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Synthesis of N-Arylisatins using NaY Heterogeneous Catalyst under Microwave Irradiations

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ABSTRACT

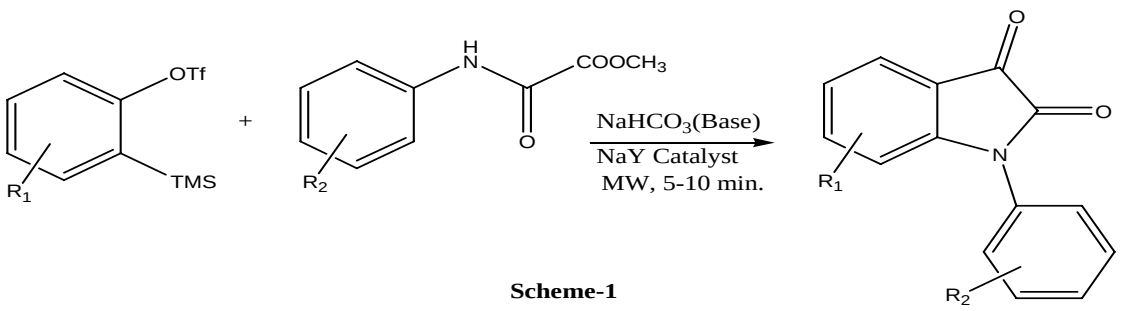
N-Arylisatins are synthesized in high yield in shorter reaction time by the reaction of 2-oxo-2-(Arylamino)acetates and arynes using NaY heterogeneous catalyst under microwave irradiations.

Key words: Catalyst, Microwave, Heterogeneous catalyst, N-Arylisatins.

INTRODUCTION

Isatin have both biological and medical properties including antifungal, antiviral, anti-HIV, anti-, AIDS, antiprotozoal, anticancer and antileukema.[1-7]

In recent years, Isatin have been synthesized by different methods but they require tedious work up and long reaction time[8-18]. Microwave assisted organic synthesis is currently gaining ground in synthetic organic chemistry largely due to the dramatic reduction in time (from days or hours to minutes or seconds)[19-20]. As a part of our ongoing research "roll of microwave technique in synthesis of organic compounds in presence of zeolites", we report a microwave assisted synthesis of N-Arylisatin by reaction of Arynes with Methyl-2-oxo-2-(arylamino)acetate. Excellent yield of N-Arylisatins were achieved in shorter time



Scheme-1

RESULTS AND DISCUSSION

We started our work by reacting methyl-2-oxo(phenyl amino)acetate with 2-(trimethylallyl)phenyltrifluoromethanesulphonat in presence of NaY zeolite under microwave irradiation selected power(400W) for 7 minutes. We obtained N-phenylisatin in high yield(91) in lower reaction time (7min.). The probable reaction mechanism is:

Take another compound and observed percentage yield and other properties. No side product is obtained by controlling temperature in the temperature monitoring microwave oven. Acetonitrile was the best solvent used for this reaction. Here electron-rich substituent seems to promote this reaction to a small extent, whereas electron deficient group lower the yield of the reaction in same way as in ordinary conditions.

It is believed that two mechanisms are possible for this process, routes A and B in Scheme 3. Both suggested rouetes share a common first step, nucleophilic attack by nitrogen on the benzyne, resulting in an aryl carbanion. From there, at least two posibilities exist with regard to how the desired isatin is formed. Route Asuggests that the aryl carbanion attacks the distant ester carbony and displaces a methoxy group. This type of mechanism has also been suggested in our earlier work. On the other hand, Greany's work(eq. 1) suggests another possibility, route B. This route involves attack of the aryl carbanion onto thenearest caronyl group, the amide carbonyl, forming a strained four-membered ring intermediate, which then fragments into a structure where the nitrogen can now attack the ester carbonyl. Both routes eventually lead to the desired isatin. However, the carbonyl groups end up in different places depending on the route. Further efforts are underway in order to shed light on this process.

EXPERIMENTAL

General

The ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5MHz or 400 and 100MHz, respectively. Thin layer chromatography was performed using commercially prepared 60-mesh

Table 1. Reaction of various Methyl 2-oxo-2(aryl amino)acetates with 2-(Trimethylallyl)phenyl Trifluoromethanesulfonate

S.No.	Substrate(R_2)	Time (Minutes)	Yield (%)	M.pt. (^{o}C)
1	H	7	91	136-139
2	4-Me	6	95	137-139
3	4-Oph	5	95	145-148
4	4-F	6	97	235-237
5	4-Cl	7	81	194-197
6	4-Br	7	83	178-180
7	4-I	7	87	198-201
8	2-1	7	94	173-176
9	4-CN	4	86	282-284
10	4-CO_2Et	10	88	127-129
11	4-CF_3	8	71	177-181
12	3-CF_3	9	75	124-127
13	2-t-Bu	8	94	109-113
14	2-Ph	8	89	157-162
15	2,5-$(Ome)_2$	5	91	114-117
16	2,4,6-Me_3	5	82	164-168
17	2,3-$(CH)_4$	5	98	130-133

silica gel plates, and visualization was effected with short wavelength UV light(254nm). All melting points uncorrected. All reagents are used directly as obtained commercially.

Typical procedure for synthesis of the Isatin derivatives[1-17]

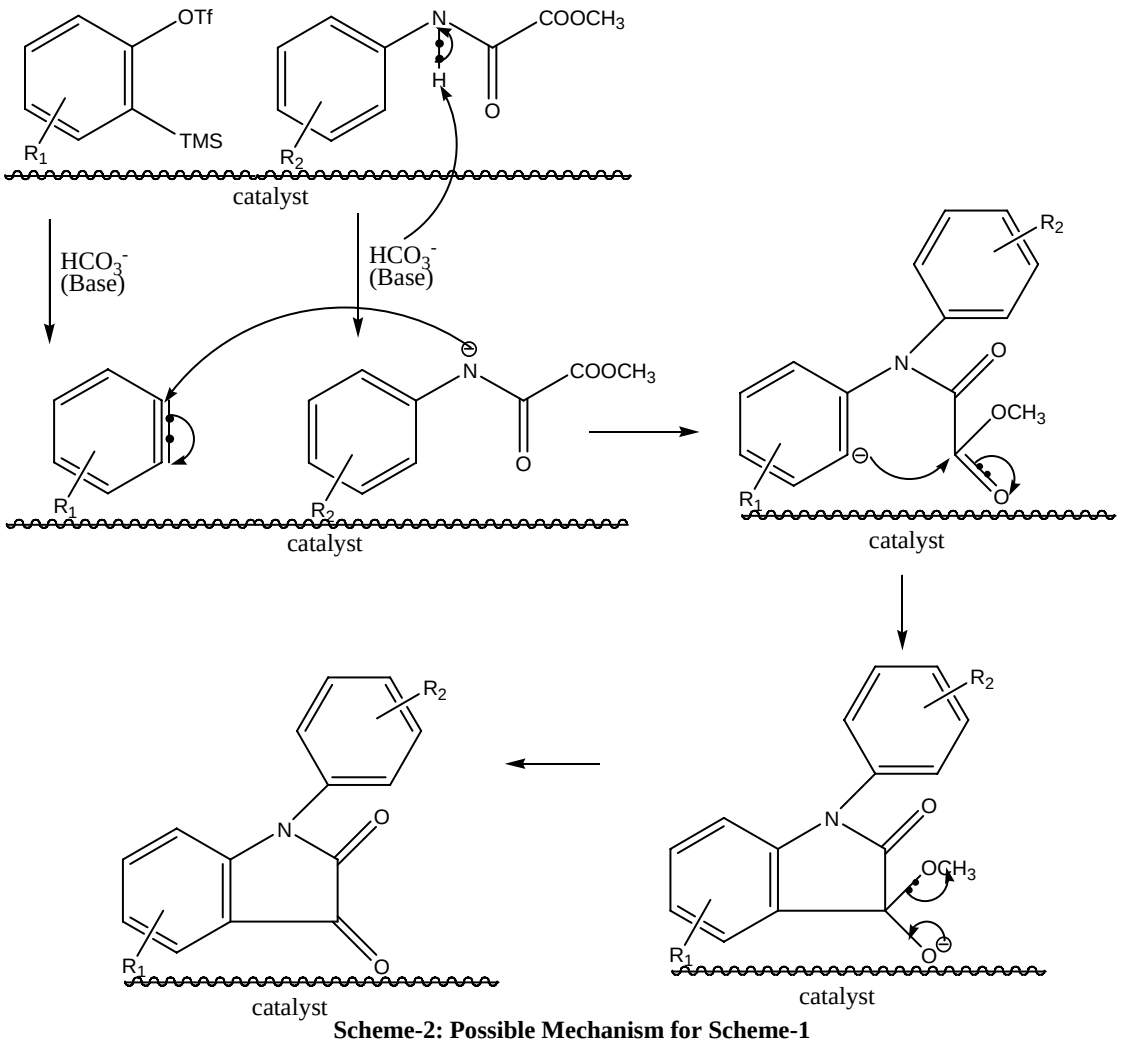
To a dry s dram vial containing a solution of the amide (0.5mmol) and the aryn precursor (1.0mmol) in MeCN (5.0ml, anhydrous) was added $NaHCO_3$ (1.0mmol) and CsF (3.0mmol). The vial was sealed and allowed to stir for 24h at rt. The reaction mixture was then filtered through a lug of silica gel using ethyl acetate, concentrated in vacuo, and purified by flash chromatography using gradient solvent combinations of ethyl acetate/ Hexanes or dichloromethane/Hexanes.

1-Phenylindoline-2,3-dione(1)

The product was isolated as an orange solid.^{1}H NMR (300MHz,$CDCl_3$) δ 7.70 (ddd,j=0.6, 1.3, 7.5Hz,1H), 7.60-7.41(m, 6H), 7.18(td,j= 0.8,7.6Hz, 1H), 6.91(d,j= 8.1Hz, 1H), ^{13}C NMR (75MHz,$CDCl_3$) δ 183.1, 157.5, 151.9, 138.5, 133.4, 130.2, 129.0, 126.2, 125.8, 124.5, 117.5; HRMS(EI) calcd for $[M+H]^+$ ($M=C_{14}H_9NO_2$) 224.0706, found 224.0707

1-p-Tolylindoline-2,3-dione(2)

The product was isolated as a red-orange



Scheme-2: Possible Mechanism for Scheme-1

solid.^{1}H NMR (400MHz,$CDCl_3$)δ 7.80 (d,j=7.5Hz,1H), 7.66(t,j=7.3Hz,1H), 7.49(d,j= 8.2Hz,2H), 7.42(d,j= 8.3Hz, 2H), 7.30(d,j=7.5Hz,1H) 7.00(d,j=8.1Hz,1H) 2.56(s,3H), ^{13}C NMR (100MHz,$CDCl_3$) δ 183.2, 157.6, 152.0, 139.1, 138.5, 130.7, 130.3, 126.0, 125.6, 124.3, 117.6, 111.4, 21.4; HRMS(EI) calcd. for $C_{18}H_{11}NO_2$ 237.0790, found 237.0791 phenoxyphenyl) indoline-2,3-dione(3)

1-(4-phenoxyphenyl)indoline-2,3-dione(3)

The product was isolated as a yellow-orange solid.^{1}H NMR (400MHz,$CDCl_3$)δ 7.66 (d,j=7.4Hz,1H), 7.54(t,j=7.8Hz,1H), 7.40-7.34(m,4H), 7.18-7.11(m,4H), 7.07(d,j= 8.2Hz,2H), 6.88(d,j= 7.97Hz, 1H), ^{13}C NMR (100MHz,$CDCl_3$)δ 183.0, 157.9, 157.6, 156.2, 151.8, 138.5, 130.1, 127.7, 127.4, 125.6, 124.4, 124.3, 119.8, 119.5, 117.5, 111.3, HRMS(EI) calcd for $C_{20}H_{13}NO_3$ 315.0895, found 315.0899

1-(4-Fluorophenyl)indoline-2,3-dione(4)

The product was isolated as a bright orange solid.^{1}H NMR (400MHz,$CDCl_3$)δ 7.72(d,j=7.5Hz,1H), 7.57(t,j=7.8Hz,1H), 7.44-7.40(m,2H), 7.29-7.24(m,2H), 7.20(t,j= 7.6Hz,1H), 6.86(d,j= 8.0Hz, 1H), ^{13}C NMR (100MHz,$CDCl_3$ extra peaks due to C-F coupling) δ 182.8, 163.7, 161.2, 157.6, 151.7, 138.6, 129.0, 128.9, 128.3, 128.2, 125.9, 124.7, 117.7, 117.4, 117.2, 111.3, HRMS(EI) calcd for $C_{14}H_8FNO_2$ 241.0539, found 241.0539

1-(4-Chlorophenyl)indoline-2,3-dione(5)

The product was isolated as an orange solid.^{1}H NMR (400MHz,$CDCl_3$)δ 7.71 (d,j=7.5Hz,1H), 7.59-7.53(m, 3H), 7.39(d,j=8.6Hz, 2H), 7.20(t,j=7.6Hz,1H), 6.90(d,j=6.9Hz, 1H); ^{13}C NMR (100MHz,$CDCl_3$) δ 128.6, 157.4, 151.3, 138.6, 134.7, 131.5, 134.4, 137.5, 126.0, 124.7, 117.7, 111.3 HRMS(EI) calcd. for $C_{14}H_8ClNO_2$ 257.0244, found 257.0248

1-(4-Bromophenyl)indoline-2,3-dione(6)

The product was isolated as a light orange solid.^{1}H NMR (400MHz,$CDCl_3$)δ 7.69-7.66(m,3H) 7.56(t,j=7.8Hz, 1H), 7.32(d,j=8.5Hz,2H), 7.20(t,j=7.5Hz, 1H), 6.90(d,j=8.0Hz, 1H); ^{13}C NMR (100MHz,$CDCl_3$) δ 182.5, 157.2,. 151.1, 138.6, 133.3, 132.0, 127.7, 125.9, 124.7, 122.6, 117.6, 111.3, HRMS(EI) calcd for $C_{14}H_8BrNO_2$ 300.9738, found 300.9742

1-(4-Iodophenyl)indoline-2,3-dione(7)

The product was isolated as an orange solid.^{1}H NMR (400MHz,$CDCl_3$)δ 7.88(d,j=8.5Hz, 2H), 7.69(d,j=7.51Hz, 1H), 7.56(t,j=7.8Hz,1H), 7.21-7.17(m, 3H), 6.90(d,j=8.0Hz, 1H); ^{13}C NMR (100MHz,$CDCl_3$) δ 182.5, 157.2, 151.1, 139.3, 138.6, 132.7, 127.8, 126.0, 124.8, 117.6, 11.3, 94.1; HRMS(EI) calcd for $C_{14}H_8INO_2$ 348.9600, found 348.9601

1-(2-Iodophenyl)indoline-2,3-dione(8)

The product was isolated as a ruby red solid.^{1}H NMR(400MHz,$CDCl_3$) δ 8.01 (d,j=7.9Hz,1H), 7.70(d,j=7.4Hz, 1H), 7.53-7.51(m, 2H), 7.36(d,j=7.6Hz, iH), 7.26-7.15(m, 2H), 6.49(d,j=8.0Hz, 1H); ^{13}C NMR(100MHz,$CDCl_3$)δ 182.6, 157.0, 151.3, 140.8, 138.7, 136.2, 131.5, 130.2, 129.7, 125.8, 124.5, 117.2, 111.8, 98.1; HRMS(EI) calcd for $[M+Na]^+$ ($M=C_{14}H_8INO_2$) 371.9492,found 371.9497

4-(2,3-Iodioxoindolin-1-yl)benzonitrile(9)

The product was isolated as a light orange solid.^{1}H NMR (400MHz,$CDCl_3$)δ 8.08(d,j=8.3Hz, 2H), 7.714-7.705(m, 3H), 7.64(t,j=7.8Hz, 1H), 7.23(t,j=7.51Hz,1H), 6.99(d,j=7.9Hz, 1H); ^{13}C NMR (100MHz,$CDCl_3$) δ181.9, 157.2, 150.0, 137.9, 137.6, 133.8, 127.0, 124.9, 124.1, 118.4, 117.9, 110.9, 110.5,; HRMS(EI) calcd. for $[M+H]^+$($M=C_{15}H_8N_2O_2$) 249.0659, found 249.0656

Ethyl-4-(2,3-dioxoindolin-1-yl)benzoate(10)

The product was isolated as a light orange solid.^{1}H NMR (400MHz,$CDCl_3$)δ 8.21(d,j=8.6Hz, 2H), 7.70(d,j=7.5Hz, 1H), 7.59-7.52(m, 3H), 7.20(t,j=7.51Hz,1H), 6.97(d,j=8.1Hz, 1H), 4.40(d,j=7.1Hz, 2H), 1.41(t,j=7.1Hz, 3H) ^{13}C NMR (100MHz,$CDCl_3$) δ 182.3, 165.6, 157.1, 150.9, 138.6, 136.9, 131.3, 130.6, 126.0, 125.5, 124.8, 117.7, 111.4, 61.5, 14.5; HRMS(EI) calcd for $C_{17}H_{13}NO_4$ 295.0839, found 295.0845

1-[4-(Trifluoromethyl)phenyl]indolin-2,3-dione(11)

The product was isolated as a bright orange solid.^{1}H NMR (400MHz,$CDCl_3$)δ 7.84(d,j=8.4Hz, 2H), 7.73(d,j=6.9Hz, 1H), 7.62-7.59(m, 3H), 7.23(t,j=7.5Hz,1H), 6.98(d,j=8.1Hz,

1H); ^{13}C NMR (100MHz,$CDCl_3$, extra peaks due to C-F coupling) δ 182.2, 157.2, 150.8, 138.7, 136.2, 131.0, 130.6, 128.9, 127.33, 127.29, 127.26, 127.22, 126.3, 126.1, 125.1, 125.0, 122.4, 117.7, 111.3, HRMS(EI) calcd. for $C_{15}H_8F_3NO_2$ 291.0507, found 291.0509

1-[3-(Trifluoromethyl)phenyl]indolin-2,3-dione(12)

The product was isolated as a yellow orange solid.^{1}H NMR (400MHz,$CDCl_3$)δ 7.74-7.65 (m, 5H), 7.60(td,j=1.2,8.0Hz, 1H), 7.23 (t,j=7.6Hz, 1H), 6.92(d,j=8.1Hz, 1H); ^{13}C NMR (100MHz,$CDCl_3$, extra peaks due to C-F coupling) δ 182.3, 157.3, 150.9, 138.7, 133.7, 130.9, 129.6, 126.1, 125.74, 125.70, 125.0, 123.04, 123.00, 117.7, 111.2; HRMS(EI) calcd. for $C_{15}H_8F_3NO_2$ 291.0507, found 291.0507

1-(2-tert-Butylphenyl)indolin-2,3-dione(13)

The product was isolated as a light orange solid.^{1}H NMR (400MHz,$CDCl_3$)δ 7.66(t,j=7.9Hz, 2H), 7.51(td,j=1.1, 7.8Hz, 1H), 7.44(t,j=7.7Hz, 1H), 7.34(td,j=1.3,7.5Hz, 1H), 7.14(t,j=7.5Hz, 1H), 7.05(dd,j=1.4,7.8Hz, 1H), 6.42(d,j=8.0Hz, 1H), 1.32(s, 9H); ^{13}C NMR (100MHz,$CDCl_3$, δ 183.4, 159.2, 154.1, 149.6, 138.7, 131.7, 130.5, 130.2, 129.4, 128.4, 125.4, 124.2, 11.8, 112.7, 35.8, 31.9; HRMS(EI) calcd. for $C_{18}H_{17}NO_2$ 279.1259, found 279.1259

1-((1,1 -Biphenyl)-2-Yl)indoline-2,3-dione(14)

The product was isolated as a red solid.^{1}H NMR(400MHz,$CDCl_3$) δ 7.56-7.53(m,4H), 7.40-7.36 (m,2H), 7.26-7.23(m,5H), 7.03(t,j=7.3Hz,1H), 6.48 (d,j=7.5Hz,1H), ^{13}C NMR(100MHz,$CDCl_3$)δ 182.8, 158.0, 152.2, 141.1, 138.3, 138.2, 131.7, 130.6, 130.1, 129.3, 128.74, 128.69, 128.2, 128.1, 125.4, 124.1, 117.2, 111.6, HRMS(EI) calcd for $C_{30}H_{11}NO_2$ 299.0946, found 299.0946

1-(2,4-Dimethoxyphenyl)indoline-2,3-dione(15)

The product was isolated as a orange solid.^{1}H NMR(400MHz,$CDCl_3$) δ 7.64(dd,j=7,7.5Hz,1H), 7.49(t,j=1.4,7.9Hz,1H), 7.11(td,j=0.73,7.5Hz, iH), 7.02-6.96(m,2H), 6.86(d,j=2.6Hz,1H), 6.59(d,j=8.0Hz,1H), 3.77(s, 3H), 3.73(s, 3H); ^{13}C NMR(100MHz,$CDCl_3$)δ 183.1, 157.7, 154.0, 152.2, 149.3, 138.4, 125.3, 124.0, 121.6, 117.6, 116.0, 114.7, 113.7, 111.8, 56.4, 56.0; HRMS(EI) calcd for $C_{16}H_{13}NO_4$ 283.0845 found 283.0839

1-Mesitylindoline-2,3-dione(16)

The product was isolated as a yellow orange solid.^{1}H NMR(400MHz,$CDCl_3$) δ 7.70(d,j=7.2Hz,1H), 7.51(t,j=7.7Hz, 1H), 7.16(t,j=7.5Hz, iH), 7.03(s,2H), 6.4(d,j=7.8Hz,1H), 2.35(s, 3H), 2.14(s, 6H); ^{13}C NMR(100MHz,$CDCl_3$)δ 13.2, 157.5, 151.7, 139.8, 138.8, 136.3, 129.9, 128.0, 125.8, 124.3, 117.7, 111.2, 21.3, 18.1; HRMS(EI) calcd for $C_{17}H_{15}NO_2$ 265.1100 found 265.1103

1-(Naphthalen-1-yl)indoline-2,3-dione(17)

The product was isolated as an orange solid.^{1}H NMR(400MHz,$CDCl_3$) δ 8.02 (d,j=8.2 Hz,1H), 7.98(d,j=8.2Hz, 1H), 7.75 (d,j=7.3Hz, iH), 7.70 (t,j=8.4Hz, 1H), 7.64-7.49 (3,4H), 7.45 (td, j=1.1, 7.9Hz,1H), 7.17(t,j=7.5Hz, 1H), 6.44(d,j=8.0Hz, 1H), 6H); ^{13}C NMR (100MHz, $CDCl_3$) δ 183.1, 158.2, 152.8, 138.8, 135.0, 130.4, 129.5, 129.0, 127.6, 127.1, 126.0,. 125.7, 124.4, 122.6, 117.6, 112.0; HRMS(EI) calcd for $C_{18}H_{11}NO_2$ 273.0790 found 273.0786.

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