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Catalytic Synthesis of Novel Fluoro-substituted Spiro[oxindole-isoxazolidine] Derivatives

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Abstract

The environmentally benign synthesis of ketonitrone may not always be accomplished by simple condensation reactions. The occasional reports of catalytic synthetic routes toward these compounds have been reported. The 1,3-dipolar cycloaddition reactions of *N*-substituted maleimides with fluoro-substituted isatin ketonitrone under catalytic conditions resulted in the synthesis of series of novel fluoro-substituted spiro[oxindole-isoxazolidine] derivatives in high yields, improved purity and short reaction times. Ecofriendly methyltrioxorhenium catalysed direct oxidation of isatin amine by urea hydrogen peroxide was substantially preferable that produces only water as a by-product. Besides the classical condensation of *N*-substituted hydroxylamines with carbonyls, direct oxidation of amines increased the rate of reaction. In present work, we described the utilization of UHP-metal catalyst systems for the direct conversion of isatin amine to isatin ketonitrone.

Keywords. *Catalytic chemistry,1,3-Dipolar cycloaddition, Spiro[oxindole-isoxazolidines]*

1. Introduction

Among all the 1,3-dipole, azomethine *N*-oxides are the building blocks of 'Huisgen reactions' which undergo cycloaddition reactions with variously substituted dipolarophiles having activated double bonds like maleimides,[1] cinnamoyl piperidines,[2] chiral Lewis acids and metal catalysed substrates.[3-6] Azomethine *N*-oxides are remarkable key intermediates, behave as electrophiles toward organic synthesis and organometallic chemistry. In recent times, metal derivatives promoted 1,3-dipolar cycloaddition reactions become an area of new research. Besides, azomethine *N*-oxides are useful spin trapping reagent in biological studies[7] and have applications as therapeutics in age-related diseases.[8] Azomethine *N*-oxides are prepared commonly by direct condensation of aldehydes with hydroxylamine and oxidation of secondary amines. Besides the classical condensation method for azomethine *N*-oxide syntheses, a number of alternative protocols become available. Whereas, only one procedure for the direct conversionof imines to azomethine *N*-oxides by using permanganate under phase-transfer conditions, along with serious drawbacks regarding selectivity[9] and disappointment to meet the expense of desired azomethine *N*-oxides from cyclic imines are reported.[10] The more availability of amines as compared to hydroxylamines, direct catalytic oxidation of amines is much more convenient.

Oxidation of imines to azomethine *N*-oxides have also been done by using the transition metal catalysts. Direct transformation of amines to azomethine *N*-oxides have employed hydrogen peroxide in water or other biphasic systems and use of hazardous materials. In recent years, the use of urea-hydrogen peroxide compex (UHP) with sodium wolframate or molybdate or selenium dioxide has many limitations.[11] Recently, Methyltrioxorhenium (MTO) is regarded as the potential candidate for desired oxidation of secondary amines to imines. UHP is a cheap, stable, easy-going and safe replacement to pure H_2O_2.[12] In continuation of above studies, oxaziridine has been synthesized by well-known procedure[13] and minimal effects of MTO and MTO/UHP in methanol has been noticed. During the past decade most of the synthetic methods for the generation of azomethine *N*-oxide took place in conventional organic solvents. Ecofriendly metal catalysed oxidation of amines by urea hydrogen peroxide is non-hazardous, safe method for the synthesis of azomethine *N*-oxide.[14]

2. Results and discussion

An insight into the literature survey reveals that azomethine *N*-oxides are usually quite unstable, frequently synthesized and react *in situ* in various chemical reactions. The two usual non-oxidative methods for azomethine *N*-oxide synthesis are direct condensation of *N*-mono substituted hydroxylamines with carbonyl compounds and the alkylation of oximes, but oxidative methods are the best techniques and are not much employed. Due to high efficacy of oxidative methods, metal catalysed per-acid oxidation of primary, secondary amines and imines has opened a new avenue for the development of different methodologies for azomethine *N*-oxide synthesis, utilizing only commercially accessible and non-hazardous materials under mild reaction conditions in aqueous medium. Therefore, this oxidative method has been used for the generation of azomethine *N*-oxide is considered as best substitute to the existing procedures for similar transformation. Eco-friendly methyltrioxorhenium catalysed direct oxidation of isatin amine by urea hydrogen peroxide in aqueous medium was substantially preferable that produces only water as a by-product. Besides the classical condensation of *N*-substituted hydroxylamines with carbonyls, direct oxidation of amines has also shown an increase in the rate of reaction. Literature survey also reveal that very small amount of work has been carried out in the catalytic synthesis of isatin ketonitrone owing to low reactivity of ketones and subsequently their 1,3-dipolar cycloaddition reaction have not been properly rationalised. So with a view to fill the gap in the literature metal catalysed oxidation method has been taken up. These considerations prompted us to establish an efficient route for the synthesis of novel fluoro-substituted isatin ketonitrones as substrates to prepare some novel fluoro-substituted spiro[oxindole-isoxazolidine] derivatives, subsequently uplifting the structural motifs of spiro-oxindole cores, which were characterized through their melting point, elemental analysis, IR, ^{1}H-NMR, ^{13}C-NMR, ^{1}H, ^{1}H-COSY, and mass spectral studies. All the

compounds have given satisfactory elemental analysis (Table 1).

Table 1. Characterisation data of spiro[oxindole -isoxazolidine]derivatives **5a-h**

Compounds	X	Yield[a] (%)	Time (min)	Melting point (°C)
5a	H	93	4	186-187
5b	4-Cl	91	6	176-177
5c	4-Br	83	9	196-198
5d	4-F	85	5	168-170
5e	4-I	86	11	205-206
5f	4-CH_3	90	8	190-191
5g	4-OCH_3	87	7	183-185
5h	4-C_2H_5	81	9	198-200

[a]Isolated yield of the pure compound

In the IR spectrum of 5-fluoro-2',5'-diphenyl-5',6a'-dihydrospiro[indoline-3,3'-pyrrolo[3,4-d]isoxazole]-2,4',6'(2'*H*,3a'*H*)-trione **5a,** revealed the presence of carbonyl stretching intense vibration band at 1776 cm^{-1} due to emergence of carbonyl stretching bands of oxindole moiety and one carbonyl group of succinimide ring while a shoulder band at frequency 1712 cm^{-1} was assigned to the second carbonyl group of succinimide ring. Absorption band at 3325 cm^{-1} was assigned to the -NH stretch of oxindole moiety.

In the ^{1}H-NMR spectrum, compound **5a** displayed two doublets at δ 5.10 with J = 7.54 Hz and δ 5.36 with J = 8.90 Hz respectively, for protons C_{3a}-H and C_{6a}-H on coupling with C_{6a}-H and C_{3a}-H. C_{6a}-H proton appears downfield in comparasion to C_{3a}-H proton due to electronegative oxygen atom attached to C_{6a}-H. Aromatic protons appeared as multiplets in the range of δ 6.94-7.33 (equivalent to 13H). It displayed a singlet at δ 10.32 for -NH proton of indolone moiety.

In the ^{13}C-NMR spectrum, compound **5a** displayed the characteristic signals at δ 172.33 and δ 171.80, which have been assigned to two succinimide carbonyl carbons. A signal at δ 169.88 has been assigned to carbonyl carbon of oxindole moiety. The signals in the range of δ 136.31-112.01 have been assigned to aromatic carbons. A signal at δ 76.45 has been assigned to spiro carbon C-3. Another two signals at δ 68.30 and δ 52.89 have been assigned to C_{6a} and C_{3a} carbon atoms, respectively. Each of the succinimide carbonyl carbon exhibited a downfield shift as compared to carbonyl carbon of oxindole moiety because of the more deshielding effect of the two carbonyl groups present in the succinimide moiety as compared to one carbonyl carbon of oxindole moiety. This is further supported by the ^{1}H-NMR data, the protons C_{3a}-H and C_{6a}-H appeared as doublets and their corresponding J values falling in the range of *cis*-orientation of the protons confirming that these two protons lie on one side thus only *cis*-isomer is formed.

3. Experimental

All the melting points are uncorrected. IR spectra were recorded on a Perkin Elmer RXIFT infrared spectrophotometer using KBr pellets. ^{1}H-NMR were recorded on 400-MHz Bruker avance spectrometer using TMS as internal standard. ^{13}C-NMR spectra were recorded on 100-MHz Bruker avance spectrometer using TMS as internal standard. MS (ESI) were recorded on Waters Micromass Q-TOF of Micro (LC-MS) spectrometer. TLC plates were coated with silica gel-G suspended in methanol-chloroform. Elemental analysis was carried out

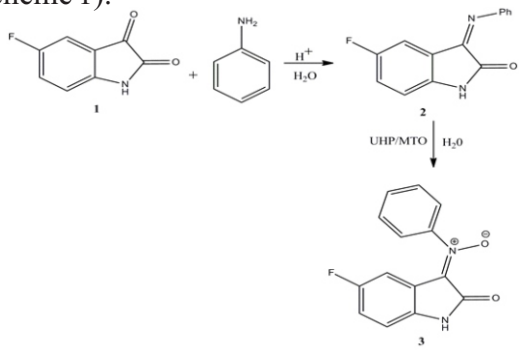
using Elementar vario MICRO cube CHN analyser.

3.1. General procedure for synthesis of isatin imine 2

All these compounds were prepared by reacting an equimolar quantities of 5-fluoroisatin **1** (1 mmol) and analine (1 mmol) in 20 mL of aqueous medium catalyzed by oxalic acid. The resulting mixture was stirred at room temperature. The progress of the reaction was monitored by TLC. On usual work up the reaction mixture provided the desired product **2 (Scheme 1)**.

3.2. General procedure for synthesis of isatin ketonitrone 3

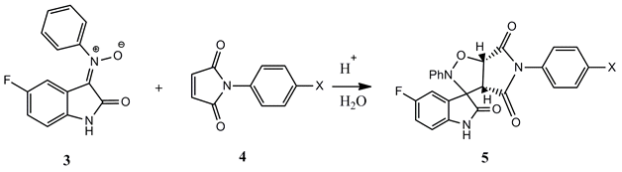
To a stirred solution of an isatin imine (1 mmol) in water (2 mL), urea hydrogen peroxide (3 mmol) and methyltrioxorhenium (0.02 mmol) were added. The resulting coloured solution was stirred at room temperature until disappearance of the starting material (as indicated by the TLC). After removal of the solvent under reduced pressure dichloromethane was added to the reaction mixture and the undissolved urea filtered off. The solvent was removed under high vacuum and the crude product was purified by flash column chromatography on silica gel (Scheme 1).



Scheme 1. Catalytic synthesis of isatin imine 2 and isatin ketonitrone 3

3.3. General procedure for synthesis of cycloadducts 5a-h

Their 1,3-dipolar cycloaddition reactions have been carried out by refluxing an equimolar quantities of the isatin ketonitrone **3** (1 mmol) and substituted maleimides **4** (1.5 mmol) in aqueous medium using catalytic amount of oxalic acid to provide cycloadducts **5a-h** in excellent yield. After completion of the reaction as judged by TLC, the reaction mixture was diluted with water, extracted with 2-MeTHF, dried over anhydrous sodium sulphate, filtered and the solvent was removed under high vacuum and the crude product was purified by column chromatography using hexane-ethyl acetate (9:1) as eluent to afford spiro-oxindole-isoxazolidine derivatives (Scheme 2).



X = -H: 4a; -Cl: 4b; -Br: 4c; -F: 4d; -I: 4e; -CH_3: 4f; -OCH_3: 4g; -C_2H_5: 4h

Scheme 2. Synthesis of cycloadducts 5a-h

3.3.1. 5-Fluoro-2',5'-diphenyl-5',6a'-dihydrospiro[indoline-3,3'-pyrrolo[3,4-d]isoxazole]-2,4',6'(2'H,3a'H)-trione (5a)

Compound obtained as a white solid (yield 93%), m.p. 186-187˚C; IR (KBr pellets, ν_{max}/cm^{-1}): 1712, 1776 (C=O), 3325 (N-H); ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 5.10 (d, 1H, J = 7.54 Hz), 5.36 (d, 1H, J = 8.90 Hz), 6.94-7.33 (m, 13H), 10.32 (s, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 52.89, 68.30, 76.45, 112.01,115.45, 122.33, 123.76, 124.24, 124.73, 126.52, 126.48, 126.45, 126.81, 127.38, 128.91, 133.13, 136.31, 169.88, 171.80, 172.33; MS: m/z: 429

[M^+], Anal. Calcd. For $C_{24}H_{16}N_3O_4F$: C, 67.13; H, 3.73; N, 9.79, Found: C, 67.15; H, 3.72; N, 9.80.

3.3.2. 5'-(4-chlorophenyl)-5-fluoro-2'-phenyl-5',6a'-dihydrospiro[indoline-3,3'-pyrrolo[3,4-d]isoxazole]-2,4',6'(2'H,3a'H)-trione (5b)

Compound obtained as a white solid (yield 91%), m.p. 176-177˚C; IR (KBr pellets, ν_{max}/cm^{-1}): 1707, 1776 (C=O), 3462 (N-H) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 4.99 (d, 1H, J = 7.43 Hz), 5.12 (d, 1H, J = 7.66 Hz), 6.35-7.87 (m, 12H), 10.02 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 52.60, 71.42, 76.34, 112.02, 115.47, 125.18, 126.89, 126.69, 127.70, 129.00, 129.06, 129.32, 129.88, 129.99, 132.99, 137.69, 142.45, 170.00, 173.62, 175.82; MS: m/z: 463 [M^+], 465 [M^+ + 2] Anal. Calcd. For $C_{24}H_{15}N_3O_4ClF$: C, 62.20; H, 3.24; N, 9.07, Found: C, 62.22; H, 3.23; N, 9.08.

3.3.3. 5'-(4-Bromophenyl)-5-fluoro-2'-phenyl-5',6a'-dihydrospiro[indoline-3,3'-pyrrolo[3,4-d]isoxazole]-2,4',6'(2'H,3a'H)-trione (5c)

Compound obtained as a white solid (yield 83%), m.p. 196-198˚C; IR (KBr pellets, ν_{max}/cm^{-1}): 1713, 1772 (C=O), 3412 (N-H) cm^{-1}, ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 4.82 (d, 1H, J = 7.64 Hz), 5.16 (d, 1H, J = 8.62 Hz), 6.66-7.84 (m, 12H), 10.42 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 53.10, 72.10, 77.66, 110.03, 117.47, 118.8, 126.00, 126.23, 126.95, 127.42, 128.06, 128.82, 129.30, 129.60, 135.02, 136.15, 140.30, 171.68, 174.42, 176.00; MS: m/z: 508 [M^+], 510 [M^++2], 512 [M^++4] Anal. Calcd. For $C_{24}H_{15}N_3O_4FBr$: C, 56.69; H, 2.95; N, 8.26, Found: C, 56.60; H, 2.92; N, 8.25.

3.3.4. 5-Fluoro-5'-(4-flourophenyl)-2'-phenyl-5',6a'-dihydrospiro[indoline-3,3'-pyrrolo[3,4-d]isoxazole]-2,4',6'(2'H,3a'H)-trione (5d)

Compound obtained as a white solid (yield 85%), m.p. 168–170˚C; IR (KBr pellets, ν_{max}/cm^{-1}): 1716, 1792 (C=O), 3457 (N-H) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ_H 4.12 (d, 1H, J = 7.06 Hz), 4.84 (d, 1H, J = 7.06 Hz), 6.48-7.79 (m, 12H), 9.90 (s, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 54.92, 70.62, 78.46, 113.03, 117.27, 125.89, 126.00, 127.70, 128.64, 128.69, 128.89, 129.90, 130.40, 132.62, 134.01, 140.36, 157.59, 171.21, 172.00, 173.35; MS: m/z: 447 [M^+] Anal. Calcd. For $C_{24}H_{15}N_3O_4F_2$: C, 64.43; H, 3.35; N, 9.39, Found: C, 64.46; H, 3.30; N, 9.40.

3.3.5. 5-Fluoro-5'-(4-iodophenyl)-2'-phenyl-5',6a'-dihydrospiro[indoline-3,3'-pyrrolo[3,4-d]isoxazole]-2,4',6'(2'H,3a'H)-trione (5e)

Compound obtained as a white solid (yield 86%), m.p. 205–207˚C; IR (KBr pellets, ν_{max}/cm^{-1}): 1710, 1782 (C=O), 3377 (N-H) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ_H 4.48 (d, 1H, J = 7.76 Hz), 4.99 (d, 1H, J = 7.80 Hz), 6.45-7.90 (m, 12H), 10.00 (s, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 64.93, 72.30, 79.62, 96.77, 113.01, 116.27, 125.54, 126.26, 126.88, 127.88, 128.04, 128.32, 128.77, 129.10, 130.30, 134.20, 139.26, 173.70, 174.99, 176.20; MS: m/z: 555 [M^+] Anal. Calcd. For $C_{24}H_{15}N_3O_4FI$: C, 51.89; H, 2.70; N, 7.56, Found: C, 51.86; H, 2.77; N, 7.49.

3.3.6. 5-Fluoro-2'-phenyl-5'-(4-methylphenyl)-5',6a'-dihydrospiro[indoline-3,3'-pyrrolo[3,4-d]isoxazole]-2,4',6'(2'H,3a'H)-trione (5f)

Compound obtained as a white solid (yield 90%)

m.p. 191-192˚C; IR (KBr pellets, ν_{max}/cm^{-1}): 1709, 1777 (C=O), 3366 (N-H) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 2.35 (s, 3H), 5.12 (d, 1H, J = 7.89 Hz), 5.48 (d, 1H, J = 8.10 Hz), 6.66-7.55 (m, 12H), 10.40 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 23.42, 59.80, 72.32, 76.48, 112.04, 116.22, 124.85, 125.90, 126.88, 126.89, 127.99, 128.15, 128.46, 128.68, 129.92, 132.99, 136.17, 139.79, 173.91, 175.26, 177.88; MS: m/z: 443 [M^+] Anal. Calcd. For $C_{25}H_{18}N_3O_4F$: C, 67.72; H, 4.06; N, 9.48, Found: C, 67.77; H, 4.00; N, 9.47.

3.3.7. 5-Fluoro-5'-(4-methoxyphenyl)-2'-phenyl-5',6a'-dihydrospiro[indoline-3,3'-pyrrolo[3,4-d]isoxazole]-2,4',6'(2'H,3a'H)-trione (5g)

Compound obtained as a white solid (yield 88%), m.p. 183-185˚C; IR (KBr pellets, ν_{max}/cm^{-1}): 1710, 1778 (C=O), 3273 (N-H) cm^{-1}, ^{1}H-NMR (400 MHz, DMSO-d_6): δ_H 3.68 (s, 3H), 4.88 (d, 1H, J = 7.86 Hz), 5.18 (d, 1H, J = 7.84 Hz), 6.16-7.70 (m, 12H), 10.06 (s, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 59.79, 66.32, 73.51, 80.06, 112.74, 115.55, 125.45, 125.99, 126.06, 126.75, 127.88, 128.40, 128.48, 128.90, 129.40, 133.13, 135.70, 142.28, 172.04, 174.08, 175.06; MS: m/z: 459 [M^+] Anal. Calcd. For $C_{25}H_{18}N_3O_5F$: C, 65.36; H, 3.92; N, 9.15, Found: C, 65.38; H, 3.72; N, 9.13.

3.3.8. 5'-(4-Ethylphenyl)-5-fluoro-2'-phenyl-5',6a'-dihydrospiro[indoline-3,3'-pyrrolo[3,4-d]isoxazole]-2,4',6'(2'H,3a'H)-trione (5h)

Compound obtained as a white solid (yield 81%), m.p. 198–200˚C; IR (KBr pellets, ν_{max}/cm^{-1}): 1710, 1782 (C=O), 3422 (N-H) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 1.24(t, 3H), 2.46(q, 2H), 4.88 (d, 1H, J = 7.79 Hz), 5.18 (d, 1H, J = 7.77 Hz), 6.89-7.72 (m, 12H), 10.04 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 15.58, 37.20, 56.82, 72.40, 76.42, 112.81, 115.67, 124.85, 125.00, 126.66, 127.79, 128.16, 128.88, 128.99, 129.25, 133.46, 136.88, 139.88, 141.42, 172.00, 174.02, 175.66; MS: m/z: 457 [M^+] Anal. Calcd. For $C_{26}H_{20}N_3O_4F$: C, 68.27; H, 4.38; N, 9.19, Found: C, 68.25; H, 4.34; N, 9.17.

4. Conclusions

This novel direct oxidation method of amines using UHP/MTO complex as catalyst in aqueous medium has been found to be an efficient, high yielding, gentle, straightforward chemo- and regioselective entry to isatin ketonitrone and ecofriendly as produces only water as a by-product. Utilization of methyltrioxorhenium in limited amount during reaction process indicates its high adaptability and wide scope of its applicability as catalyst in oxidation of many organic compounds. The striking features of this practice are significant yield in less time, easy to work-up and clean reaction methodology.

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