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Catalyst free synthesis of spiro derivatives of isatin using multicomponent reactions

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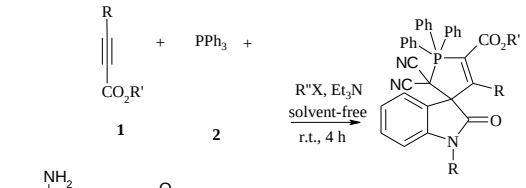
Abstract: The reaction of aniline, oxalylchloride, malononitrile, activated acetylenic compounds and PPh_3 led to spirocompounds of isatines in excellent yields under solvent free conditions at room temperature.

Keywords: Acid chlorides, Ammonium thiocyanate, *N*-formylmorpholine, 3-Hydroxy-2-butanone, Esterification.

Introduction

Spiro compounds having cyclic structures fused at a central carbon are of interest due to their interesting conformational features and their structural implications on biological systems [1]. The asymmetric characteristic of the molecule due to the chiral spiro carbon is one of the important criteria of the biological activities. The presence of the sterically constrained spiro structure in various natural products also adds to the interest in the investigations of spiro compounds [2]. The basic principles of dipolar cycloaddition reactions were provided by the work of Huisgen and co-workers [3]. Recently, multicomponent reactions (MCRs) are more interesting type of reaction due to mixing three or more reactants in one-pot and generating one product [4-10] and economically useful and environmentally secure than to multi-step methods. MCRs are very important in the synthesis of new drugs and agrochemicals [11-18]. In the multistep reaction generally due to multiple stages of separation of product, generate large amounts of waste that often involve the employ of pricey, poisonous or unsafe solvents in all stage.

The one-pot generation of compounds with small heterocycle display of different and intricate compounds with little heterocycles shows a powerful method in synthetic chemistry [19]. As a result, a large number of methods have appeared describing novel syntheses of spiro compounds. The reaction of aniline **1**, oxalylchloride **2**, malononitrile **3**, activated acetylenic compounds **4** and PPh_3 **5** led to spirocompounds of isatines **6** in excellent yields (Scheme **1**).



6	R	R'	R"	%Yield of **6**
a	CO_2Me	Me	Me	95
b	CO_2Me	Me	Et	92
c	CO_2Me	Me	Bn	90
d	H	Me	Me	87
e	H	Et	Et	90
f	H	Et	Bn	93

Scheme 1: Synthesis of spiro derivatives

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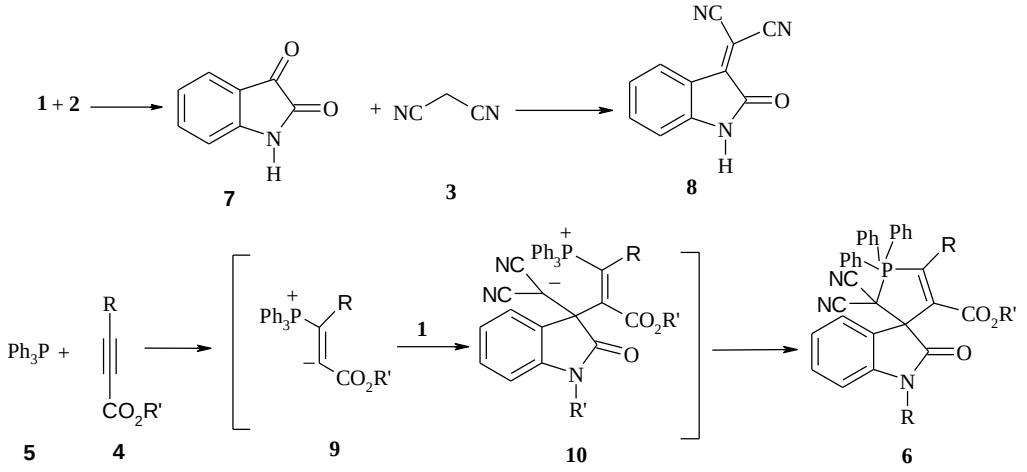
Result and Discussion

Structures of compounds **6a**–**6f** were apparent from their mass spectra, which displayed, in each case, the molecular ion peak at appropriate *m/z* values. The ^{1}H- and ^{13}C-NMR spectroscopic data, as well as IR spectra, are in agreement with the proposed structures. The ^{1}H-NMR spectrum of **6a** exhibited a singlet at (δ = 3.25 ppm) arising from the *N*Me proton. The carbonyl groups resonances in the ^{13}C-NMR spectra of **6a** appear at δ = 168.4 ($^{3}J_{CP}$ = 21.2) and 169.7 ppm. The mass spectrum of **6a** displayed the molecular ion peak at *m*/*z* = 521, which is consistent with the 1:1:1:1:1 adduct of aniline, oxalylchloride, malononitrile, activated acetylenic compounds and PPh_3.

Mechanistically, it is conceivable that the reaction involves the initial formation of a 1,3-dipolar intermediate **5** between triphenylphosphine **5** and activated acetylenic compounds **4**, which reacts with the carbonyl group of *N*-alkylisatin to produce **10**. Cyclization of this zwitterionic intermediate leads to the spiro compound **6** (Scheme **2**).



Scheme 2: Proposed mechanism for the synthesis of **4**

Conclusion

In summary, the reaction of aniline, oxalylchloride, malononitrile, activated acetylenic compounds and PPh_3 led to spiro derivatives with potential synthetic interest. The present procedure has the advantage that the reaction is performed under neutral conditions, and the starting material can be used without any activation or modification.

Experimental

M.p.: *Electrothermal-9100* apparatus; uncorrected. IR Spectra: *Shimadzu IR-460* spectrometer. ^{1}H-, ^{13}C-, and ^{31}P-NMR spectra: Bruker DRX-500 AVANCE instrument; in $CDCl_3$ at 500.1, 125.7, and 202.4 MHz, resp.; δ in ppm, *J* in Hz. EI-MS (70 eV): Finnigan-MAT-8430 mass spectrometer, in *m/z*. Elemental analyses (C, H, N) were performed with a Heraeus CHN-O-Rapid analyzer.

All of chemicals were obtained from *Fluka* and were used without further purification. Alkylisatins were prepared according to the literature procedure [20].

General procedure for preparation of compounds 6a-f

To a stirred solution of aniline **1** (2 mmol), oxalylchloride **2** (2 mmol) after 20 min was added malononitrile **3** (2 mmol) and new mixture was stirred for 30 min. the mixture of activated acetylenic compounds and PPh_3 was added to final mixture and the reaction mixture was stirred for 4 h. After completion of reactions (monitored by TLC (5:1) n-hexane/ethyl acetate, 15 mL water poured into the mixture of reaction. The solid residue was filtered and washed with Et_2O to afforded pure title compounds.

Methyl 1,2-dihydro-2-oxo-1-methyl-spiro-[3H-indol-2,2,2-triphenyl-2,5-dihydro-oxaphosphole]-4-carboxylate (6a):

Yellow crystals, mp 210-212°C, 0.98 g, yield 94%. IR (KBr) (ν_{max}/cm^{-1}): 1726, 1682, 1459, 1110, 1031

and 1009. MS, *m/z* (%): 521(M^+, 5), 476 (66), 278 (85), 243(64), 201 (62), 111 (34), 169 (100), 45 (100). Anal. Calcd for $C_{32}H_{28}NO_4P$ (521.5): C, 73.69; H, 5.41; N, 2.69; found: C, 73.70; H, 5.40; N, 2.70%. ^{1}H-NMR: δ 1.25 (3 H, t, $^3J_{HH}$ = 7.2 Hz, Me), 3.25 (3 H, s, NMe), 4.17 (2 H, q, $^3J_{HH}$ = 7.2 Hz, OCH_2), 6.89 (1 H, d, $^2J_{HP}$ = 22.7 Hz, CH), 7.09 (1 H, d, $^3J_{HH}$ = 7.2 Hz, CH), 7.32 (1 H, t, $^3J_{HH}$ = 7.3 Hz, CH), 7.42 (1 H, d, $^3J_{HH}$ = 7.3 Hz, CH), 7.48 (1 H, d, $^3J_{HH}$ = 7.2 Hz, CH), 7.52-7.78 (15 H, m, 15 CH). ^{13}C-NMR: δ 14.3 (Me), 28.1 (NMe), 61.7 (OCH_2), 91.2 (d, $^2J_{CP}$ = 49.1 Hz, C_{ipso}), 116.7 (CH), 120.3 (CH), 123.6 (CH), 128.1 (CH), 128.6 (d, $^3J_{CP}$ = 10.2 Hz, C), 129.2 (d, $^3J_{CP}$ = 21.1 Hz, 6 CH), 129.4 (3 CH), 131.9 (d, $^2J_{CP}$ = 31.9 Hz, CH), 135.1 (d, $^1J_{CP}$ = 230.1 Hz, 3 C), 149.3 (d, $^1J_{CP}$ = 192.3 Hz, CH), 150.4 (C), 157.3 (d, $^2J_{CP}$ = 19.3 Hz, C), 168.4 (d, $^3J_{CP}$ = 21.2 Hz, C=O), 169.7 (d, $^3J_{CP}$ = 17.4 Hz, C=O). ^{31}P-NMR: δ 50.35.

Methyl 1,2-dihydro-2-oxo-1-ethyl-spiro-[3H-indol-2,2,2-triphenyl-2,5-dihydro-oxaphosphole]-4-carboxylate (6b):

Yellow powder, mp 196-198°C, 0.96 g, yield 90%. IR (KBr) (ν_{max}/cm^{-1}): 1727, 1680, 1450, 1100, 1029 and 1010. MS, *m/z* (%): 535(M^+, 15), 490 (74), 461(54), 278 (68), 257 (62), 175 (34), 74 (46), 45 (94). Anal. Calcd for $C_{33}H_{30}NO_4P$ (535.6): C, 74.01; H, 5.65; N, 2.62; found: C, 74.00; H, 5.60; N, 2.60%. ^{1}H-NMR: δ 1.24 (3 H, t, $^3J_{HH}$ = 7.2 Hz, Me), 1.37 (3 H, t, $^3J_{HH}$ = 7.2 Hz, Me), 4.13 (2 H, q, $^3J_{HH}$ = 7.2 Hz, OCH_2), 4.35 (2 H, m, CH_2), 6.75 (1 H, d, $^2J_{PH}$ = 25.4 Hz, CH), 7.34 (1 H, d, $^3J_{HH}$ = 7.2 Hz, CH), 7.42 (1 H, t, $^3J_{HH}$ = 7.2 Hz, CH), 7.50 (1 H, d, $^3J_{HH}$ = 7.3 Hz, CH), 7.73 (1 H, d, $^3J_{HH}$ = 7.2 Hz, CH), 7.45-7.84 (15H, m, 15 CH).^{13}C-NMR: δ 13.3 (Me), 14.0 (Me), 38.4 (CH_2), 62.1 (OCH_2), 93.2 (d, $^2J_{CP}$ = 35.4 Hz, C_{ipso}), 118.3 (CH), 120.4 (CH), 124.2 (CH), 127.4 (CH), 127.9 (d, $^3J_{CP}$ = 8.0 Hz, C), 128.4 (d, $^3J_{CP}$ = 21.1 Hz, 6 CH), 129.1 (3 CH), 132.0 (d, $^2J_{CP}$ = 31.9 Hz, 6 CH), 135.4 (d,$^1J_{CP}$ = 226.5 Hz, 3 C), 144.1 (d, $^1J_{CP}$ = 194.1 Hz, CH), 149.2 (C), 154.2 (d, $^2J_{CP}$ = 15.4 Hz, C), 166.5 (d, $^3J_{CP}$ = 21.2 Hz, C=O), 168.7 (d, $^3J_{CP}$ = 19.8 Hz, C=O). ^{31}P-NMR: δ 52.42.

Methyl 1,2-dihydro-2-oxo-1-benzyl-spiro-[3H-indol-2,2,2-triphenyl-2,5-dihydro-oxaphosphole]-4-carboxylate (6c):

Pale yellow crystals, mp 223-225°C, 1.01 g, yield 85%. IR (KBr) (ν_{max}/cm^{-1}): 1730, 1685, 1462, 1210, 1054 and 1022. MS, *m/z* (%): 597(M^+, 10), 506 (70), 319 (64), 278 (64), 217 (62), 91 (96), 45 (100). Anal. Calcd for $C_{38}H_{32}NO_4P$ (597.65): C, 76.37; H, 5.40; N, 2.34; found: C, 76.40; H, 5.40; N, 2.35%. ^{1}H-NMR: δ 1.23 (3 H, t, $^3J_{HH}$ = 7.2 Hz, Me), 4.24 (2 H, q, $^3J_{HH}$ = 7.2 Hz, OCH_2), 4.82 (2 H, m, CH_2), 6.94 (1 H, d, $^2J_{PH}$ = 20.8 Hz, CH), 7.15 (1 H, d, $^3J_{HH}$ = 7.2 Hz, CH); 7.26-7.29 (3 H, m, 3 CH), 7.34 (1 H, d, $^3J_{HH}$ = 7.2 Hz, 2 CH), 7.37 (1 H, t, $^3J_{HH}$ = 7.2 Hz, CH), 7.44 (1 H, d, $^3J_{HH}$ = 7.3 Hz, CH), 7.45-7.80 (16 H, m, 16 CH). ^{13}C-NMR: δ 14.1 (Me), 49.2 (CH_2), 61.4 (OCH_2), 91.7 (d, $^2J_{CP}$ = 30.2 Hz, C_{ipso}), 117.4 (CH), 120.0 (CH), 122.4 (2 CH), 123.9 (CH), 125.8 (CH), 127.9 (2 CH), 128.2 (CH), 128.6 (d, $^3J_{CP}$ = 9.4 Hz, C), 129.1 (*d*, $^3J_{CP}$ = 18.5 Hz, 6 CH), 129.9 (3 CH), 132.4 (d, $^2J_{CP}$ = 28.4 Hz, 6 CH), 135.6 (C), 137.4 (d,$^1J_{CP}$ = 230.2 Hz, 3 C), 145.4 (d, $^1J_{CP}$ = 201.3 Hz, CH), 150.4 (C), 157.1 (d, $^2J_{CP}$ = 16.2 Hz, C), 169.5 (d, $^3J_{CP}$ = 23.5 Hz, C=O), 170.1 (d, $^3J_{CP}$ = 20.1 Hz, C=O). ^{31}P-NMR: δ 59.58.

Dimethyl 1,2-dihydro-2-oxo-1-methyl-spiro-[3H-indol-2,2,2-triphenyl-2,5-dihydro-oxaphosphole]-3,4-dicarboxylate (6d):

Pale yellow crystals, mp 195-197°C, 0.85 g, yield 75%. IR (KBr) (ν_{max}/cm^{-1}): 1752, 1732, 1672, 1478, 1135, 1097 and 1019. MS, *m/z* (%): 565 (M^+, 15), 533 (85), 502 (72), 403 (54), 278 (96), 161 (38), 146 (88), 31 (100).Anal. Calcd for $C_{33}H_{28}NO_6P$ (565.56): C, 70.08; H, 4.99; N, 2.48; found: C, 70.10; H, 5.00; N, 2.45%. ^{1}H-NMR: δ 3.27 (3 H, s, NMe), 3.69 (3 H, s, OMe), 3.98 (3 H, s, OMe), 6.91 (1 H, d, $^3J_{HH}$ = 7.2 Hz, CH), 7.08 (1 H, t, $^3J_{HH}$ = 7.3 Hz, CH), 7.11 (1 H, d, $^3J_{HH}$ = 7.3 Hz, CH), 7.43 (1 H, d, $^3J_{HH}$ = 7.2 Hz, CH), 7.47-7.84 (15 H, m, 15 CH). ^{13}C-NMR: δ 26.9 (NMe), 51.7 (OMe), 52.3 (OMe), 90.1 (d, $^2J_{CP}$ = 51.2 Hz, C_{ipso}), 116.7 (CH), 120.3 (CH), 123.6 (CH), 128.1 (CH), 128.6 (d, $^3J_{CP}$ = 22.4 Hz, C), 129.2 (d, $^3J_{CP}$ = 21.1 Hz, 6 CH), 129.4 (3 CH), 131.9 (d, $^2J_{CP}$ = 31.9 Hz, 6 CH), 135.1 (d, $^1J_{CP}$ = 230.1 Hz, 3 C), 149.3 (C), 150.4 (d, $^1J_{CP}$ = 192.3 Hz, C), 163.0 (d, $^2J_{CP}$ = 24.2 Hz, C=O), 165.1 (C), 168.4 (d, $^3J_{CP}$ = 21.2 Hz, C=O), 169.7 (C=O). ^{31}P-NMR: δ79.45.

Diethyl 1,2-dihydro-2-oxo-1-methyl-spiro-[3H-indol-2,2,2-triphenyl-2,5-dihydro-oxaphosphole]-3,4-dicarboxylate (6e):

Yellow powder, mp 190-192°C, 0.89 g, yield 75%. IR (KBr) (ν_{max}/cm^{-1}): 1727, 1720, 1643, 1478, 1166, 1086 and 1004. MS, *m/z* (%): 593 (M^+, 10), 548 (82), 503 (76), 315 (54), 278 (96), 161 (46), 146 (88), 45 (100). Anal. Calcd for $C_{35}H_{32}NO_6P$ (593.6): C, 70.82; H, 5.43; N, 2.36; found: C, 70.80; H, 5.40; N, 2.35%. ^{1}H-NMR: δ 1.23 (3 H, t, $^3J_{HH}$ = 7.2 Hz, Me), 1.48 (3 H, t, $^3J_{HH}$ = 7.2 Hz, Me), 3.25 (3 H, s, NMe), 3.84 (2 H, q, $^3J_{HH}$ = 7.2 Hz, OCH_2), 4.08 (2 H, q, $^3J_{HH}$ = 7.2 Hz,

OCH_2), 6.95 (1 H, t, $^3J_{HH}$ = 7.2 Hz, CH), 7.08 (1 H, d, $^3J_{HH}$ = 7.2 Hz, CH), 7.33 (1 H, d, $^3J_{HH}$ = 7.2 Hz, CH), 7.35-7.72 (16 H, m, 16 CH). ^{13}C-NMR: δ 13.0 (Me), 13.2 (Me), 26.4 (NMe), 61.4 (OCH_2), 62.4 (OCH_2), 92.0 (d, $^2J_{CP}$ = 49.5 Hz, C_{ipso}), 116.2 (CH), 119.5 (CH), 122.9 (CH), 127.9 (CH), 128.4 (d, $^3J_{CP}$ = 23.9 Hz, C), 130.1 (d, $^3J_{CP}$ = 20.1 Hz, 6 CH), 130.5 (3 CH), 132.0 (d, $^2J_{CP}$ = 32.9 Hz, 6 CH), 134.9 (d, $^1J_{CP}$ = 230.1 Hz, 3 C), 149.2 (C), 150.4 (d, $^1J_{CP}$ = 195.3 Hz, C), 162.9 (d, $^2J_{CP}$ = 23.6 Hz, C=O), 166.1 (C), 168.2 (d, $^3J_{CP}$ = 23.2 Hz, C=O), 169.2 (C=O). ^{31}P-NMR: δ 75.45.

Dimethyl 1,2-dihydro-2-oxo-1-benzyl-spiro-[3H-indol-2,2,2-triphenyl-2,5-dihydro--oxaphosphole]-3,4-dicarboxylate (4f):

Pale yellow crystals, mp 178-180°C, 0.89 g, yield 70%. IR (KBr) (ν_{max}/cm^{-1}): 1725, 1720, 1642, 1472, 1165, 1090 and 1012. MS, *m/z* (%): 641 (M^+, 10), 610 (84), 579 (74), 368 (54), 278 (96), 237 (46), 146 (88), 91 (96), 31 (100). Anal. Calcd for $C_{39}H_{32}NO_6P$ (641.66): C, 73.00; H, 5.03; N, 2.18; found: C, 73.00; H, 5.05; N, 2.20%. ^{1}H-NMR: δ 3.75 (3 H, s, OMe), 4.11 (3 H, s, OMe), 4.80 (1 H, d, $^2J_{HH}$ = 15.6 Hz, CH), 5.01 (1 H, d, $^2J_{HH}$ = 15.6 Hz, CH), 7.15 (1 H, d, $^3J_{HH}$ = 7.4 Hz, CH), 7.30 (1 H, t, $^3J_{HH}$ = 7.5 Hz, CH), 7.36 (1 H, d, $^3J_{HH}$ = 7.5 Hz, CH), 7.38 (2 H, t, $^3J_{HH}$ = 7.5 Hz, 2 CH), 7.45 (2 H, t, $^3J_{HH}$ = 7.7 Hz, 2 CH), 7.54 (2 H, d, $^3J_{HH}$ = 7.5 Hz, 2 CH), 7.62-7.84 (15 H, m, 15 CH). ^{13}C-NMR: δ 46.2 (NCH_2), 51.4 (OMe), 52.2 (OMe), 89.3 (d, $^2J_{CP}$ = 47.8 Hz, C_{ipso}), 116.5 (CH), 119.1 (CH), 123.4 (2 CH), 123.6 (CH), 125.9 (CH); 127.7 (2 CH), 128.3 (CH), 128.5 (d, $^3J_{CP}$ = 24.2 Hz, C), 128.9 (d, $^3J_{CP}$ = 20.1 Hz, 6 CH), 130.2 (3 CH), 132.4 (d, $^2J_{CP}$ = 34.2 Hz, 6 CH), 135.9 (C), 136.2 (d, $^1J_{CP}$ = 234.5 Hz, 3 C), 148.4 (C), 151.2 (d, $^1J_{CP}$ = 190.1 Hz, C), 162.4 (d, $^2J_{CP}$ = 26.5 Hz, C=O), 164.8 (C), 167.5 (d, $^3J_{CP}$ = 20.3 Hz, C=O), 169.5 (C=O). ^{31}P-NMR: δ 44.2.

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