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Heterocyclic Chemistry

Investigation of a Late-Stage Derivatization Approach to Isatogens: Discovery of New Reaction Pathways

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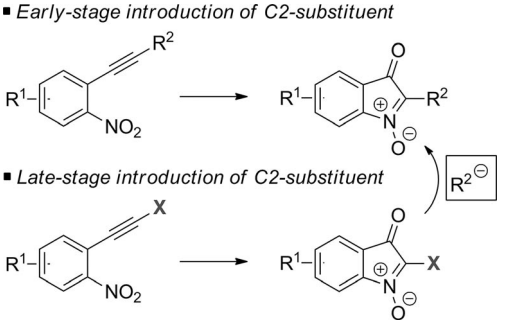
Abstract: We have developed a new strategy for preparing 2-substituted indolone *N*-oxides (isatogens) by substitution reactions with aryl- and alkyl-organometallic reagents. This approach allows a range of substituents to be incorporated at a late stage and complements existing methods that necessitate their early stage incorporation during substrate preparation. Further chemistry has been found to take place at the nitrone moiety; intramolecular dipolar cycloaddition provides access to angularly fused tricyclic heterocycles. More unusually however, these compounds are prone to further addition by organozinc reagents leading to 2,2-disubstituted 3-oxindole products.

Introduction

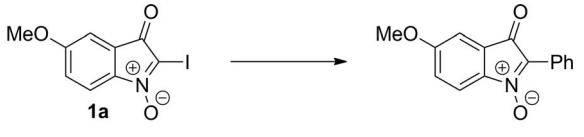
Indolone *N*-oxides (isatogens) were first prepared by Baeyer[1] and constitute an interesting class of stable dipolar compounds that have been shown to display a variety of useful biological properties.[2] These compounds are typically generated from 2-nitrophenylacetylenes in the presence of acid or base,[3] or by transition metal catalysis.[4] Recent studies in our labs sought to develop a new strategy that allowed the late-stage functionalization of isatogens. Specifically, as shown in Scheme 1, while traditional approaches have necessitated the incorporation the C2 substituent by appending this group at the alkyne, we envisaged that a more divergent approach to isatogens could comprise the employment of a nucleofuge bearing alkyne that would offer the potential to incorporate C2-substituents in the final step by a nucleophilic substitution or cross-coupling process (Scheme 1). In the event, we were able to devise a Cu-promoted cyclization of 2-nitrophenyl iodoacetylenes to generate a range of 2-iodoisatogens.[5] Preliminary studies showed that 2-iodoisatogens could undergo Sonogashira coupling reactions, but the suitability of these compounds to access more widely utilized 2-aryl/alkyl-isatogens was less well established. We therefore undertook a more detailed study into the arylation and alkylation of 2-iodoisatogens and report our findings herein.



Scheme 1. Late-stage functionalization of isatogens.

Results and Discussion

We began our studies by investigating the Negishi cross-coupling of arylzinc halides to iodoisatogens as a means of accessing 2-arylisatogens, and our results are summarized in Scheme 2. Our preliminary attempts to promote the cross-coupling with the Pd/SPhos catalyst system delivered the expected product **2**, however, the yields were poor and the reaction mixtures were rather complex. We were aware of the potential of Pd-catalyst to promote conversion of isatogens to isatins[4c] and so decided to establish whether or not this transformation could proceed smoothly in the absence of the Pd-ligand system. Pleasingly, the addition of PhZnCl alone resulted in the formation of **2** in good yield.



PhZnCl (5 equiv.), 2.5 % Pd_2dba_3, 5 % SPhos, THF, r.t.; **2**; 30 %
PhZnCl (5 equiv.), THF, rt; **2**; 65 %

Scheme 2. Synthesis of 2-arylisatogens.

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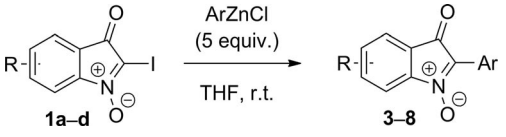
We next decided to examine the scope of this transformation and our results are summarized in Table 1. Isatogen **1a** underwent smooth substitution with a small selection of 4-substituted arylzinc reagents in good yield (entries 1–3). The chemistry could be extended to 6-halo-substituted substrates, albeit in more modest yield (entries 4,5). Finally, 7-chloro substituted isatogen **8** was also generated in modest yield, although the instability of this product hampered our efforts to isolate this compound in pure form.

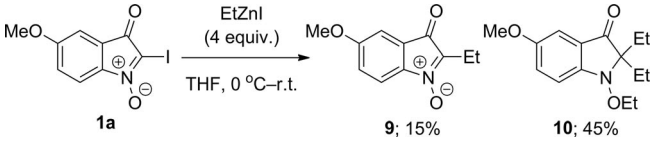
Table 1. Synthesis of 2-arylisatogens.



Entry	R	Ar	Yield
1	5-MeO; **1a**	4-ClC_6H_5	**3**; 65 %
2	5-MeO; **1a**	4-$MeOC_6H_5$	**4**; 66 %
3	5-MeO; **1a**	4-$F_3CC_6H_5$	**5**; 59 %
4	6-F; **1b**	Ph	**6**; 40 %
5	6-Br; **1c**	Ph	**7**; 48 %
6	7-Cl; **1d**	Ph	**8**; 46 %[a]

[a] Isatogen **8** was found to decompose after isolation and could not be generated in analytically pure form. See supporting information for ^1H, ^{13}C spectra.

With simple and practical conditions in hand to generate 2-arylisatogens, we decided to explore the potential of this transformation to deliver the corresponding 2-*alkyl* analogs. To our surprise however, treatment of **1a** with freshly prepared EtZnI returned the expected isatogen in low yield, together with the *N*-ethoxy-3-oxindole **10** (Scheme 3).

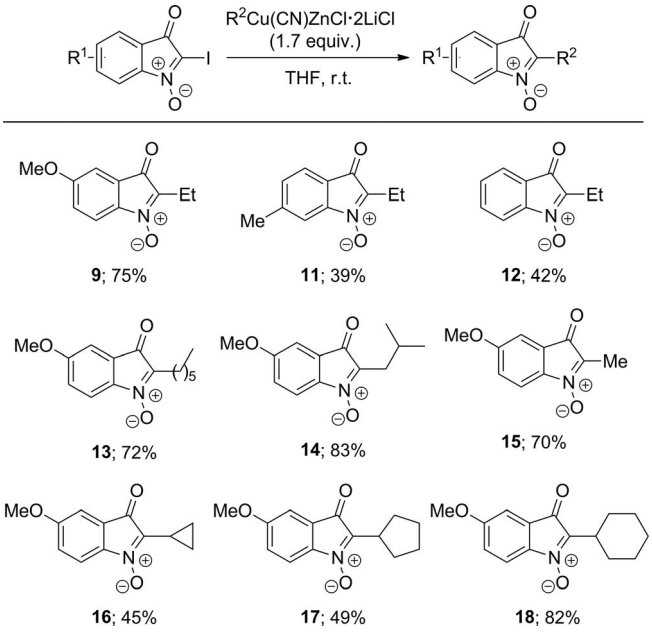


Scheme 3. Alkylation of 2-iodoisatogen **1a**.

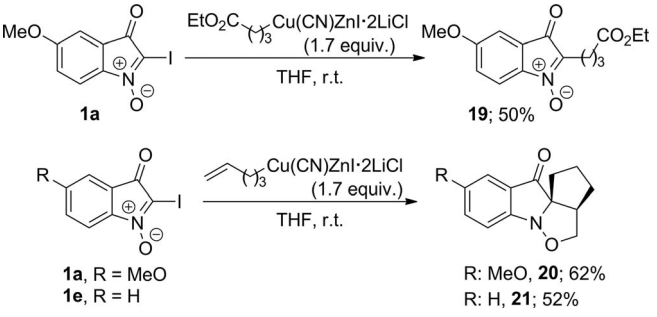
The formation of **10** was unexpected and the mechanism of its formation unclear (vide infra) but in an effort to optimize the formation of 2-alkylisatogens such as **9** we decided to screen alternative organometallic reagents. In the event, mixed copper reagents[6] proved to be most effective, and allowed a range of alkyl and cycloalkyl groups to be incorporated in modest to high yield (Scheme 4). Notably, the organocopper reagents did not preclude formation of the *N*-alkoxy-3-oxindole by-products, and minor amounts (typically about 5–10 %) of these were isolated in each case.

The incorporation of more functionalized alkyl groups was also found to be viable. Isatogen **19** bearing a terminal ester was prepared in 50 % yield. Interestingly, attempts to prepare isatogens containing a terminal olefin instead generated angularly fused tricycles **20** and **21**, presumably after substitution and in situ [3 + 2] dipolar cycloaddition (Scheme 5).[7]

Returning to the formation of the *N*-ethoxy-3-oxindole derivative **10** (Scheme 3), we were intrigued by this unexpected result and decided to explore this reaction further. Interestingly, the utilization of dialkylzinc reagents allowed these compounds to be isolated in synthetically useful yields. Moreover, the structure of these unusual compounds was confirmed in the case of **24** which was isolated as a crystalline solid allowing its characterization by X-ray analysis (Scheme 6).[8]

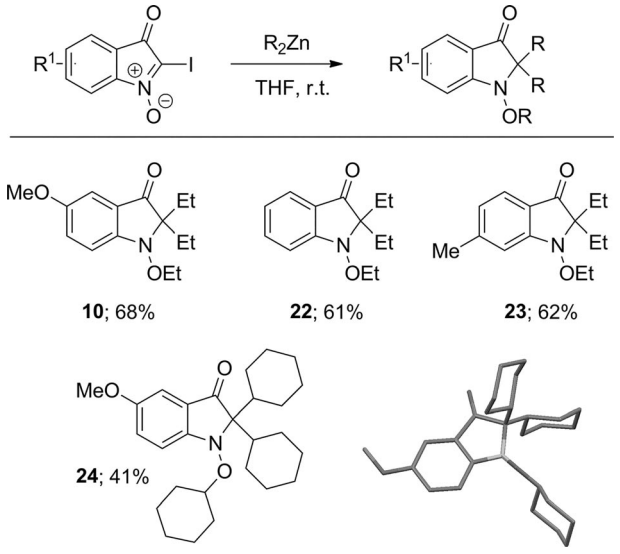


Scheme 4. Synthesis of 2-alkylisatogens.

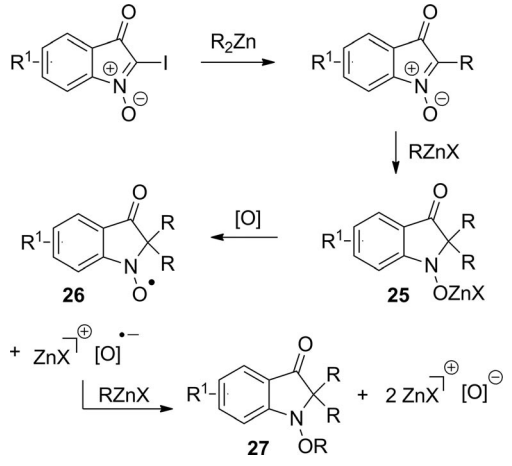


Scheme 5. Addition of functionalized organometallics.

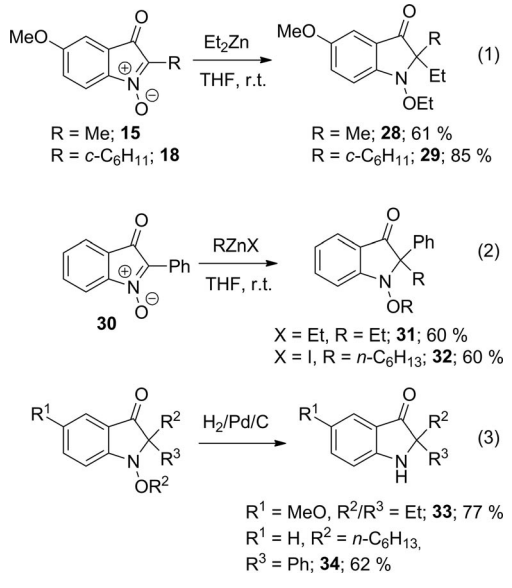
The mechanism of formation of the *N*-alkoxy-3-oxindoles is intriguing, and a proposed pathway is outlined in Scheme 7. The propensity of alkylzinc reagents to generate 2-alkylisatogens suggests that the first step involves the displacement of the iodide. Nucleophilic addition would then provide zinc alkoxide **25** which undergoes oxidation to a nitroxyl radical **26**. The oxidation of related zinc alkoxides in the presence of dialkylzinc reagents has been reported by Maury et al.,[9] moreover, *N*-hydroxy 3-indolones are known to readily form the corresponding nitroxyl radicals.[10] Although the nature of the oxidant is unclear at present, adventitious oxygen and/or the *N*-alkoxy-3-oxindole products themselves can all function as electron acceptors. The final step requires the addition of an alkylzinc reagent to the nitroxyl radical. In this respect, Curran and coworker has shown that various organometallic reagents can convert TEMPO into the corresponding ethers.[11]



Scheme 6. Synthesis of *N*-alkoxy-3-oxindoles.



Scheme 7. Synthesis of *N*-alkoxy-3-oxindoles.



Scheme 8. Synthesis of 2,2-disubstituted oxindoles.

The proposed mechanistic scheme implied that this chemistry should be amenable to the synthesis of unsymmetrical 2,2-disubstituted oxindoles and so we set out to confirm this. As shown in Scheme 8, diethylzinc underwent smooth addition to isatogen **1a** to provide the corresponding adducts in good yield [Equation (1)]. The limited availability of dialkylzinc reagents as compared to alkylzinc halides prompted us to explore the reactivity of the latter reagents. Pleasingly, as shown in Equation (2), 2-phenylisatogen **30** underwent addition of alkylzinc iodides to give the corresponding products in similar yields. Finally, these products underwent hydrogenolysis to the corresponding 2,2-disubstituted 3-oxindoles as exemplified by the synthesis of compounds **33** and **34**.

Conclusions

In conclusion, 2-iodoisatogens function as useful precursors to a range of new dipolar intermediates through substitution reactions with aryl- and alkyl-organometallic reagents. Further chemistry has been found to take place at the nitrone moiety; intramolecular dipolar cycloaddition provides access to angularly fused tricyclic heterocycles. More unusually however, these compounds are prone to further addition by organozinc reagents leading to 2,2-disubstituted 3-oxindole products.

Experimental Section

General Procedure for the Addition of Cuprates to 2-Iodoisatogens. Synthesis of 2-Ethyl-5-methoxy-3-oxo-3*H*-indole 1-Oxide (9): A flame dried flask equipped with magnetic stirrer bar was charged with 2-iodo-5-methoxy-3-oxo-3*H*-indole 1-oxide (**1a**) (0.050 g, 0.165 mmol) in anhydrous THF (5.0 mL) at 20 °C. EtCu(CN)ZnI•2LiCl (0.62 mL, 0.281 mmol, 0.45 M THF) was added dropwise over 5 min. The reaction mixture was stirred at 20 °C for 18 h then quenched with saturated $NH_4Cl_{(aq)}$ (5.0 mL) and brine (10.0 mL) then extracted with EtOAc (2 × 15.0 mL). The organic extracts were combined, dried with $MgSO_4$ and concentrated under vacuum to afford a red amorphous solid which was purified via flash column chromatography on silica gel (1:18 ethyl acetate/petroleum ether) providing the title compound as a red crystalline solid (0.025 g, 75 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (d, J = 8.5 Hz, 1 H), 7.08 (d, J = 2.5 Hz, 1 H), 7.01 (dd, J = 8.5, 2.5 Hz, 1 H), 3.87 (s, 3 H), 2.65 (q, J = 7.5 Hz, 2 H), 1.21 ppm (t, J = 7.5 Hz, 3 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 186.6, 162.3, 140.3, 139.6, 125.0, 117.3, 115.0, 108.2, 56.2, 15.0, 9.8 ppm. FTIR (film): 2937 (w), 1704 (s), 1618 (w), 1531 (s), 1486 (s), 1435 (m), 1390 (s), 1356 (s), 1280 (m), 1230 (m), 1097 (m), 821 (m), 801 (w) cm^{-1}. HRMS (TOF MS ES+) *m/z* calcd. for $[C_{11}H_{12}NO_3]^+$: 206.0817 $[M + H]^+$, found 206.0807; M.p. 51–55 °C (CH_2Cl_2).

General Procedure for the Addition of Diethylzinc to Isatogens. Synthesis of 1,2-Dihydro-1-ethoxy-2,2-diethyl-3*H*-indol-3-one (10): A flame dried flask equipped with magnetic stirrer bar was charged with 2-iodo-3-oxo-3*H*-indole 1-oxide (**1a**) (0.030 g, 0.100 mmol) in anhydrous THF (3.0 mL) at 20 °C. Et_2Zn (0.25 mL, 0.150 mmol, 0.6 M hexanes) was added dropwise and the reaction mixture stirred under nitrogen for 18 h. The reaction mixture was quenched with H_2O (1.8 mL), extracted with ethyl acetate (10.0 mL) and washed with brine (5.0 mL). The organic layer was dried with $MgSO_4$ and concentrated under vacuum to give a viscous orange oil, which was purified by flash column chromatography on silica

gel (5:95 ethyl acetate/petroleum ether) providing the title compound as a bright yellow oil (0.018 g, 68 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20 (dd, J = 9.0, 2.5 Hz, 1 H), 7.14 (d, J = 9.0 Hz, 1 H), 7.02 (d, J = 2.5 Hz, 1 H), 4.10 (q, J = 7.0 Hz, 2 H), 3.79 (s, 3 H), 1.92 (dq, J = 14.5, 7.0 Hz, 2 H), 1.77 (dq, J = 14.5, 7.0 Hz, 2 H), 1.37 (t, J = 7.0 Hz, 3 H), 0.70 (t, J = 7.0 Hz, 6 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 201.4, 158.3, 155.3, 126.8, 122.6, 114.8, 103.1, 80.3, 71.7, 55.8, 29.3, 14.4, 8.8 ppm. FTIR (film): 2969 (w), 2929 (w), 1706 (s), 1488 (s), 1439 (m), 1266 (m), 1229 (w), 1145 (w), 1030 (m), 826 (w), 804 (w) cm^{-1}. HRMS (TOF MS ES+) m/z calcd. for $[C_{15}H_{22}NO_3]^+$: 264.1600 $[M + H]^+$, found 264.1593.

Acknowledgments

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Keywords: Synthetic methods · Fused-ring systems · Nitrogen heterocycles

[1] A. Baeyer, *Ber. Dtsch. Chem. Ges.* **1881**, *14*, 1741.
[2] For recent examples and lead references, see: H. Ibrahim, A. Pantaleo, F. Turrini, P. Arese, J.-P. Nallet, F. Nepveu, *Med. Chem. Commun.* **2011**, *2*, 860.
[3] P. N. Preston, G. Tennant, *Chem. Rev.* **1972**, *72*, 627.
[4] a) G. M. Rosen, P. Tsai, E. D. Barth, G. Dorey, P. Casara, M. Spedding, H. J. Halpern, *J. Org. Chem.* **2000**, *65*, 4460; b) N. Asao, K. Sato, Y. Yamamoto, *Tetrahedron Lett.* **2003**, *44*, 5675; c) B. C. G. Söderberg, S. P. Gorugantula, C. R. Howerton, J. L. Petersen, S. W. Dantale, *Tetrahedron* **2009**, *65*, 7357; d) C. V. Ramana, P. Patel, K. Vanka, B. Miao, A. Degterev, *Eur. J. Org. Chem.* **2010**, 5955; e) P. Patel, C. V. Ramana, *Org. Biomol. Chem.* **2011**, *9*, 7327; f) P. Patel, C. V. Ramana, *J. Org. Chem.* **2012**, *77*, 10509; g) B. N. Reddy, C. V. Ramana, *Chem. Commun.* **2013**, *49*, 9767.
[5] E. J. M. Maduli, S. J. Edeson, S. Swanson, P. A. Procopiou, J. P. A. Harrity, *Org. Lett.* **2014**, *17*, 390.
[6] a) P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390; b) H. Gilman, R. G. Jones, L. A. Woods, *J. Org. Chem.* **1952**, *17*, 1630; c) B. H. Lipshutz, R. S. Wilhelm, J. A. Kozlowski, *Tetrahedron* **1984**, *40*, 5005; d) B. H. Lipshutz, *Synthesis* **1987**, 325; e) B. H. Lipshutz, *Synlett* **1990**, 119.
[7] a) J. P. Freeman, M. J. Haddadin, J. F. Hansen, *J. Org. Chem.* **1979**, *44*, 4978; b) L. Greci, G. Tommasi, P. Bruni, P. Sgarabotto, L. Righi, *Eur. J. Org. Chem.* **2001**, 3147; c) P. Astolfi, P. Bruni, L. Greci, P. Stipa, L. Righi, C. Rizzoli, *Eur. J. Org. Chem.* **2003**, 2626; d) N. Marien, B. Brigou, B. Pinter, F. De Proft, G. Verniest, *Org. Lett.* **2014**, *17*, 270.
[8] CCDC-1428616 contains the supplementary crystallographic data for compound **24**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[9] J. Maury, L. Feray, S. Bazin, J.-L. Clément, S. R. A. Marque, D. Siri, M. P. Bertrand, *Chem. Eur. J.* **2011**, *17*, 1586. For a related addition/oxidation to a nitrone that generates a nitroxyl radical, see: J. Einhorn, C. Einhorn, F. Ratajczak, I. Gautier-Luneau, J.-L. Pierre, *J. Org. Chem.* **1997**, *62*, 9385.
[10] R. Amorati, M. Lucarini, V. Mugnaini, G. F. Pedulli, F. Minisci, F. Recupero, F. Fontana, P. Astolfi, L. Greci, *J. Org. Chem.* **2003**, *68*, 1747.
[11] T. Nagashima, D. P. Curran, *Synlett* **1996**, 330.

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