An Efficient Room Temperature Oxygen Radical Anion ($O_2^{\bullet-}$) Mediated One–Pot Multi–Component Synthesis of Spirooxindoles

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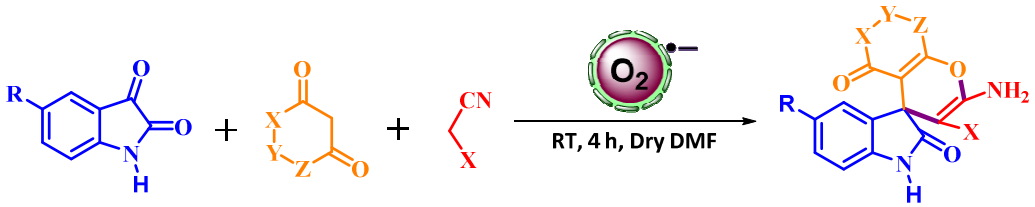
Abstract:



The present report highlights an efficient use of oxygen radical anion to promote a room temperature multi–component synthesis of spirooxindoles (**4a–l)** under mild reaction conditions. The potassium superoxide (KO_2) and tetraethylammonium bromide (TEAB) combination generate the oxygen radical anion *in situ* to promote this transformation. This method offers a sustainable and direct access to the biologically important spirooxindole derivatives in good to excellent yields.

***Keywords*:** Sustainable synthesis, Superoxide ion, Heterocycle synthesis, Room temperature transformation, Spirooxindoles.

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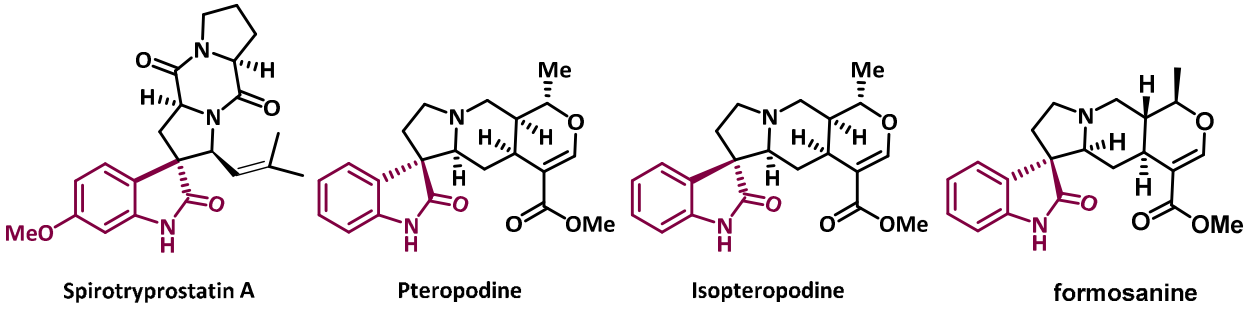
1. Introduction

The nitrogen–containing heterocycles are the prominent entities present in natural products and drug molecules. In particular, indole heterocycles exhibit a large spectrum of biological activities such as agonists of migraine associated $5HT_{1B}$ and $5HT_{1D}$ serotonin receptors [1], anti–convulsant [2], anti–depressant [3], anti–histamine [4], anti–obesity [5], anti–diabetic [6], and anti–allergic [7].

Spirocyclic structures are frequently found in numerous natural products, and their efficient synthesis is a formidable challenge for synthetic organic chemists [8-9]. Also, the creation of spirooxindole derivatives through the involvement of 3–carbon of indole further elevate the bioactivity of the indole core [10-13]. The high disease control properties of spirooxindole moiety is frequently utilized in the formulation of many active pharmaceutical ingredients [14-18]; for example spirotryprostatin A, an anti–mitotic agent[19], pteropodine and isopteropodine, modulators of rat muscarinic M1 and 5–HT2 receptors [20], and formosanine, which serves as an active anti–cancer agent (**Figure 1**)[21].



Spirotryprostatin A | Pteropodine | Isopteropodine | formosanine

Figure 1. Some biologically active spirooxindole–containing molecules.

The spirooxindole compounds are the most wanted synthetic targets because of their exclusive structural features and attractive drug like properties [22]. The fusion of the spirooxindole

ring system with pyranopyrimidine has significant biological relevance because of the analgesic and anticonvulsant activity and the effects of amphetamine–induced stereotypy of the resultant derivatives [23].

Azaspiro derivatives are frequently found in nature [24-28], however, the synthesis of the subsequent oxa analogs have received less attention [29]. Particularly, the chromene–indole hybrid molecules that display potential anti–depressant, anti–hypertensive, anti–tubulin, anti–viral and anti–oxidative activities [30-37]. Recent studies highlighted the potential application of tetrahydro–4*H*–chromene derivatives bearing nitrile functionality, i.e., 2–amino–5–oxo–5,6,7,8–tetrahydro–4*H*–chromene–3–carbonitriles for the effective treatment of human neurodegenerative disorders [38].

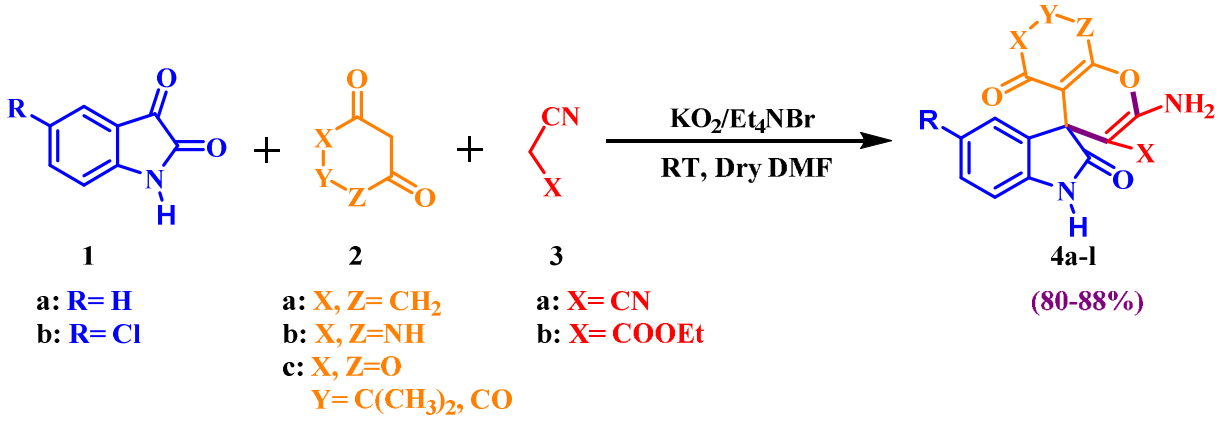
Because of their attractive biological activities, extensive efforts have been made to synthesize chromene based spirooxindoles by employing various metals and metal–free protocols [39-62]. The methods previously reported are helpful to access spirooxindoles in one–pot, but still they were suffered from various operational and practical issues ranging from the use of uncommon starting materials, specifically fabricated magnetic catalysts, strong acidic catalysts, and specialized reaction conditions. So, there is still enough room for the exploration of a highly efficient method for the synthesis of spirooxindoles.

The use of molecular oxygen as a promoter is an emerging area [63]. The academic and industrial research is currently focusing more on the search for new methods which generate molecular oxygen *in situ* and use it more efficiently to promote synthetic transformations [64]. The problems associated with the use of molecular oxygen as a promoter is its less reactivity, an essential requirement of low temperatures for activation, the necessity of highly expensive metals/metal surfaces and expensive techniques are needed to generate the more reactive species

or to bind an oxygen molecule [65]. Alternatively, reactive oxygen species (ROS) are the better and promising oxygen containing radicals, which show better reactivity to promote synthetic conversions[66-67]. The most interesting point to observe in all molecular oxygen promoted reactions is the intermediacy of ROS.

Superoxide ion ($O_2^{\bullet -}$) is a reactive oxygen species and have significant biological and synthetic relevance and the molecule of interest for current scientific investigations. Therefore, the research on the reactions promoted by $O_2^{\bullet -}$ can certainly provide better insights to understand the nature and behavior of $O_2^{\bullet -}$. The $O_2^{\bullet -}$ is a green oxidant and a reactive replacement of oxygen [68-69]. The *in situ* generation of $O_2^{\bullet -}$ from molecular oxygen requires an expensive and costlier electrochemical or electric arc methods. Alternatively, the simple and cheapest method includes the decomposition of a stable superoxide salt in the presence of a stable superoxide salt and a phase transfer catalyst [70-71].

In view of all the above facts, we are exploring an insitu generation of $O_2^{\bullet -}$ and first time utilizing it for a one–pot multicomponent synthesis of spirooxindoles **4** in excellent yields (80–88%) through the reaction of isatins **1**, dimedone/ barbituric acid and meldrum's acid **2** and malononitrile/ethyl cyanoacetate **3**, at room temperature (**Scheme 1**).



Scheme 1 Superoxide promoted one–pot three-component synthesis of spirooxindoles **4a–l.**

2. Experimental (Materials and methods)

2.1. General Information

The isatins, 1,3–diketones, malononitriles, promoters, additives, and solvents were purchased from Sigma–Aldrich Chemicals, USA, and E. Merck, Germany and were used as received. The Thin Layer Chromatography (TLC) was carried out on Merck Kieselgel 60 GF254 plates (thickness 0.25 mm). The solvent system employed was ethyl acetate: n–hexane (2:1) and the **TLC** spots were determined by UV or staining the TLC plate to iodine vapors. Infra Red (IR) spectra were recorded on a Perkin-Elmer FT–IR spectrometer. The NMR was conducted using a JEOL AL300 FT–NMR spectrometer (^{1}H NMR at 300 MHz, ^{13}C NMR at 75 MHz); chemical shifts are given in δ ppm, relative to TMS as an internal standard. Melting points were measured with a Stuart SMP 10 digital melting point apparatus.

2.2 General experimental procedure for the synthesis of compounds 4a–l

Potassium superoxide (2 mmol) and tetraethylammonium bromide (1 mmol) were weighed under N_2 atmosphere using an atmosbag and transferred into a three necked R. B. flask, dry DMF (20 mL) was added to it and the mixture was thoroughly mixed using a magnetic stirrer for 15 min to facilitate the formation of tetraethylammonium superoxide. To the stirred reaction mixture, ethylcyanoacetate/malononitrile (**3a, b)** (1 mmol) was added. After 10 min, the isatin derivatives (**1)** (1 mmol) and cyclic 1, 3–diketones (**2a–c)** (1 mmol) were introduced, and the stirring was continued for 4 h. After the reaction was over as indicated by TLC, the reaction mixture was treated with cold brine solution (2 mL) followed by saturated sodium hydrogen carbonate solution (2 mL) to decompose the unreacted KO_2. The mixture was then extracted with dicholoromethane (3 × 15 mL) and the combined organic phase was dried over anhydrous

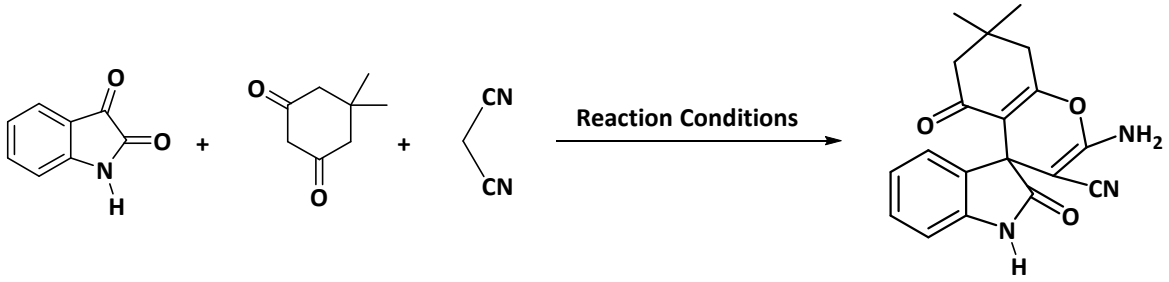
Na_2SO_4, filtered, and evaporated to give the products **4a–l**, which was purified by column chromatography.

3. Results and discussion

In order to establish an optimized reaction condition for the synthesis of spirooxindoles at room temperature a model reaction of isatin **1a**, dimedone **2a** and malononitrile **3a** was carried out in the presence of various unexplored oxidants under nitrogen atmosphere in different solvents like DMF, THF, CH_3CN, CH_2Cl_2, PEG, DMSO and H_2O at room temperature (**Table 1**). The solvent study showed that dry DMF provided the best yield. All the reactions were conducted in an inert atmosphere to avoid a possible helping hand from the oxygen present in the atmosphere. As it was reported in several investigations that atmospheric air/oxygen serves as a terminal oxidant for the regeneration of the catalytic species. In the present study, the investigations were carried out by using 50 mol% iodine as a catalyst in DMF for the synthesis of spirooxindoles at room temperature, but the iodine delivered the desired product in 27% yield only (entry 1). Some potential oxidants like tetrabutylammonium iodide (TBAI), sodium hypochlorite (NaOCl), perchloric acid ($HClO_4$), *tert*–butylhydroperoxide (TBHP), ceric ammonium nitrate (CAN), potassium periodide (KIO_3), diacetoxyiodobenzene ($PhI(OAC)_2$), ferrocene, potassium persulfate ($K_2S_2O_8$), hydrogen peroxide (H_2O_2), manganese dioxide (MnO_2), copper perchlorate ($CuClO_4$), calcium oxychloride ($CaOCl_2$), and sulphur (S_8) were screened but none of them provided a significant yield (entries 2–15). However, when 50 mol% of potassium superoxide (KO_2) was applied, the desired spirooxindole was formed in 57% yield (entry 16). This encouraging result further indicates that the potassium superoxide (K_2O) can be efficiently used for the optimization of the experimental protocol. A thorough revision of the literature suggested that the superoxide ion released from the KO_2 must act as a promoter. So, it

was envisioned that the additives which fasten the decomposition of KO_2 must increase the yield of the reaction (entries 17–19, 32–34). To test this, various phase transfer catalysts as additives were screened. And it was discovered that 200 mol% of KO_2 and 100 mol% of tetraethylammonium bromide (TEAB) act as the best combination to deliver the spirooxindoles in 88% yield at room temperature (entry 25).

Table 1 Evolution of reaction parameters the synthesis of **4a.**



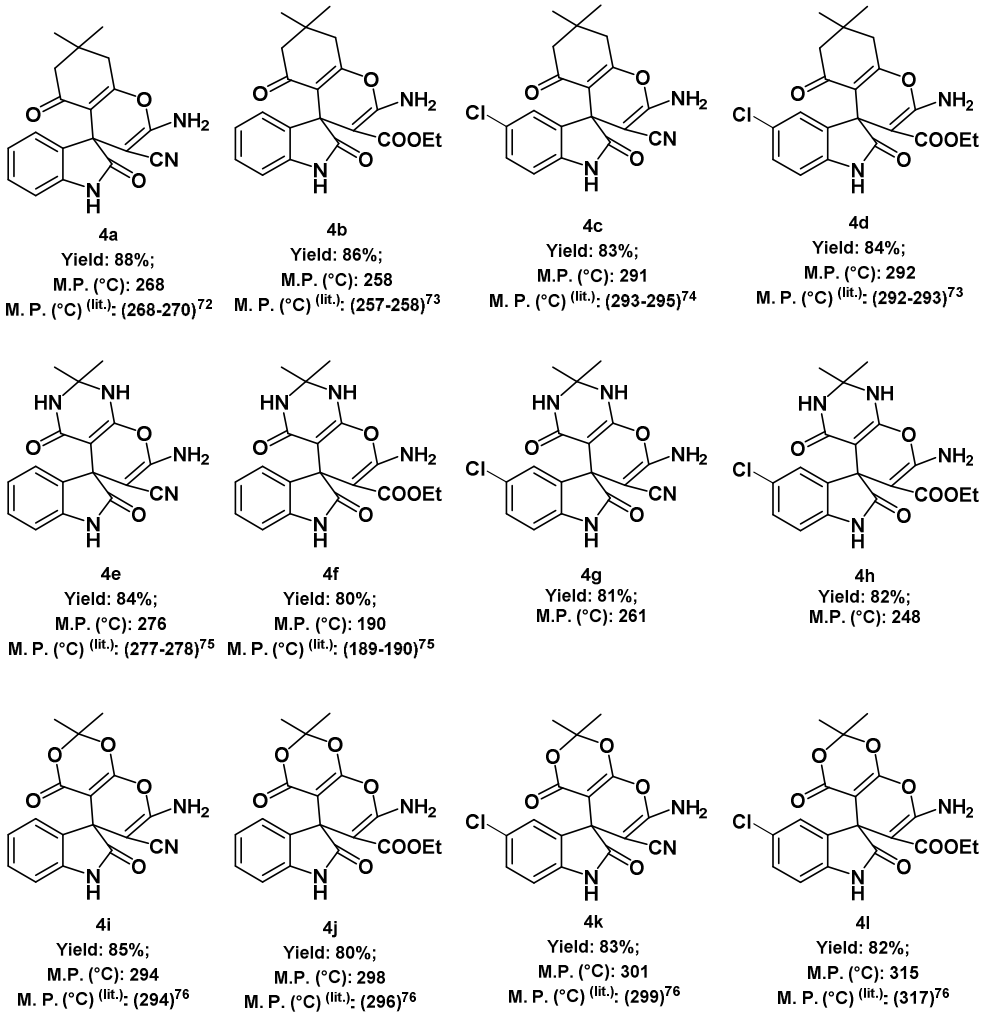
1a **2a** **3a** **4a**

Entry	Promoter (mol %)	Additive (mol %)	Atmosphere	Solvent	Temp (^{0}C)	Time (h)	Yield[a] (%)
1	I_2 (50)	—	N_2	DMF	rt	2	27
2	TBAI (50)	—	N_2	DMF	rt	2	15
3	NaOCl (50)	—	N_2	DMF	rt	2	30
4	$HClO_4$ (50)	—	N_2	DMF	rt	2	26
5	TBHP (50)	—	N_2	DMF	rt	2	20
6	CAN (50)	—	N_2	DMF	rt	2	17
7	KIO_3 (50)	—	N_2	DMF	rt	2	24
8	$PhI(OAc)_2$ (50)	—	N_2	DMF	rt	2	—
9	Ferrocene (50)	—	N_2	DMF	rt	2	35
10	$K_2S_2O_8$ (50)	—	N_2	DMF	rt	2	37
11	H_2O_2 (50)	—	N_2	DMF	rt	2	40
12	MnO_2 (50)	—	N_2	DMF	rt	2	22
13	$CuClO_4$ (50)	—	N_2	DMF	rt	2	28
14	$CaOCl_2$	—	N_2	DMF	rt	2	25
15	S_8 (50)	—	N_2	DMF	rt	2	33
16	KO_2 (50)	—	N_2	DMF	rt	2	57
17	KO_2 (50)	TBAF (50)	N_2	DMF	rt	2	30
18	KO_2 (50)	Et_3BnNCl (50)	N_2	DMF	rt	2	41
19	KO_2 (50)	TEAB (50)	N_2	DMF	rt	2	52
20	KO_2 (100)	TEAB (50)	N_2	DMF	rt	2	65
21	KO_2 (200)	TEAB (50)	N_2	DMF	rt	2	58
22	KO_2 (300)	TEAB (50)	N_2	DMF	rt	2	55
23	KO_2 (200)	TEAB (100)	N_2	DMF	rt	2	75
24	KO_2 (200)	TEAB (200)	N_2	DMF	rt	2	72
25	**KO_2 (200)**	**TEAB (100)**	**N_2**	**DMF**	**rt**	**4**	**88**

26	KO_2 (200)	TEAB (100)	O_2	DMF	rt	4	70
27	KO_2 (200)	TEAB (100)	air	DMF	rt	4	65
28	KO_2 (200)	TEAB (100)	N_2	DMSO	rt	4	15
29	KO_2 (200)	TEAB (100)	N_2	CH_3CN	rt	4	73
30	KO_2 (200)	TEAB (100)	N_2	CH_2Cl_2	rt	4	20
31	KO_2 (200)	TEAB (100)	N_2	THF	rt	4	45
32	KO_2 (200)	Aliquat 336 (100)	N_2	DMF	rt	4	35
33	KO_2 (200)	18–crown–6 (100)	N_2	DMF	rt	4	28
34	KO_2 (200)	TEAB (100)	N_2	DMF	60	4	15

[a]Reaction conditions: Isatin (**1a**) (**1 mmol**), dimedone (**2a**) (**1 mmol**), malononitrile (**3a**) (**1 mmol**). [b] Isolated yield after column chromatography.

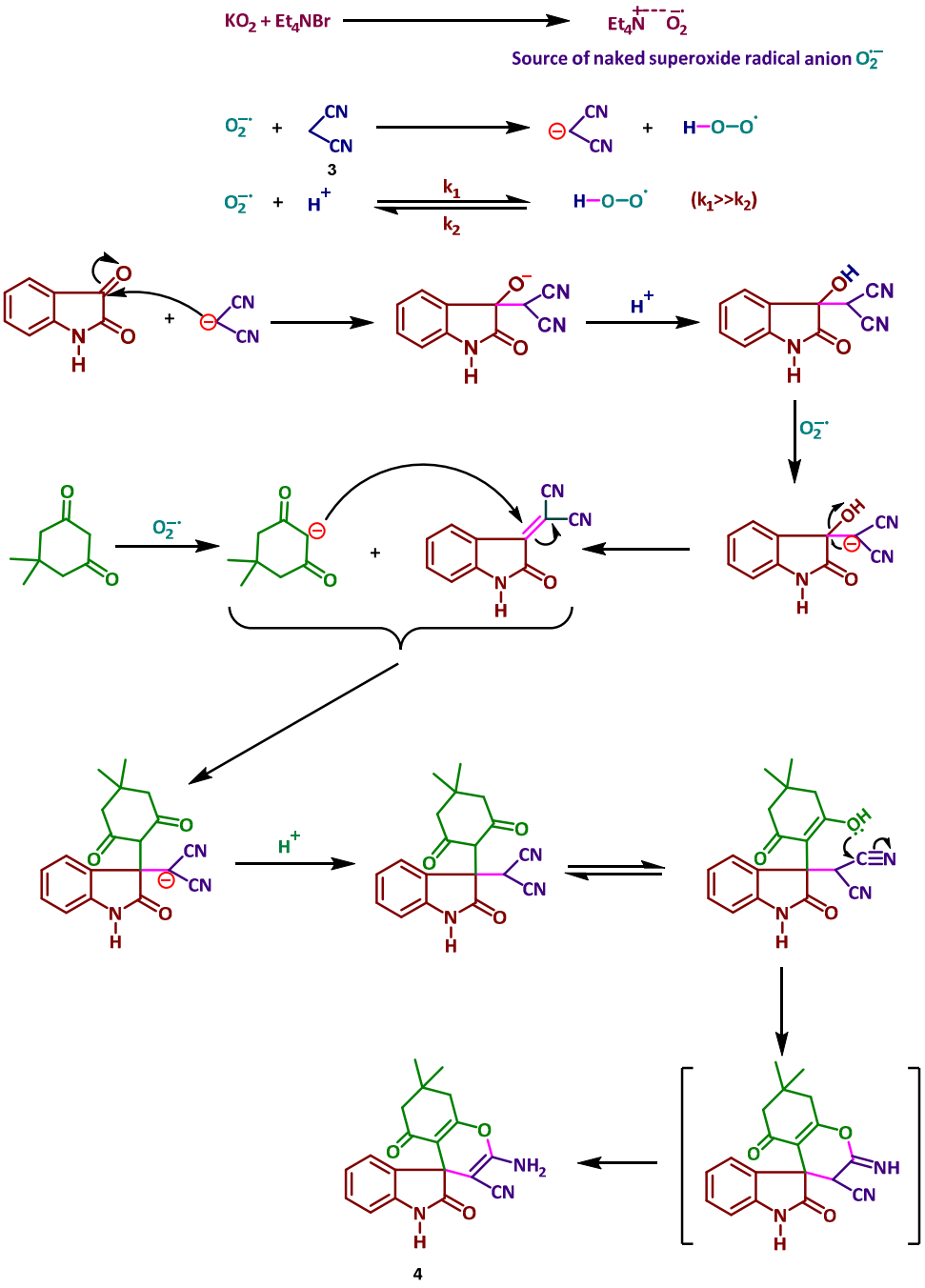
Table 2: Superoxide-mediated multicomponent synthesis of spirooxindole derivatives **4**[a,b.]



[a]Reaction of isatin derivatives (**1)** (1 mmol), cyclic 1, 3–diketones (**2a–c)** (1 mmol), and ethylcyanoacetate/malononitrile (**3a, b)** (1 mmol) using KO_2 (2 mmol) and TEAB (1 mmol) in dry DMF at rt for 4 h. [b]Isolated yield after column chromatography.

The optimized reaction conditions in hand, the generality of the reaction was further explored. A set of isatin (**1a**) and 5–chloroisatin (**1b**) were allowed to undergo a KO_2/TEAB promoted reaction with dimedone (**2a**), barbituric acid (**2b**) and meldrum's acid (**2c**); and malononitrile (**3a**)/ethyl cyanoacetate (**3b**) in DMF at room temperature. The unsubstituted isatin served as a best partner in these reactions, when compared with 5–chloroisatin. Out of the three cyclic active methylene compounds used dimedone (**2a**) exhibited the best reactivity. A diverse set of pure substituted spirooxindoles (**4a–4l)** have synthesized in good to excellent yields (88–80). All the products were fully characterized based on their melting points, and spectral data (IR, ^{1}H NMR, and ^{13}C NMR).

Based on the reported literature[71, 77-79] and isolation of products, a plausible mechanism is proposed for the superoxide ion induced multicomponent synthesis of spirooxindoles **4a–l** has been described in the **Scheme 2**.



Scheme 2. Plausible reaction mechanism.

The reaction was triggered by the abstraction of a proton from active methylene compound **3** by the naked superoxide ion which was *in–situ* generated by the reaction of potassium superoxide with tetraethylammonium bromide. Now, Knoevenagel condensation takes

place between isatin 2 and active methylene compound 3; this gives the formation of *α, β*–unsaturated adduct. The 1,4–addition of 1,3–dione on *α, β*–unsaturated adduct followed by an intramolecular cyclization and subsequent [1,3]–sigmatropic proton shift led to the formation of product **4**.

3.1 Characterization data for synthesized spirooxindoles (4a–l)

2–Amino–7,7–dimethyl–2',5–dioxo–5,6,7,8–tetrahydrospiro[chromene–4,3'–indoline]–3–carbonitrile (4a):

Colorless solid; m.p. = 268 °C; IR (KBr, υ = cm^{-1}) 3403, 3252, 3017, 2981, 2978, 2838, 2802, 2213, 1708, 1691, 1669, 1610, 1600, 1558, 1453, 1386, 1270, 1184. ^{1}H NMR (300 MHz, DMSO–d_6): δ = 0.98 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 2.10–2.16 (m, 2H, CH_2), 2.55–261 (m, 2H, CH_2), 6.79–7.21 (m, 4H, ArH), 7.22 (s, 2H, NH_2), 11.02 (s, 1H, NH) ppm. ^{13}C NMR (75 MHz, DMSO–d_6): δ = 26.9, 27.6, 31.1, 36.2, 46.5, 50.1, 61.2, 111.2, 117.5, 120.5, 122.1, 127.3, 134.2, 145.4, 157.1, 162.8, 170.0, 191.8 ppm.

Ethyl–2–amino–7,7–dimethyl–2',5–dioxo–5,6,7,8–tetrahydrospiro[chromene–4,3'–indoline]–3–carboxylate (4b):

Colorless solid; m.p. = 258 °C; IR (KBr, υ = cm^{-1}): 3451, 3301, 3158, 2999, 2944, 2861 2815, 1733, 1711, 1685, 1675, 1621, 1608, 1590, 1551 1485, 1380, 1255, 1196; ^{1}H NMR (300 MHz, DMSO–d_6): δ = 0.77 (t, J = 6.5 Hz, 3H, Me), 0.99 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 2.04– 2.11 (m, 2H, CH_2), 2.61–2.65 (m, 2H, CH_2), 3.84 (q, 2H, J = 6.9 Hz, CH_2), 6.66–7.06 (m, 4H, ArH), 7.76 (s, 2H, NH_2), 10.54 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO–d_6): δ = 14.6, 26.2, 27.1, 30.9, 35.1., 46.9, 50.4, 59.6, 79.3, 106.8, 118.3, 121.2, 122.6, 126.9, 132.7, 143.4, 159.1, 165.0, 167.8, 174.2, 194.3 ppm.

2–Amino–5–chloro–7,7–dimethyl–2',5–dioxo–5,6,7,8–tetrahydrospiro[chromene–4,3'–indoline]–3–carbonitrile (4c): Colorless solid; m.p. = 291 °C; IR (KBr, υ = cm^{-1}) 3425, 3300, 3013, 2911, 2890, 2851, 2210, 1701, 1678, 1659, 1616, 1605, 1569, 1458, 1348, 1257, 1173; ^{1}H NMR (300 MHz, DMSO–d_6): δ = 0.97 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 2.16–2.22 (m, 2H, CH_2), 2.47–2.54 (m, 2H, CH_2), 6.80 –7.21(m, 3H, ArH), 7.24 (s, 2H, NH_2), 11.11 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO–d_6): δ = 26.8, 32.2, 37.3, 48.1, 50.5, 61.0, 109.3, 116.8, 121.7, 122.9, 127.1, 133.2, 142.5, 156.9, 160.1, 168.5, 191.1 ppm.

Ethyl–2–amino–5–chloro–7,7–dimethyl–2',5–dioxo–5,6,7,8–tetrahydrospiro[chromene–4,3'–indoline]–3–carboxlate (4d): Colorless solid; m.p. = 292 °C; IR (KBr, υ = cm^{-1}) 3393, 3203, 3022, 2985, 2941, 2878, 2815, 1729, 1712, 1694, 1672, 1610, 1606, 1569, 1481, 1375, 1224, 1170; ^{1}H NMR (300 MHz, DMSO–d_6): δ = 0.80 (t, 3H, J = 6.9 Hz, CH_3), 0.97 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 2.10–2.16 (m, 2H, CH_2), 2.51–2.58 (m, 2H, CH_2), 3.68 (q, 2H, J = 7.2 Hz, CH_2), 6.67–7.12 (m, 3H, ArH), 7.84 (s, 2H, NH_2), 10.51 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO–d_6): δ = 16.5., 27.2 27.5, 32.8, 37.6., 45.4, 48.9, 57.6, 74.1, 108.9, 117.5, 121.1, 122.8, 127.2, 135.7, 144.3, 158.1, 164.9, 167.1, 172.1, 190.1 ppm.

7'–amino–2,2',4'–trioxo–1',2',3',4'–tetrahydrospiro[indoline–3,5'–pyrano[2,3–d]pyrimidine]–6'–carbonitrile (4e):

Colorless solid; m.p. = 276 °C; IR (KBr, υ = cm^{-1}) 3423, 3298, 3134, 3001, 2213, 1701, 1682, 1620, 1609, 1566, 1453, 1372, 1289, 1192; ^{1}H NMR (300 MHz, DMSO–d_6): δ = 6.88–7.26 (m, 4H, aromatic protons), 7.56 (s, 2H, NH_2), 10.01 (s, 1H, NH), 11.10 (s, 1H, NH), 11.25 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO–d_6): δ = 48.1, 74.5, 87.2, 111.1, 121.1, 123.2, 126.4, 133.1, 142.5, 148.7, 151.2, 159.1, 162.2, 167.6, 175.1 ppm.

Ethyl7'–amino–2,2',4'–trioxo–1',2',3',4'–tetrahydrospiro[indoline–3,5'–pyrano[2,3–d]pyrimidine]–6'–carboxylate (4f):

Pale yellow solid; m.p. = 190 °C; IR (KBr, υ = cm^{-1}) 3405, 3315, 3188, 3014, 1732, 1705, 1680, 1621, 1614, 1558, 1491, 1347, 1270, 1188; ^{1}H NMR (300 MHz, DMSO–d_6): δ = 1.05–1.10 (t, J = 6.6, 3H, CH_3), 4.25–4.30 (q, J= 7.4, 2H, CH_2), 7.00–7.31 (m, 4H, aromatic protons), 7.86 (s, 2H, NH_2), 10.12 (s, 1H, NH), 10.99 (s, 1H, NH), 11.20 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO–d_6) δ = 13.9, 44.9., 60.3, 74.8, 88.1, 109.1, 119.3, 122.6, 127.8, 134.1, 144.1, 150.1, 153.2, 159.5, 163.2, 166.3, 177.1 ppm.

7'–amino–5–chloro–2,2',4'–trioxo–1',2',3',4'–tetrahydrospiro[indoline–3,5'–pyrano[2,3–d]pyrimidine]–6'–carbonitrile (4g):

Colorless solid; m.p. = 261 °C; IR (KBr, υ = cm^{-1}) 3430, 3263, 3111, 3020, 2234, 1710, 1685, 1622, 1612, 1572, 1460, 1352, 1248, 1171; ^{1}H NMR (300 MHz, DMSO–d_6): δ = 6.79–7.17 (m, 3H, aromatic protons), 7.95 (s, 2H, NH_2), 10.15 (s, 1H, NH), 11.18 (s, 1H, NH), 11.23 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO–d_6): δ = 48.9, 76.1, 89.5, 106.2, 120.9, 123.5, 127.1, 134.1, 144.3, 149.6, 152.7, 158.9, 162.2, 169.2, 179.3 ppm.

Ethyl 7'–amino–5–chloro–2,2',4'–trioxo–1',2',3',4'–tetrahydrospiro[indoline–3,5'–pyrano[2,3–d]pyrimidine]–6'–carboxylate (4h):

Pale yellow solid; m.p. = 248 °C; IR (KBr, υ = cm^{-1}) 3391, 3281, 3112, 2990, 1739, 1705, 1684, 1625, 1613, 1605, 1562, 1478, 1380, 1271, 1183; ^{1}H NMR (300 MHz, DMSO–d_6): δ = 1.15–1.21 (t, J= 7.2, 3H, CH_3), 4.21–4.26 (q, J= 7.2, 2H, CH_2), 6.92–7.23 (m, 3H, aromatic protons), 8.00 (s, 2H, NH_2), 10.20 (s, 1H, NH), 11.02 (s, 1H, NH), 11.21 (s, 1H, NH) ppm; ^{13}C NMR (75

MHz, DMSO–d_6): δ = 14.5, 49.1, 59.5, 76.6, 88.4, 106.2, 120.2, 122.3, 127.9, 134.1, 143.5, 148.3, 153.3, 158.2, 162.1, 168.1, 179.1 ppm.

7'–amino–2',2'–dimethyl–2,4'–dioxo–4'H–spiro[indoline–3,5'–pyrano[2,3–d][1,3]dioxine]–6'–carbonitrile (4i):

Pale yellow solid; m.p. = 294 °C; IR (KBr, υ = cm^{-1}) 3413, 3251, 3011, 2946, 2933, 2838, 2827, 2211, 1706, 1698, 1661, 1615, 1609, 1600, 1568, 1455, 1456, 1378, 1351, 1255, 1200; ^{1}H NMR (300 MHz, DMSO–d_6): δ = 1.41 (s, 6H, CH_3), 7.11–7.75 (m, 4H, aromatic protons), 8.12 (s, 2H, NH_2), 11.14 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO–d_6): δ = 24.9, 46.4, 75.6, 88.6, 105.0, 118.2, 122.6, 129.1, 135.9, 144.3, 145.6, 161.2, 163.4, 169.2 ppm.

Ethyl 7'–amino–2',2'–dimethyl–2,4'–dioxo–4'H–spiro[indoline–3,5'–pyrano[2,3–d][1,3]dioxine]–6'–carboxylate (4j):

Yellow solid; m.p. = 298 °C; IR (KBr, υ = cm^{-1}) 3391, 3259, 3033, 2968, 2941, 2823, 2810, 1735, 1710, 1701, 1658, 1620, 1613, 1599, 1571, 1449, 1435, 1389, 1363, 1251, 1185; ^{1}H NMR (300 MHz, DMSO–d_6): δ = 1.10–1.15 (t, J = 6.9, 3H, CH_3), 1.68 (s, 6H, CH_3), 4.20– 4.28 (q, J = 6.9, 2H, CH_2), 6.88–7.63 (m, 4H, aromatic protons), 8.00 (s, 2H, NH_2), 11.29 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO–d_6): δ = 13.9, 27.8, 48.5, 58.7, 79.2, 86.5, 110.0, 117.6, 121.2, 127.5, 129.2, 134.1, 142.5, 145.2, 158.1, 162.2, 164.2, 168.1, 188.8 ppm.

7'–amino–5–chloro–2',2'–dimethyl–2,4'–dioxo–4'H–spiro[indoline–3,5'–pyrano[2,3–d][1,3]dioxine]–6'–carbonitrile (4k):

Yellow solid; m.p. = 301 °C; IR (KBr, υ = cm^{-1}) 3400, 3261, 3023, 2978, 2959, 2877, 2855, 2227, 1711, 1703, 1665, 1618, 1610, 1590, 1570, 1465, 1435, 1372, 1352, 1264, 1192; ^{1}H NMR (300 MHz, DMSO–d_6): δ = 1.63 (s, 6H, CH_3), 6.92–7.54 (m, 3H, aromatic protons), 8.05 (s, 2H,

NH_2), 10.80 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO–d_6): δ = 25.1, 48.2, 72.2, 89.5, 107.3, 117.9, 123.5, 127.4, 132.1, 141.3, 145.7, 158.1, 162.3, 164.1, 167.8 ppm.

Ethyl 7'–amino–5–chloro–2',2'–dimethyl–2,4'–dioxo–4'H–spiro[indoline–3,5'–pyrano[2,3–d][1,3]dioxine]–6'–carboxylate (4l):

Yellow solid; m.p. = 315 °C; IR (KBr, υ = cm^{-1}) 3400, 3231, 3008, 2970, 2953, 2829, 2823, 1732, 1711, 1703, 1667, 1617, 1611, 1601, 1560, 1463, 1446, 1388, 1295, 1189; ^{1}H NMR (300 MHz, DMSO–d_6): δ = 1.02–1.08 (t, J = 7.2, 3H, CH_3), 1.56 (s, 6H, CH_3), 4.12–4.19 (q, J = 6.9, 2H, CH_2), 6.96–7.51 (m, 3H, aromatic protons), 8.12 (s, 2H, NH_2), 11.13 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO–d_6) δ = 14.2, 26.1, 46.5, 60.1, 75.2, 89.4, 112.8, 119.2, 122.7, 127.6, 128.8, 135.1, 141.9, 144.2, 159.1, 161.6, 164.5, 167.5, 184.1 ppm.

4. Conclusion

In conclusion, this work addresses the successful synthesis of a variety of spirooxindoles by employing a superoxide ion mediated one–pot multicomponent reaction of isatin derivatives, ethyl cyanoacetate/malononitrile and cyclic 1,3–diketones under ambient temperature. Further, the developed protocol explores the new avenues of the superoxide ion reactivity and focuses a limelight on the unexplored side of the superoxide ion chemistry.

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References

1. Kochanowska-Karamyan, A. J.; Hamann, M. T., *Chemical reviews* **2010,** *110* (8), 4489.
2. Gribble, G. W. *Indole Ring Synthesis: From Natural Products to Drug Discovery*. John Wiley & Sons2016.
3. Sarris, J.; Byrne, G. J., *Sleep medicine reviews* **2011,** *15* (2), 99.
4. Jain, R. P.; Chakravarty, S. Google Patents2017.
5. Kang, M.-C.; Ding, Y.; Kim, E.-A.; Choi, Y. K.; De Araujo, T.; Heo, S.-J.; Lee, S.-H., *Marine Drugs* **2017,** *15* (4), 119.
6. Singh, A.; Verma, R. K.; Kuhad, A.; Mall, R., *Medicinal Chemistry Research* **2017,** *26* (4), 745.
7. Zhao, Y.-L.; Cao, J.; Shang, J.-H.; Liu, Y.-P.; Khan, A.; Wang, H.-S.; Qian, Y.; Liu, L.; Ye, M.; Luo, X.-D., *Phytomedicine* **2017,** *27*, 63.
8. Verano, A. L.; Tan, D. S., *Israel Journal of Chemistry* **2017**.
9. Janssen-Müller, D.; Fleige, M.; Schlüns, D.; Wollenburg, M.; Daniliuc, C. G.; Neugebauer, J.; Glorius, F., *ACS Catalysis* **2016,** *6* (9), 5735.
10. Lindemann, M.; Deuther-Conrad, W.; Moldovan, R.; Sekhar, K. V. G. C.; Brust, P.; Wenzel, B., *Bioorganic & Medicinal Chemistry* **2017**.
11. Asif, M., *Universal Journal of Chemistry (UJC)* **2017,** *1* (1), 17.
12. Liu, T.; Li, C. B.; Yu, Y. Q.; Xu, D. Z., *ChemistrySelect* **2017,** *2* (10), 2917.
13. Sharma, A.; Piplani, P.; Mohamed, M. I.; Kandile, N. G.; Zaky, H. T.; Mahajan, P. S.; Nikam, M. D.; Chate, A. V.; Bobade, A. S.; Gill, C. H.
14. Fan, L.; Liao, C.-H.; Kang, Q.-R.; Zheng, K.; Jiang, Y.-C.; He, Z.-D., *Molecules* **2016,** *21* (8), 968.
15. Khandelwal, S.; Rajawat, A.; Kumar Tailor, Y.; Kulhari, A.; Kumar, M., *Current Organocatalysis* **2017,** *4* (1), 69.
16. Tang, M.-C.; Zou, Y.; Watanabe, K.; Walsh, C. T.; Tang, Y., *Chemical Reviews* **2016**.
17. Rottmann, M.; McNamara, C.; Yeung, B. K.; Lee, M. C.; Zou, B.; Russell, B.; Seitz, P.; Plouffe, D. M.; Dharia, N. V.; Tan, J., *science* **2010,** *329* (5996), 1175.
18. Wells, T. N., *Science* **2010,** *329* (5996), 1153.
19. Borthwick, A. D., *Chemical reviews* **2012,** *112* (7), 3641.
20. Kang, T.-H.; Matsumoto, K.; Tohda, M.; Murakami, Y.; Takayama, H.; Kitajima, M.; Aimi, N.; Watanabe, H., *European journal of pharmacology* **2002,** *444* (1), 39.
21. Pavlovska, T. L.; Redkin, R. G.; Lipson, V. V.; Atamanuk, D. V., *Molecular diversity* **2016,** *20* (1), 299.
22. Kattela, S.; Heerdt, G.; Correia, C. R., *Advanced Synthesis & Catalysis* **2017,** *359* (2), 260.
23. Wang, S.; Izquierdo, J.; Rodríguez-Escrich, C.; Pericàs, M. A., *ACS Catalysis* **2017,** *7*, 2780.
24. Vitnik, Ž. J.; Popović-Đorđević, J. B.; Vitnik, V. D., *Journal of Molecular Structure* **2017,** *1137*, 97.
25. Jung, H.; Aman, W.; Hah, J.-M., *Bioorganic & Medicinal Chemistry Letters* **2017**.
26. Moradi, R.; Ziarani, G. M.; Lashgari, N., *Organic Chemistry* **2017,** (part i), 148.
27. Roh, H. J.; Kim, S. Y.; Min, B. K.; Kim, J. N., *Tetrahedron Letters* **2017,** *58* (1), 21.
28. Xia, M.; Ma, R. Z., *Journal of Heterocyclic Chemistry* **2014,** *51* (3), 539.
29. Wang, X. N.; Zhang, Y. Y.; Ye, S., *Advanced Synthesis & Catalysis* **2010,** *352* (11-12), 1892.
30. Kaushik, N. K.; Kaushik, N.; Attri, P.; Kumar, N.; Kim, C. H.; Verma, A. K.; Choi, E. H., *Molecules* **2013,** *18* (6), 6620.
31. Gupta, N.; Goyal, D., *Chemistry of Heterocyclic Compounds* **2015,** *51* (1), 4.
32. Chen, L. Google Patents2004.
33. Arshad, M.; Bhat, A. R.; Hoi, K. K.; Choi, I.; Athar, F., *Chinese Chemical Letters* **2017**.
34. Ellis, G. P. *The chemistry of heterocyclic compounds, chromenes, chromanones, and chromones*. Vol. 31; John Wiley & Sons2009.

35. Zheng, B.-J.; Chan, K.-W.; Lin, Y.-P.; Zhao, G.-Y.; Chan, C.; Zhang, H.-J.; Chen, H.-L.; Wong, S. S.; Lau, S. K.; Woo, P. C., *Proceedings of the National Academy of Sciences* **2008,** *105* (23), 8091.
36. Smith, B. J.; Colman, P. M.; Von Itzstein, M.; Danylec, B.; Varghese, J. N., *Protein Science* **2001,** *10* (4), 689.
37. Honda, T.; Masuda, T.; Yoshida, S.; Arai, M.; Kaneko, S.; Yamashita, M., *Bioorganic & medicinal chemistry letters* **2002,** *12* (15), 1925.
38. Canul-Tec, J. C.; Assal, R.; Cirri, E.; Legrand, P.; Brier, S.; Chamot-Rooke, J.; Reyes, N., *Nature* **2017,** *544* (7651), 446. doi: 10.1038/nature22064.
39. Hojati, S. F.; Amiri, A. H.; Raouf, H., *Applied Organometallic Chemistry* **2017,** *31* (5). doi: 10.1002/aoc.3595.
40. Javanshir, S.; Saghiran Pourshiri, N.; Dolatkhah, Z.; Farhadnia, M., *Monatshefte fur Chemie* **2017,** *148* (4), 703. doi: 10.1007/s00706-016-1779-6.
41. Esmaeilpour, M.; Javidi, J.; Divar, M., *Journal of Magnetism and Magnetic Materials* **2017,** *423*, 232. doi: 10.1016/j.jmmm.2016.09.020.
42. Keshavarz, M., *Journal of the Iranian Chemical Society* **2016,** *13* (3), 553. doi: 10.1007/s13738-015-0765-y.
43. Chandam, D. R.; Mulik, A. G.; Patil, D. R.; Deshmukh, M. B., *Research on Chemical Intermediates* **2016,** *42* (2), 1411. doi: 10.1007/s11164-015-2093-3.
44. Kumari, P.; Nandi, S.; Kumar, G.; Khan, N. H.; Kureshy, R. I.; Abdi, S. H. R.; Suresh, E.; Bajaj, H. C., *RSC Advances* **2016,** *6* (57), 52384. doi: 10.1039/c6ra06812j.
45. Sadeghi, B.; Ghasemi Pirbaluti, M.; Farokhi Nezhad, P.; Abbasi Nezhad, R., *Research on Chemical Intermediates* **2015,** *41* (6), 4047. doi: 10.1007/s11164-013-1509-1.
46. Karimi, A. R.; Sourinia, M.; Dalirnasab, Z.; Karimi, M., *Canadian Journal of Chemistry* **2015,** *93* (5), 546. doi: 10.1139/cjc-2014-0345.
47. Sadeghi, B.; Lasemi, Z.; Azimi, R., *Oriental Journal of Chemistry* **2015,** *31* (2), 1175. doi: 10.13005/ojc/310272.
48. Zakeri, M.; Nasef, M. M.; Abouzari-Lotf, E.; Moharami, A.; Heravi, M. M., *Journal of Industrial and Engineering Chemistry* **2015,** *29*, 273. doi: 10.1016/j.jiec.2015.03.035.
49. Heravi, M. M.; Hashemi, E.; Azimian, F., *Journal of the Iranian Chemical Society* **2015,** *12* (4), 647. doi: 10.1007/s13738-014-0523-6.
50. Niknam, K.; Abolpour, P., *Monatshefte fur Chemie* **2015,** *146* (4), 683. doi: 10.1007/s00706-014-1343-1.
51. Azizi, N.; Dezfooli, S.; Mahmoudi Hashemi, M., *Journal of Molecular Liquids* **2014,** *194*, 62. doi: 10.1016/j.molliq.2014.01.009.
52. Baghbanian, S. M.; Tajbakhsh, M.; Farhang, M., *Comptes Rendus Chimie* **2014,** *17* (12), 1160. doi: 10.1016/j.crci.2013.12.005.
53. Wang, H.; Guo, L. N.; Duan, X. H., *Organic Letters* **2013,** *15* (20), 5254. doi: 10.1021/ol402473m.
54. Bazgir, A.; Hosseini, G.; Ghahremanzadeh, R., *ACS Combinatorial Science* **2013,** *15* (10), 530. doi: 10.1021/co400057h.
55. Dandia, A.; Parewa, V.; Jain, A. K.; Rathore, K. S., *Green Chemistry* **2011,** *13* (8), 2135. doi: 10.1039/c1gc15244k.
56. Chen, W. B.; Wu, Z. J.; Pei, Q. L.; Cun, L. F.; Zhang, X. M.; Yuan, W. C., *Organic Letters* **2010,** *12* (14), 3132. doi: 10.1021/ol1009224.
57. Liang, B.; Kalidindi, S.; Porco Jr, J. A.; Stephenson, C. R. J., *Organic Letters* **2010,** *12* (3), 572. doi: 10.1021/ol902764k.
58. Wang, L. M.; Jiao, N.; Qiu, J.; Yu, J. J.; Liu, J. Q.; Guo, F. L.; Liu, Y., *Tetrahedron* **2010,** *66* (1), 339. doi: 10.1016/j.tet.2009.10.091.

59. Dabiri, M.; Bahramnejad, M.; Baghbanzadeh, M., *Tetrahedron* **2009,** *65* (45), 9443. doi: 10.1016/j.tet.2009.08.070.
60. Zhang, M.; Fu, Q.-Y.; Gao, G.; He, H.-Y.; Zhang, Y.; Wu, Y.; Zhang, Z.-H., *ACS Sustainable Chemistry & Engineering* **2017**.
61. Yan, L. J.; Wang, Y. C., *ChemistrySelect* **2016,** *1* (21), 6948.
62. Guo, R.-Y.; An, Z.-M.; Mo, L.-P.; Wang, R.-Z.; Liu, H.-X.; Wang, S.-X.; Zhang, Z.-H., *ACS Combinatorial Science* **2013,** *15* (11), 557. doi: 10.1021/co400107j.
63. Turner, J., *Nat Mater* **2008,** *7* (10), 770.
64. Li, R.; Zhu, X.; Yan, X.; Kobayashi, H.; Yoshida, S.; Chen, W.; Du, L.; Qian, K.; Wu, B.; Zou, S.; Lu, L.; Yi, W.; Zhou, Y.; Fan, J., *ACS Catalysis* **2017,** *7* (2), 1478. doi: 10.1021/acscatal.6b03370.
65. Haruta, M., *Nature* **2005,** *437* (7062), 1098.
66. Pöschl, U.; Shiraiwa, M., *Chemical reviews* **2015,** *115* (10), 4440.
67. Lakey, P. S.; Berkemeier, T.; Tong, H.; Arangio, A. M.; Lucas, K.; Pöschl, U.; Shiraiwa, M., *Scientific reports* **2016,** *6*.
68. Sawyer, D. T. *Oxygen chemistry*. Oxford university press1991.
69. Halliwell, B.; Gutteridge, J., *Free radicals in biology and medicine* **1999,** *3*, 1.
70. Stoin, U.; Shames, A. I.; Malka, I.; Bar, I.; Sasson, Y., *ChemPhysChem* **2013,** *14* (18), 4158.
71. Hayyan, M.; Hashim, M. A.; AlNashef, I. M., *Chemical reviews* **2016,** *116* (5), 3029.
72. Moosavi-Zare, A. R.; Zolfigol, M. A.; Salehi-Moratab, R.; Noroozizadeh, E., *Canadian Journal of Chemistry* **2016,** *95* (2), 194.
73. Pogosyan, S.; Avakimyan, D. A.; Stepanyan, H., *Russian Journal of Organic Chemistry* **2016,** *9* (52), 1308.
74. Mohamadpour, F.; Maghsoodlou, M. T.; Heydari, R.; Lashkari, M., *Research on Chemical Intermediates* **2016,** *42* (12), 7841. doi: 10.1007/s11164-016-2565-0.
75. Niknam, K.; Khataminejad, M.; Zeyaei, F., *Tetrahedron Letters* **2016,** *57* (3), 361. doi: http://dx.doi.org/10.1016/j.tetlet.2015.12.034.
76. Sachdeva, H.; Saroj, R.; Dwivedi, D., *The Scientific World Journal* **2014,** *2014*.
77. Chin, D. H.; Chiericato Jr, G.; Nanni Jr, E. J.; Sawyer, D. T., *Journal of the American Chemical Society* **1982,** *104* (5), 1296.
78. Nosaka, Y.; Nosaka, A. Y., *Chemical Reviews* **2017**.
79. Hayyan, M.; Alakrach, A. M.; Hayyan, A.; Hashim, M. A.; Hizaddin, H. F., *ACS Sustainable Chemistry & Engineering* **2017,** *5* (2), 1854. doi: 10.1021/acssuschemeng.6b02573.