArH), 7.22－7.19 (m, 2H, ArH), 7.14 (d, J=7.2 Hz, 4H, ArH), 6.77－6.74 (m, 4H, ArH), 6.06 (d, J=13.2 Hz, 2H, CH), 4.82 (s, 1H, CH), 3.72 (s, 3H, OCH_3), 3.44 (s, 6H, OCH_3), 3.33－3.29 (m, 2H, CH_2), 3.28－3.26 (m, 2H, CH_2), 2.71－2.70 (m, 4H, CH_2); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 169.0, 156.9, 151.9, 138.8, 136.8, 129.1, 128.7, 128.3, 126.1, 113.1, 95.8, 54.8, 50.1, 49.3, 41.6, 37.2; IR (KBr) v: 3324, 3061, 2946, 1664, 1605, 1507, 1440, 1357, 1318, 1270, 1175, 1108, 1080, 987, 856, 836, 793, 751 cm^{-1}; HRMS (ESI) calcd for $C_{32}H_{35}N_2O_5$ ($[M-H]^-$): 527.2551, found 527.2543.

(2*Z*,4*Z*)-Dimethyl 3-(4-chlorophenyl)-2,4-bis((phenethylamino)methylene)pentanedioate (1p) White solid, 63%. m.p. 115－118 ℃; ^1H NMR (600 MHz, DMSO-d_6) δ: 7.88 (brs, 2H, NH), 7.28 (brs, 4H, ArH), 7.22 (brs, 4H, ArH), 7.17 (brs, 4H, ArH), 6.86－6.85 (m, 2H, ArH), 6.06 (d, J=12.6 Hz, 2H, CH), 4.83 (s, 1H, CH), 3.44 (s, 6H, OCH_3), 3.28 (brs, 4H, CH_2), 2.72 (brs, 4H, CH_2); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 168.9, 152.2, 144.4, 138.8, 129.9, 129.7, 128.8, 128.5, 128.3, 128.1, 127.7, 126.1, 94.9, 50.1, 49.4, 42.1, 37.2; IR (KBr) v: 33322, 3046, 3023, 1664, 1584, 1490, 1440, 1358, 1313, 1270, 1182, 1112, 1085, 1015, 978, 856, 789 cm^{-1}; HRMS (ESI) calcd for $C_{31}H_{32}ClN_2O_4$ ($[M-H]^-$): 531.2056, found 531.2050.

(2*Z*,4*Z*)-Dimethyl 3-(4-bromophenyl)-2,4-bis((phenethylamino)methylene)pentanedioate (1q) White solid, 62%. m.p. 113－115 ℃; ^1H NMR (600 MHz, DMSO-d_6) δ: 7.88 (brs, 2H, NH), 7.35 (d, J=7.2 Hz, 2H, ArH), 7.28－7.27 (m, 4H, ArH), 7.22－7.20 (m, 2H, ArH), 7.17－7.16 (m, 4H, ArH), 6.80 (d, J=7.2 Hz, 2H, ArH), 6.07 (d, J=13.2 Hz, 2H, CH), 4.81 (s, 1H, CH), 3.44 (s, 6H, OCH_3), 3.28－3.27 (m, 4H, CH_2), 2.72－

2.71 (m, 4H, CH_2); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 168.8, 152.2, 144.8, 138.8, 130.6, 130.4, 128.8, 128.3, 126.1, 118.2, 94.7, 50.1, 49.4, 42.1, 37.1; IR (KBr) v: 3349, 3063, 2946, 1663, 1607, 1488, 1439, 1354, 1192, 1176, 1109, 1079, 986, 857, 790 cm^{-1}; HRMS (ESI) calcd for $C_{31}H_{32}BrN_2O_4$ ([M–H]$^-$): 575.1551, found 575.1545.

General procedure for the preparation of compounds 2a－2d from one-pot domino reactions of benzylamine, methyl propiolate and isatins

In a round bottom flask, a mixture of benzylamine (2.0 mmol, 0.214 g) and methyl propiolate (2.0 mmol, 0.168 g) in 5.0 mL ethanol was stirred at room temperature for 8－12 h. Then isatins (2.0 mmol) and $FeCl_3$ (0.2 mmol, 0.032 g) were added to it. The solution was stirred at room temperature for an additional 24 h. The resulting precipitates were collected by filtration and washed with cold alcohol to give the solid product, which were recrystallized from ethanol to give the pure product.

(*Z*)-Methyl-3-(benzylamino)-2-(3-hydroxy-2-oxoindolin-3-yl)acrylate (2a) White solid, 48%. m.p. 158－160 ℃; ^1H NMR (600 MHz, DMSO-d_6) δ: 10.03 (s, 1H, NH), 8.16－8.14 (m, 1H, NH), 7.54 (d, J=13.8 Hz, 1H, CH), 7.41－7.38 (m, 2H, ArH), 7.35－7.34 (m, 2H, ArH), 7.31－7.29 (m, 1H, ArH), 7.13－7.10 (m, 1H, ArH), 6.94 (d, J=7.2 Hz, 1H, ArH), 6.85－6.82 (m, 1H, ArH), 6.74 (d, J=7.6 Hz, 1H, ArH), 6.00 (s, 1H, OH), 4.48 (d, J=6.0 Hz, 2H, CH_2), 3.27 (s, 3H, OCH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 179.1, 167.0, 151.0, 142.7, 139.9, 134.3, 128.5, 128.3, 127.2, 123.0, 120.9, 108.9, 93.5, 74.1, 51.6, 49.7; IR (KBr) v: 3333, 3032, 2946, 1719, 1674, 1617, 1447, 1377, 1331, 1221, 1179, 1099, 1072, 1049, 1011, 939, 906, 764 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{17}N_2O_4$ ([M–H]$^-$): 337.1194, found 337.1195.

(*Z*)-Methyl 3-(benzylamino)-2-(3-hydroxy-5-methyl-2-oxoindolin-3-yl)acrylate (2b) White solid, 63%. m.p. 97－99 ℃; ^1H NMR (600 MHz, DMSO-d_6) δ: 9.94 (s, 1H, NH), 8.16 (s, 1H, NH), 7.53 (d, J=12.2 Hz, 1H, CH), 7.40－7.31 (m, 5H, ArH), 6.92 (s, 1H, ArH), 6.76 (s, 1H, ArH), 6.63 (s, 1H, ArH), 5.97 (s, 1H, OH), 4.48 (s, 2H, CH_2), 3.29 (s, 3H, OCH_3), 2.19 (s, 3H, CH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 179.1, 167.0, 150.9, 140.3, 139.9, 134.3, 129.5, 128.5, 127.3, 127.2, 123.8, 108.7, 93.7, 74.2, 51.6, 49.8, 20.6; IR (KBr) v: 3335, 3025, 2950, 1713, 1672, 1617, 1492, 1445, 1369, 1324, 1219, 1188, 1158, 1123, 1050, 1010, 960, 892, 814 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{19}N_2O_4$ ([M–H]$^-$): 351.1350, found 351.1347.

(*Z*)-Methyl 3-(benzylamino)-2-(5-fluoro-3-hydroxy-2-oxoindolin-3-yl)acrylate (2c) White solid, 57%. m.p. 146－149 ℃; ^1H NMR (600 MHz, DMSO-d_6) δ: 10.07 (s, 1H, NH), 8.17 (s, 1H, NH), 7.53 (d, J=13.8 Hz, 1H, CH), 7.41－7.29 (m, 5H, ArH), 6.95－6.93 (m, 1H, ArH), 6.77－6.76 (m, 1H, ArH), 6.73－6.71 (m, 1H, ArH), 6.17 (s, 1H, OH), 4.48 (d, J=5.7 Hz, 2H, CH_2), 3.30 (s, 3H, OCH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 179.1, 166.9, 160.2, 158.5, 156.9, 151.2, 139.8, 138.8, 136.2, 132.7, 128.5, 127.2, 114.4, 114.3, 110.7, 110.6, 109.6, 109.5, 93.0, 76.2, 74.4, 51.7, 49.8; IR (KBr) v: 3336, 2951, 1719, 1676, 1611, 1484, 1448, 1372, 1322, 1259, 1220, 1185, 1159, 1048, 1010, 965, 882, 807 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{16}FN_2O_4$ ([M–H]$^-$): 355.1100, found 355.1102.

(*Z*)-Methyl-3-(benzylamino)-2-(5-chloro-3-hydroxy-2-oxoindolin-3-yl)acrylate (2d) White solid, 60%. m.p. 144－146 ℃; ^1H NMR (600 MHz, DMSO-d_6) δ: 10.19 (s, 1H, NH), 8.17－8.15 (s, 1H, NH), 7.53 (d, J=13.8 Hz, 1H, CH), 7.41－7.38 (m, 2H, ArH), 7.36－7.35 (m, 2H, ArH), 7.32－7.29 (m, 1H, ArH), 7.17 (d, J=7.5 Hz, 1H, ArH), 6.92 (s, 1H, ArH), 6.75 (d, J=8.1 Hz, 1H, ArH), 6.21 (s, 1H, OH), 4.48 (d, J=5.8 Hz, 2H, CH_2), 3.31 (s, 3H, OCH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 178.8, 166.8, 151.1, 141.6, 139.8, 136.5, 128.5, 128.1, 127.3, 127.2, 124.9, 123.1, 110.4, 92.8, 74.2, 51.7, 49.8; IR (KBr) v: 3330, 2951, 1717, 1676, 1619, 1444, 1370, 1320, 1222, 1174, 1072, 1007, 957, 887, 817, 790 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{16}ClN_2O_4$ ([M–H]$^-$): 371.0804, found 371.0805.

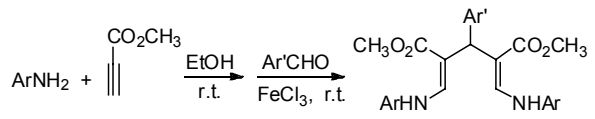
Results and Discussion

Recently we reported that $FeCl_3$ catalyzed domino reactions of arylamines, methyl propiolate, aromatic aldehydes and indole in ethanol to give methyl 2-(1*H*-indol-3-yl)arylmethyl-3-arylaminoacrylates in good yields.[24] In this domino reaction process we found that a new compound could be separated occasionally from reaction mixture, which was characterized as arylidene bis(3-arylaminoacrylates). Thus the domino reactions of primary amines, methyl propiolate and aldehydes with $FeCl_3$ as catalyst were systematically investigated. In our initial endeavour, *p*-methoxyaniline reacted firstly with methyl propiolate in ethanol overnight to give the desired β-enamino ester according to the previously reported method.[19-22] Then the sequential reaction of this *in situ* generated β-enamino ester with *p*-chlorobenzaldehyde as a simple model substrate was investigated to establish the feasibility of the strategy and optimize the reaction conditions. When the reaction was carried out at room temperature in ethanol for 24 h with anhydrous $FeCl_3$ (20% mole) as catalyst, we are pleased to find that the polysubstituted acrylate **1c** was obtained in 69% yields. Under this simple condition various arylamine and aromatic aldehydes are employed in the reactions, and the results are listed in Table 1 (Entries 1－9). It is clearly seen that all reactions preceded very smoothly and a series of arylidene bis(3-arylaminoacrylates) **1a**－**1i** were obtained in moderate to good yields. Benzylamine and 2-phenylethylamine were also utilized in the reaction and the higher yields of the desired products were successfully obtained (Table 1, Entries 10－17).

The structures of the bis(3-arylaminoacrylates) (**1a**－**1q**) were established on the spectroscopic methods

CHINESE JOURNAL OF CHEMISTRY

Table 1 Synthesis of arylidene bis(3-arylaminoacrylates) **1a**—**1q**



Entry	Compd.	Ar	Ar'	Yield/%
1	**1a**	*p*-$CH_3OC_6H_4$	*p*-$CH_3OC_6H_4$	45
2	**1b**	*p*-$CH_3OC_6H_4$	*p*-$CH_3C_6H_4$	68
3	**1c**	*p*-$CH_3OC_6H_4$	*p*-ClC_6H_4	69
4	**1d**	*p*-$CH_3C_6H_4$	*p*-$CH_3OC_6H_4$	46
5	**1e**	*p*-$CH_3C_6H_4$	*p*-$(CH_3)_3CC_6H_4$	66
6	**1f**	*p*-$CH_3C_6H_4$	*m*-$NO_2C_6H_4$	73
7	**1g**	*p*-$CH_3C_6H_4$	*p*-BrC_6H_4	61
8	**1h**	C_6H_5	*p*-ClC_6H_4	75
9	**1i**	*p*-ClC_6H_4	*p*-$CH_3OC_6H_4$	42
10	**1j**	$C_6H_5CH_2$	*p*-$CH_3OC_6H_4$	60
11	**1k**	$C_6H_5CH_2$	*p*-$CH_3C_6H_4$	63
12	**1l**	$C_6H_5CH_2$	*p*-ClC_6H_4	68
13	**1m**	$C_6H_5CH_2$	*p*-BrC_6H_4	62
14	**1n**	$C_6H_5CH_2$	C_6H_5	65
15	**1o**	$C_6H_5CH_2CH_2$	*p*-$CH_3OC_6H_4$	60
16	**1p**	$C_6H_5CH_2CH_2$	*p*-ClC_6H_4	63
17	**1q**	$C_6H_5CH_2CH_2$	*p*-BrC_6H_4	62

and were ambiguously confirmed by single-crystal structure determinations of compounds **1a** (Figure 1) and **1c** (Figure 2). ^{1}H NMR spectra of compounds **1a**—**1q** usually show a one set of absorption peaks for each characterized groups, which clearly means only one isomer existed in each sample. Single crystal structures of **1a** and **1c** clearly indicated that both units of acrylates are in *E*-configuration with 3-arylamino group and ester group existing in *cis*-position of double band. One N—H—O hydrogen bond was formed between the amino group and the carbonyl group. These results also indicates that this domino reaction is a highly stereoselective reaction.

To explain the formation of the arylidene bis(3-arylaminoacrylates), a proposed mechanism is outlined

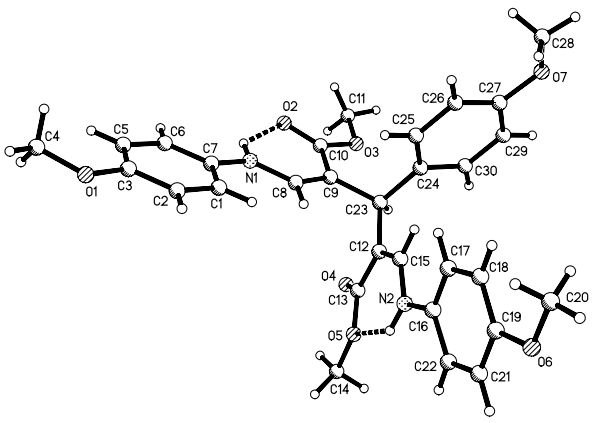


Figure 1 Molecular structure of compound **1a**.

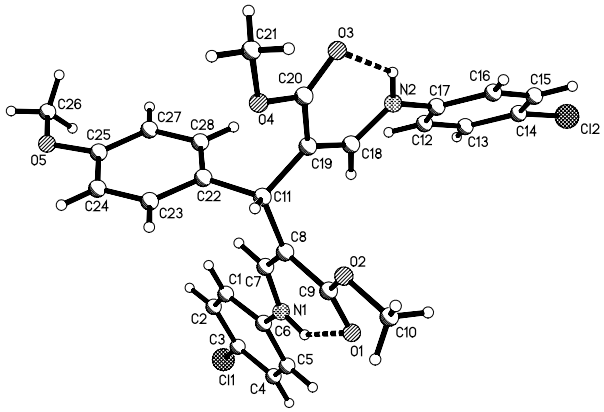
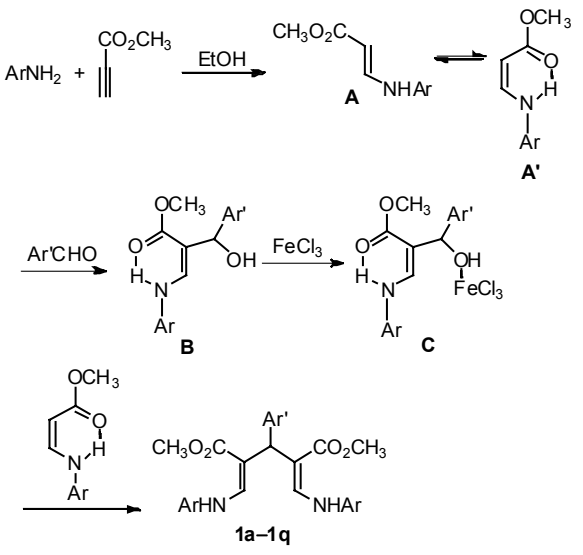


Figure 2 Molecular structure of compound **1c**.

in Scheme 1. At first arylamine adds to methyl propiolate to form the *β*-enamino ester (**A**). Secondly nucleophilic addition of *β*-enamino ester to carbonyl group of aromatic aldehyde forms the adduct intermediate (**B**). Thirdly in the presence of Lewis acid $FeCl_3$ as the catalyst, the new generated electrophilic reagent (**C**) reacted with another molecular *β*-enamino ester (**A**) to give the final arylidene bis(3-arylaminoacrylate) **1**. The stereochemistry of bis(3-arylaminoacrylates) was obviously controlled by the *cis/trans* configuration of the *in situ* formed *β*-enamino ester (**A**) and the sequential reaction steps in the reaction mechanism. It has been reported that the *trans*-isomer (**A**) and *cis*-isomer (**A'**) is in equilibrium and the different ratios of two isomers were found to be variable with solvent, substituent and concentration of the reactants.[25-27] The sequential reactions are all reversible and in thermodynamically equilibrium. Thus the substituted acrylates exist in both *Z*- and *E*-isomers. In *Z*-isomer one intramolecular hydrogen bond can be formed between the amino group and ester group, which might increase the stability of the

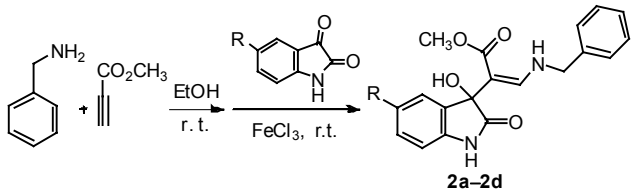
Scheme 1 The proposed formation mechanism for bis(3-arylaminoacrylates)



Z-isomer.

Under the similar reaction conditions, when isatins were employed to replace aromatic aldehydes in the one-pot domino reactions, the oxindolyl substituted acrylates (**2a**—**2d**) were obtained in moderate yields (Table 2). The reason for no bis(3-arylaminoacrylate) being formed in this reaction might be due to that the dehydration of 3-hydroxyoxindole unit is very slow under such mild conditions. The single crystal structure determination of compound **2a** (Figure 3) also showed that one hydrogen bond formed between the benzylamino group and methoxycarbonyl group, and the *Z*-configuration of the substituted acrylate exists.

Table 2 Synthesis of oxindolyl substituted acrylates



2a–2d

Compd.	**2a**	**2b**	**2c**	**2d**
R	H	CH_3	F	Cl
Yield/%	48	63	57	60

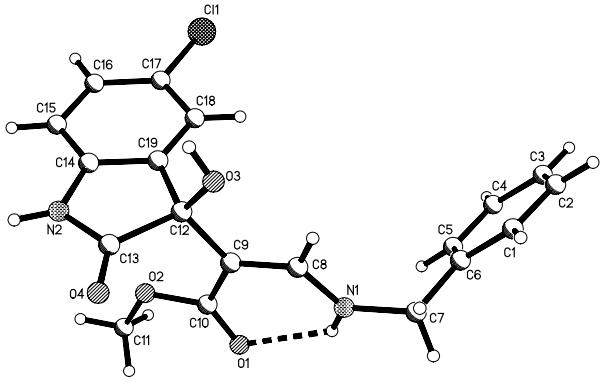


Figure 3 Molecular structure of compound **2a**.

Conclusions

In conclusion, we have systematically investigated the one-pot domino reactions of primary amine, methyl propiolate and aromatic aldehydes with Lewis acid as catalyst. The scope and limitation of this domino reaction was established and the reaction mechanism was briefly discussed. Thus an efficient and diastereoselective synthetic protocol for the functionalized arylidene bis(3-arylaminoacrylates) in good yields was successfully developed. This protocol has advantages of mild reaction conditions, easily accessible starting material and easy purification of the products, which makes it a useful and attractive method for the synthesis of the complex acrylates in synthetic and medicinal chemistry.

Acknowledgement

This work was financially supported by the National Natural Science Foundation of China (Grant No. 21172189) and the Priority Academic Program Development of Jiangsu Higher Education Institutions.

Supplementary Information

Single crystal data for compounds **1a** (CCDC 892280), **1c** (CCDC 888177), and **1a** (CCDC 888176) have been deposited in the Cambridge Crystallographic Data Center.

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(Pan, B.; Qin, X.)

