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An Efficient Room Temperature Oxygen Radical Anion ($O2^{\bullet-}$) Mediated Synthesis of *N*- Substituted Isatin Derivatives

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Abstract: The present report demonstrates an efficient use of oxygen radical anion to promote the synthesis of *N*-substituted isatin derivatives (3a–j) under mild reaction conditions. The combination of potassium superoxide (KO_2) and tetraethylammonium bromide (TEAB) generate the oxygen radical anion *in situ* that promote this synthetic transformation. This method offers a sustainable and direct access to the *N*-substituted isatin derivatives in good to excellent yields.

Keywords: Tetraethyl ammonium bromide, Superoxide ion, Isatin, *N*- substituted isatin derivatives Bromo alkyl derivatives

Introduction

The industrial and academic research is now focusing on the search for new methods which generate molecular oxygen *in situ* and apply it more efficiently to promote synthetic conversions (Turner, 2008, Li et al 2017). However, There are some problems associated with the use of molecular oxygen as a promoter is its less reactivity, requirement of low temperature, the necessity of expensive metals/metal surfaces and also expensive techniques are needed to generate the more reactive species or to bind an oxygen molecule (Haruta, 2005). Alternatively, reactive oxygen species (ROS) are the superior and promising oxygen containing radicals that show better reactivity to promote synthetic transformations (Pöschl et al 2005, Lakey et al 2016) . The most interesting point to observe in all molecular oxygen promoted reactions is the intermediacy of reactive oxygen species (ROS).

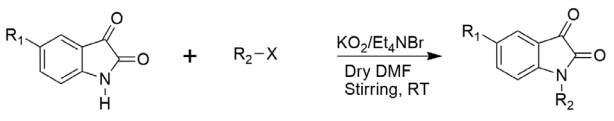
Superoxide ion ($O_2^{\bullet-}$), being a reactive oxygen species (ROS) shows significant biological and synthetic relevance and it is the molecule of interest for current scientific investigations. Therefore, the research on the reactions promoted by

$O_2^{\bullet-}$ can surely provide better view to understand the nature and behavior of $O_2^{\bullet-}$. The $O_2^{\bullet-}$ is a green oxidant and a reactive replacement of oxygen (Sawyer 1991, Halliwell and Gutteridge 2015). 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 a phase transfer catalyst (Stoin et al 2013, Hayyan et al 2016).

Isatin and its derivatives are reported to show various biological activities (Andreani el al 2010, Khan et al 2010, Chiyanzu et al 2005, Medvedev et al 2005, Medvedev et al 2006). *N*-substituted isatin derivatives are also used as a synthetic precursor for synthesis of a variety of heterocyclic moieties of biological interest (Veeranna et al 2022, Bajpai and Singh 2023, Bajpai et al 2017, Jiang el al 2022, Singh el al 2023).
In the view of above, we herein report super oxide mediated simple and an efficient procedure for synthesis of *N*-substituted Isatin Derivatives at room temperature.

Results and discussion

In order to establish an optimized reaction condition for the synthesis of *N*- substituted isatin derivatives at room temperature a model reaction of isatin **1a** and Ethyl bromide **2a** was carried out in the presence of various unexplored oxidants under nitrogen atmosphere in different solvents like DMF, THF, CH_3CN, PEG, DMSO, and CH_2Cl_2 at room temperature. The solvent study showed that dry DMF is the best solvent which provides the highest yield of the product. All reactions were performed 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. Some potential reagents like sodium hypochlorite (NaOCl), perchloric acid ($HClO_4$), *tert*–butylhydroperoxide (TBHP), potassium periodide (KIO_3), diacetoxyiodobenzene ($PhI(OAC)_2$), potassium persulfate ($K_2S_2O_8$), hydrogen peroxide (H_2O_2), manganese dioxide (MnO_2), copper perchlorate ($CuClO_4$), and calcium oxychloride ($CaOCl_2$), were employed but none of them provided a significant yield of the product. However, when 50 mol% of potassium superoxide (KO_2) was applied, the desired product was formed in 54% yield. 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. 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 *N*- substituted isatin derivatives 94 % yield at room temperature.



1a, b 2a-e 3a-j

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 ethyl bromide (**2a**), ethylbromo acetate (**2b**), n-bromopropane (**2c**), benzyl bromide (**2d**), 1,4- dibromobutane (**2e)** in dry DMF at room temperature. The unsubstituted isatin served as a best partner in these reactions, when compared with 5–chloroisatin. Out of these alkyl derivatives ethyl bromide (**2a**) exhibited the best reactivity. A diverse set of pure *N*- substituted isatin derivatives **(3a–j)** have synthesized in good to excellent yields (94–81). All the products were fully characterized based on their melting points, and spectral data (IR, NMR).

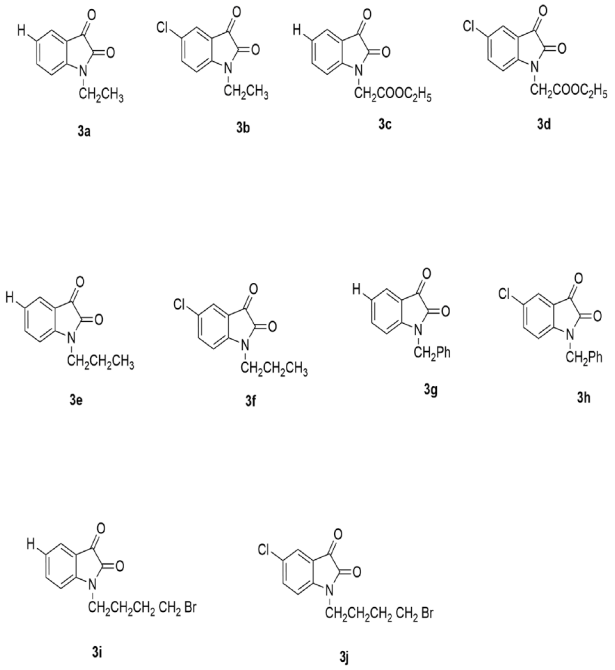


Figure1 Synthesized *N*- substituted isatin derivatives

Experimental

General: All chemicals were procured from Aldrich, USA, and E. Merck, Germany and used without further purification. TLC was carried out on SiO_2 gel (HF254, 200 mesh). The solvent system employed was ethyl acetate: n hexane (2: 1) and the spots were identified by placing the plate in Iodine chamber. IR spectra were recorded on a PerkinElmer FT/IR version 10.03.05 spectrometer. NMR spectra were run on a JEOL AL300 FTNMR spectrometer; chemical shifts are given in δ ppm, relative to TMS as internal standard. Elemental microanalysis was performed on Exeter Analytical Inc Model CE- 440 CHN Analyzer. Melting points were measured in open capillaries and are uncorrected.

General procedure for synthesis of compounds 3a-j

Potassium superoxide and tetraethylammonium bromide (2:1) were weighed under nitrogen atmosphere using an atmosbag and were transferred into a three necked R. B. flask, dry DMF (20 mL) was added to it and the mixture was agitated magnetically for 15 min to facilitate the formation of superoxide ion. To the stirred reaction mixture, were added isatin/ 5-chloroisatin **1a, b** (0.01 mol). After 10 min, bromo hydrocarbon **2a-e** (0.01 mol) were introduced, and the stirring was continued 4-6 h. After the reaction was over as indicated by TLC, 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 **3a-j**, which were purified by column

chromatography.

Characterization data for synthesized *N*- Substituted isatin derivatives (3a–j)

1-Ethylindoline-2, 3-dione (3a) (Chen el al 2011)

Dark-red solid, Mp 86 ^{0}C, Yield: 94%, **IR (KBr) υ**: 3100, 3008, 1749, 1729, 1600, 1469, 1351, 1272, 1163, 1148, 751, 689 cm-1. **^{1}H-NMR (300 MHz, CDCl$_3$) δ**: 1.39 (t, 3H, *J*= 6.9 Hz, CH_3), 3.72 (q, 2H, *J*=7.0 Hz, CH2), 7.09- 7.89 (m, 4H, Ar-H) ppm. Anal. Calc. For ($C_{10}H_9NO_2$): C, 68.60; H, 5.21; N, 7.99; O, 18.20 (%). Found: C, 68.55; H, 5.20; N, 8.03; O, 18.21 (%).

5-Chloro-1-ethylindoline-2, 3-dione (3b)

Red solid, Mp 110 ^{0}C, Yield: 86 %, **IR (KBr) υ**: 3067, 2928, 1727, 1715, 1621, 1568, 1454, 1361, 1250, 1121, 1067, 760, 698 cm^{-1}. **^{1}H-NMR (300 MHz, CDCl$_3$) δ**: 1.17 (t, 3H, *J*=7.2 Hz, CH_3), 3.45 (q, 2H, *J*=6.9 Hz, CH_2), 7.21- 7.78 (m, 3H, Ar- H) ppm. Anal. Calc. For ($C_{10}H_8ClNO_2$): C, 57.30; H, 3.85; N, 6.68; O, 15.26 (%). Found: C, 57.35; H, 3.80; N, 6.74; O, 15.25 (%).

Ethyl 2-(2, 3-dioxoindolin-1-yl)acetate (3c) (Chen el al 2011)

Yellow-brown solid, Mp 118 ^{0}C**,** Yield: 92%, **IR (KBr) υ**: 3072, 2970, 1743, 1729, 1710, 1621, 1472, 1358, 1337, 1263, 1214, 1188, 1081, 765, 711 cm^{-1}. **^{1}H-NMR (300 MHz, CDCl$_3$) δ**: 1.29 (t, 3H, *J*=7.0 Hz, CH_3), 3.98 (q, 2H, *J*=7.2 Hz, CH_2), 4.21 (s, 2H, CH_2), 6.84- 7.72 (m, 4H, Ar-H) ppm. Anal. Calc. For $C_{12}H_{11}NO_4$: C, 61.82; H, 4.74; N, 6.00; O, 27.44 (%). Found: C, 61.72; H, 4.83; N, 6.00; O, 27.45 (%).

Ethyl 2-(5-chloro-2, 3-dioxoindolin-1-yl)acetate (3d)

Yellow solid, Mp 140 ^{0}C, Yield: 85%, **IR (KBr) υ**: 3155, 2969, 1735, 1722, 1702, 1620, 1560, 1472, 1365, 1311, 1263, 1199, 1127, 1089, 753, 739 cm-1. **1H-NMR (300 MHz, CDCl3) δ**: 1.62 (t, 3H, *J*=7.2 Hz, CH_3), 4.20 (q, 2H, *J*=7.2 Hz, CH_2), 4.51 (s, 2H, CH_2), 6.98- 7.84 (m, 3H, Ar-H) ppm. Anal. Calc. For ($C_{12}H_{10}ClNO_4$): C, 53.85; H, 3.77; N, 5.23; O, 23.91 (%). Found: C, 53.80; H, 3.80; N, 5.20; O, 23.94 (%).

1-Propylindoline-2, 3-dione (3e) (Chen el al 2011)

Red solid, Mp 107 ^{0}C, Yield: 90%, **IR (KBr) υ**: 3116, 3089, 2978, 2849, 1726, 1703, 1611, 1560, 1465, 1318, 1254, 1140, 1032, 753, 719 cm-1. **^{1}H NMR (300 MHz, DMSO) δ**: 1.10-1.15 (t, *J*= 7.0 Hz , 3H), 1.66-1.76 (m, 2H), 3.25-3.31 (t, *J*=7.2 Hz, 2H), 7.11- 7.98 (m, 4H, aromatic protons) ppm. Anal. Calcd for: $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40; O, 16.91Found: C, 69.89; H, 5.81; N, 7.43; O, 16.87.

5-Chloro-1-propylindoline-2, 3-dione (3f)

Red solid, Mp 136 ^{0}C, Yield: 87%, **IR (KBr) υ**: 3181, 3060, 2953, 2841, 1731, 1717, 1622, 1568, 1459, 1354, 1239, 1175, 1023, 768, 713 cm^{-1}. **^{1}H NMR (300 MHz, DMSO) δ**: 1.11-1.15 (t, *J*= 7.0 Hz, 3H), 1.82-1.89 (m, 2H), 3.18-3.23 (t, *J*=7.2 Hz, 2H), 7.09- 7.67 (m, 3H, aromatic protons) ppm. Anal. Calcd for: $C_{11}H_{10}ClNO_2$: C, 59.07; H, 4.51; N, 6.26; O, 14.31Found: C, 59.00; H, 4.60;

N, 6.21; O, 14.27.

1-Benzylindoline-2, 3-dione (3g) (Chen el al 2011)

Red solid, Mp 128 ^{0}C, Yield: 94%, **IR (KBr) υ**: 3187, 3054, 2970, 2822, 1723, 1701, 1628, 1581, 1461, 1349, 1271, 1139, 1063, 742 cm^{-1}. **^{1}H NMR (300 MHz, DMSO) δ**: 5.48 (s, 2H), 7.23-8.10 (m, 9H, aromatic protons) ppm. Anal. Calcd for: $C_{15}H_{11}NO_2$: C, 75.94; H, 4.67; N, 5.90; O, 13.49 Found: C, 75.90; H, 4.71; N, 5.89; O, 13.49.

1-Benzyl-5-chloroindoline-2, 3-dione (3h)

Red solid, Mp 136 ^{0}C, Yield: 89 %, **IR (KBr) υ**: 3180, 3078, 2913, 2854, 1721, 1711, 1615, 1560, 1478, 1353, 1285, 1151, 1037, 767 cm^{-1}. **^{1}H NMR (300 MHz, DMSO) δ**: 5.58 (s, 2H), 7.22- 8.05 (m, 8H, aromatic protons) ppm. Anal. Calcd for: $C_{15}H_{10}ClNO_2$: C, 66.31; H, 3.71; N, 5.16; O, 11.78 Found: C, 66.30; H, 3.70; N, 5.22; O, 11.72.

1-(4-Bromobutyl) indoline-2, 3-dione (3i) (Chen el al 2011)

Reddish- yellow solid, Mp 186 ^{0}C, Yield: 84% **IR (KBr) υ**: 3100, 2965, 1739, 1614, 1464, 1363, 1323, 1198, 1124, 756, 713 cm^{-1}. **^{1}H NMR (300 MHz, $CDCl_3$) δ**: 1.66 (m, 2H, CH_2), 2.05 (m, 2H, CH_2), 3.91 (t, 2H, *J*=7.2 Hz, CH_2), 4.00 (t, 2H, *J*=7.2 Hz, CH_2), 7.22-7.87 (m, 4H, Ar-H) ppm. Anal. Calcd. For $C_{12}H_{12}BrNO_2$: C, 51.09; H, 4.29; N, 4.96; O, 11.34 (%). Found: C, 51.13; H, 4.30; N, 4.95; O, 11.32 (%).

1-(4-bromobutyl)-5-chloroindoline-2,3-dione (3j)

Brown- yellow solid, Mp 205 ^{0}C, Yield: 81%, **IR (KBr) υ**: 3163, 2971, 1730, 1713, 1611, 1457, 1345, 1332, 1173, 1100, 764, 698 cm^{-1}. **^{1}H NMR (300 MHz, $CDCl_3$) δ**: 1.78 (m, 2H, CH_2), 2.25 (m, 2H, CH_2), 3.99 (t, 2H, *J*=7.2 Hz, CH_2), 4.22 (t, 2H, *J*=7.0 Hz, CH_2), 7.35-7.94 (m, 3H, Ar-H) ppm. Anal. Calcd. For $C_{12}H_{11}BrClNO_2$: C, 45.53; H, 3.50; N, 4.42; O, 10.11 (%). Found: C, 45.50; H, 3.53; N, 4.40; O, 10.13 (%).

Conclusions

In conclusion, a novel and mild approach for the synthesis of *N*- substituted isatin derivatives has been achieved by using superoxide ion in non-aqueous medium under room temperature in good to excellent yield. The utility of the described methodology is highly promising as it allows for the combination of synthetic virtues of conventional reaction with biochemical species i.e. superoxide ion.

References

1. Andreani, A., Burnelli, S., Granaiola, M., Leoni, A., Locatelli, A., Morigi, R., ... & Greco, E. (2010). New isatin derivatives with antioxidant activity. *European journal of medicinal chemistry*, *45*(4), 1374-1378.
2. Bajpai, S. & Singh, S. (2023). Anti cancer potential of some indole based quinoxaline derivatives against dalton's lymphoma (DL) cells. *Research Journal of Pharmacy and Technology*, *16* (7), 3165-3171.
3. Bajpai, S., Singh, S., & Srivastava, V. (2017). Monoclinic zirconia nanoparticle-catalyzed regioselective synthesis of some novel substituted spirooxindoles through one-pot multicomponent reaction in a ball mill: A step toward green and sustainable chemistry. *Synthetic Communications*, *47*(16), 1514-1525.
4. Chiyanzu, I., Clarkson, C., Smith, P. J., Lehman, J., Gut, J., Rosenthal, P. J., & Chibale, K. (2005). Design, synthesis and anti-plasmodial evaluation in vitro of new 4-aminoquinoline isatin derivatives. *Bioorganic & medicinal chemistry*, *13*(9), 3249-3261.
5. Chen, G., Wang, Y., Hao, X., Mu, S., & Sun, Q. (2011). Simple isatin derivatives as free radical scavengers: Synthesis, biological evaluation and structure-activity relationship. *Chemistry Central Journal*, *5*, 1-5.

6. Halliwell, B.; Gutteridge, J., *Free radicals in biology and medicine* Oxford university press 2015.
7. Haruta, M. (2005). Gold rush. *Nature*, *437*(7062), 1098-1099.
8. Hayyan, M., Hashim, M. A., & AlNashef, I. M. (2016). Superoxide ion: generation and chemical implications. *Chemical reviews*, *116*(5), 3029-3085.
9. Jiang, X., Li, J., Viayna, A., Luque, F. J., Woodson, M., Jing, L., & Zhan, P. (2023). Identification of novel 1, 2, 3-triazole isatin derivatives as potent SARS-CoV-2 3CLpro inhibitors via click-chemistry-based rapid screening. *RSC Medicinal Chemistry*, *14*(10), 2068-2078.
10. Lakey, P. S., Berkemeier, T., Tong, H., Arangio, A. M., Lucas, K., Pöschl, U., & Shiraiwa, M. (2016). Chemical exposure-response relationship between air pollutants and reactive oxygen species in the human respiratory tract. *Scientific reports*, *6*(1), 32916.
11. Li, R., Zhu, X., Yan, X., Kobayashi, H., Yoshida, S., Chen, W., & Fan, J. (2017). Oxygen-controlled hydrogen evolution reaction: molecular oxygen promotes hydrogen production from formaldehyde solution using Ag/MgO nanocatalyst. *Acs Catalysis*, *7*(2), 1478-1484.
12. Medvedev, A., Igosheva, N., Crumeyrolle-Arias, M., & Glover, V. (2005). Isatin: role in stress and anxiety. *Stress*, *8*(3), 175-183.
13. Medvedev, A., Buneeva, O., Gnedenko, O., Fedchenko, V., Medvedeva, M., Ivanov, Y., ... & Sandler, M. (2006). Isatin interaction with glyceraldehyde-3-phosphate dehydrogenase, a putative target of neuroprotective drugs: partial agonism with deprenyl. *Oxidative Stress and Neuroprotection*, 97-103.
14. Pöschl, U.; Shiraiwa, M., (2015) Multiphase chemistry at the atmosphere-biosphere interface influencing climate and public health in the anthropocene *Chemical reviews*, *115* (10), 4440-4075.
15. Sawyer, D. T. *Oxygen chemistry*. Oxford university press 1991.
16. Stoin, U., Shames, A. I., Malka, I., Bar, I., & Sasson, Y. (2013). In situ generation of superoxide anion radical in aqueous medium under ambient conditions. *ChemPhysChem*, *14*(18), 4158-4164.
17. Turner, J. (2008). The other half of the equation. *Nature materials*, *7*(10), 770-771.