University of Huddersfield Repository

Moran, Wesley J., MacRory, Kerry L. and Rodriguez, Arantxa

Oxidative rearrangement of indoles to oxindoles

Original Citation

Moran, Wesley J., MacRory, Kerry L. and Rodriguez, Arantxa (2012) Oxidative rearrangement of indoles to oxindoles. RSC Advances, 2 (24). pp. 8962-8964. ISSN 2046-2069

This version is available at http://eprints.hud.ac.uk/id/eprint/14923/

ARTICLE TYPE

Oxidative Rearrangement of Indoles to Oxindoles

Wesley J. Moran,* Kerry L. MacRory and Arantxa Rodríguez*

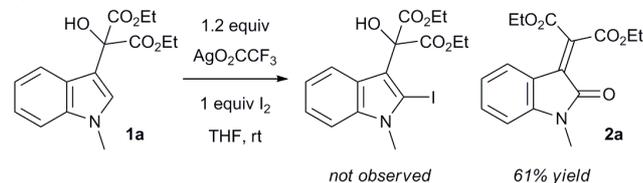5 **An unexpected oxidative rearrangement was observed when indoles substituted with 2-hydroxymalonates were subjected to typical iodination conditions. This unusual and unprecedented transformation is successful for a number of derivatives.**

10 Indoles are important structural motifs present in many compounds of pharmacological significance.[1-3] Methods to elaborate the structure of simple indoles into more substituted variants are of immense importance to enable the synthesis of new structures of potential value.[4]
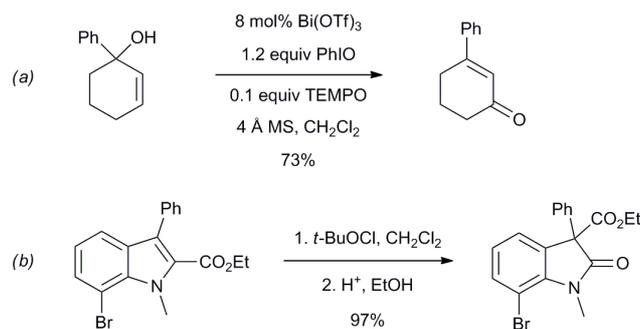
15 During an attempted total synthesis of a bisindole natural product we required the introduction of an iodine atom at the two-position of a 1,3-disubstituted indole. Due to a lack of literature methods for the iodination of 1,3-disubstituted indoles,[5] we decided to treat indole derivative **1a** with silver 20 trifluoroacetate and iodine in THF at room temperature. However, instead of the desired iodination, an oxidative rearrangement occurred generating the oxindole **2a** (Scheme 1).

25 **Scheme 1** Attempted iodination of substituted indole **1**

The oxidative rearrangement of tertiary allylic alcohols to α,β-unsaturated ketones has been known for some time (Scheme 2a),[6] however the generation of α,β-unsaturated 30 amides by this route is unknown. Indoles are known to undergo oxidative rearrangement to oxindoles upon treatment with hypochlorite or other oxidant species (Scheme 2b),[7] but this is distinct from the work reported herein.

35

Department of Chemical & Biological Sciences, University of Huddersfield, Queensgate, Huddersfield HD1 3DH, UK. Tel: +44 (0)1484 473741; E-mail: w.j.moran@hud.ac.uk;
40 *a.r.menendez@hud.ac.uk*

45 **Scheme 2** Examples of rearrangements in the literature

At this stage, we looked to optimize the reaction conditions for this oxidative rearrangement (Table 1). Initially different silver salts were tested, but no rearrangement occurred with 50 any but the silver trifluoroacetate (entries 1-4). Running the reaction without either the iodine or the silver salt led to no conversion (entries 5-6). Interestingly, running the reaction with one equivalent of *N*-iodosuccinimide did lead to product formation, albeit in low yield (entry 7). Increasing the amount 55 of *N*-iodosuccinimide to five equivalents did increase conversion to product however a low yield was still obtained (entry 8). In addition, no desired reaction was observed using typical conditions for the oxidative rearrangement of indoles as described above, i.e. with *tert*-butylhypochlorite as oxidant 60 in dichloromethane (entry 9).

Table 1 Optimization of reaction conditions for the conversion of indole **1a** into oxindole **2a**

Entry	Conditions[a]	Yield/%[b]
1	1.2 equiv AgO_2CCF_3, 1 equiv I_2, THF	61
2	1.2 equiv AgOAc, 1 equiv I_2, THF	0
3	1.2 equiv $AgBF_4$, 1 equiv I_2, THF	0
4	1.2 equiv $AgNO_3$, 1 equiv I_2, THF	0
5	1.2 equiv AgO_2CCF_3, THF	0
6	1 equiv I_2, THF	0
7	1 equiv *N*-iodosuccinimide, THF	21
8	5 equiv *N*-iodosuccinimide, THF	30
9	*t*-BuOCl, CH_2Cl_2	0

[a] All reactions run at room temperature. [b] Yield of pure isolated product **2a**.

We then prepared a range of hydroxymalonate substituted indoles simply by heating to reflux toluene solutions of indoles with commercially available diethyl ketomalonate (Table 2).[8] This reaction worked very well for 1-methyl indole **3a** and 1-ethyl indole **3b**, however 1-benzyl **3c** and 1-phenyl **3d** indoles only reacted in moderate yields (entries 1-4). A range of substituted 1-methyl indoles were subjected to these conditions, however only indoles with bromo and chloro substituents were found to be successful (entries 5-7). Reactions of indoles with methoxy, ethyl, methyl and nitro substituents gave very messy reaction mixtures and no desired product could be isolated.

In order to prepare indole substrates with electron donating substituents, alternative reaction conditions were required. A range of Lewis acids were screened and it was found that cerium chloride efficiently promoted the reaction at room temperature in dichloromethane.[9] Indole **3h** bearing a 5-methoxy substituent underwent smooth addition providing the product in 95% yield (entry 8). Indoles with a 7-ethyl and a 5-methyl substituent provided the products in 74% and 69% respectively (entries 9 and 10).

Table 2 Reaction of indoles with diethyl ketomalonate

Entry	R^1	R^2	Method	Yield/%[a]
1	Me	-	**A**	95 (**1a**)
2	Et	-	**A**	89 (**1b**)
3	Bn	-	**A**	51 (**1c**)
4	Ph	-	**A**	43 (**1d**)
5	Me	5-Br	**A**	53 (**1e**)
6	Me	6-Cl	**A**	78 (**1f**)
7	Me	7-Cl	**A**	98 (**1g**)
8	Me	5-OMe	**B**	95 (**1h**)
9	Me	7-Et	**B**	74 (**1i**)
10	Me	5-Me	**B**	69 (**1j**)

[a] Yield of pure isolated product.

With these substituted indoles in hand, the rearrangement reactions were investigated (Table 3).[10] 1-Ethyl indole **1b** rearranged in a moderate 42% yield (entry 2), whereas the 1-benzyl indole **1c** provided a 62% yield (entry 3). The 1-phenyl indole **1d** was not as effective in the rearrangement, furnishing only 34% yield of product (entry 4), showing that methyl and benzyl activating groups are preferable. The remainder of the mass balance was unidentifiable in all of these reactions. The bromo and chloro substituted indoles **1e-g** rearranged in moderate yields, 51%, 45% and 34% respectively (entries 5-7), however unreacted starting material could be isolated from these reaction mixtures and resubjected to the reaction conditions.[11] The indoles with electron donating substituents (**1h-j**) were reacted at 0 °C as superior yields were obtained compared to at room temperature. In these cases, complete conversion of the starting material was evident with the identity of the rest of the mass balance being unknown. Oxindole **2h** was isolated in 68% yield, which demonstrates that electron donating substituents aid this transformation (entry 8). The presence of alkyl substituents led to rearrangement to oxindoles **2i** and **2j** in 58% and 53% respectively (entries 9 and 10).

An X-ray crystal structure of the *N*-ethyl oxindole **2b** was obtained to provide confirmation of the structure (Fig. 1).[12] Interestingly, this shows that only one of the two ester groups is in conjugation with the alkene in the solid state.
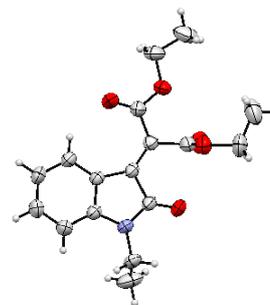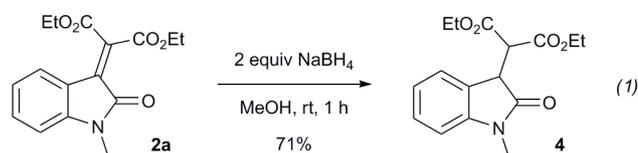
Fig. 1 X-ray crystal structure of *N*-ethyl oxindole **2b**

In an attempt to elucidate the mechanism of this process a number of experiments were undertaken; however, a lack of availability of suitably ^{18}O-labelled compounds hampered progress. The possibility of adventitious water being key to rearrangement in the reactions mediated by either *N*-iodosuccinimide or silver trifluoroacetate was explored. In both cases, addition of five equivalents of water led to considerably messier reaction mixtures however the yield was slightly augmented in the former case and diminished in the latter. Repeating both reactions with $H_2^{18}O$ led to similar results, however [18]O was not incorporated into either product. In addition, running the reactions with activated 4Å molecular sieves did not lead to product inhibition. It remains unclear as to whether the carbonyl oxygen in the product originates from the hydroxyl of the starting material or from the *N*-iodosuccinimide or silver trifluoroacetate. Attempts to make ^{18}O-labelled diethylketomalonate were unsuccessful.

These oxindole products are amenable to further synthetic transformations such as the chemoselective reduction of the alkene with sodium borohydride (eqn 1).

$$(1)$$

In conclusion, we have demonstrated an unprecedented oxidative rearrangement of hydroxymalonate substituted indoles to oxindoles.

Table 3 Scope of oxidative rearrangement

Entry	Indole	Product	Yield/%[b]
1	R = Me (**1a**)		61 (**2a**)
2	R = Et (**1b**)		42 (**2b**)
3	R = Bn (**1c**)		62 (**2c**)
4	R = Ph (**1d**)		34 (**2d**)
5	(**1e**)		51[c] (**2e**)
6	(**1f**)		45[c] (**2f**)
7	(**1g**)		34[c] (**2g**)
8	(**1h**)		68[d] (**2h**)
9	(**1i**)		58[d] (**2i**)
10	(**1j**)		53[d] (**2j**)

[a] 1.2 equiv AgO_2CCF_3, 1 equiv I_2, THF, rt, 16 h. [b] Yield of pure isolated product. [c] Remainder of mass balance is unreacted starting material. [d] Reaction run at 0 °C.

4 For selected recent examples, see: (a) S. Lucarini, F. Bartoccini, F. Battistoni, G. Diamantini, G. Piersanti, M. Righi, G. Spadoni, *Org. Lett.*, 2010, **12**, 3844; (b) Z. Shi, Y. Cui, N. Jiao, *Org. Lett.*, 2010, **12**, 2908; (c) C. C. Silveira, S. R. Mendes, L. Wolf, G. M. Martins, *Tetrahedron Lett.*, 2010, **51**, 4560; (d) M. Bandini, A. Eichholzer, *Angew. Chem. Int. Ed.*, 2009, **48**, 9608; (e) M. Yamashita, H. Horiguchi, K. Hirano, T. Satoh, M. Miura, *J. Org. Chem.*, 2009, **74**, 7481; (f) G. R. Humphrey, J. T. Kuethe, *Chem. Rev.*, 2006, **106**, 2875.

5 For the bromination and chlorination of 1,3-disubstituted indoles, see: S. Tang, J.-H. Li, Y.-X. Xie, N.-X. Wang, *Synthesis*, 2007, 1535.

6 (a) J.-M. Vatèle, *Tetrahedron*, 2010, **66**, 904. For other recent examples, see: (b) M. Uyanik, R. Fukatsu, K. Ishihara, *Org. Lett.*, 2009, **11**, 3470; (c) M. Shibuya, S. Ito, M. Takahashi, Y. Iwabuchi, *Org. Lett.*, 2008, **10**, 4715; (d) M. Shibuya, S. Ito, M. Takahashi, Y. Iwabuchi, *Org. Lett.*, 2004, **6**, 4303.

7 (a) C. Poriel, M. Lachia, C. Wilson, J. R. Davies, C. J. Moody, *J. Org. Chem.*, 2007, **72**, 2978. For other examples, see: (b) T. Lindel, L. Bräuchle, G. Golz, P. Böhrer, *Org. Lett.*, 2007, **9**, 283. (c) M. Lachia, C. Poriel, A. M. Z. Slawin, C. J. Moody, *Chem. Commun.*, 2007, 286; (d) M. Pettersson, D. Knueppel, S. F. Martin, *Org. Lett.*, 2007, **9**, 4623; (e) P. S. Baran, J. M. Richter, *J. Am. Chem. Soc.*, 2005, **127**, 15394; (f) M. Ito, C. W. Clark, M. Mortimore, J. B. Goh, S. F. Martin, *J. Am. Chem. Soc.*, 2001, **123**, 8003; (g) X. Zhang, C. S. Foote, *J. Am. Chem. Soc.*, 1993, **115**, 8867; (h) D. V. C. Awang, A. Vincent, D. Kindack, *Can. J. Chem.*, 1984, **62**, 2667; (i) A. Walser, J. F. Blount, R. I. Fryer, *J. Org. Chem.*, 1973, **38**, 3077; (j) R. M. Acheson, R. W. Snaith, J. M. Vernon, *J. Chem. Soc.*, 1964, 3229; (k) N. Finch, W. I. Taylor, *J. Am. Chem. Soc.*, 1962, **84**, 3871.

8 1-Methylindole and some 1-methyl-2-vinylindoles are known to react with diethyl ketomalonate: (a) U. Pindur, M.-H. Kim, *Tetrahedron*, 1989, **45**, 6427; (b) U. Pindur, M.-H. Kim, *Arch. Pharm.*, 1992, **325**, 353.

9 Other Lewis acids have been reported to promote double addition of indoles to diethyl ketomalonate or to mediate indole dimerization: see ref. 6a.

10 Typical experimental procedure: Iodine (83 mg, 0.328 mmol) in dry THF (0.90 mL) was added via cannula to silver trifluoroacetate (87 mg, 0.393 mmol) and diethyl 2-hydroxy-2-(1-methyl-1*H*-indol-3-yl)malonate **1a** (100 mg, 0.328 mmol) in dry THF (1.8 mL). The reaction mixure was stirred at room temperature for 16 hours under a nitrogen atmosphere and then quenched with saturated sodium thiosulfate and extracted with EtOAc. The organic layer was dried over $MgSO_4$, concentrated and purified by flash chromatography on silica gel (5:1 petroleum ether/ethyl acetate) to provide diethyl 2-(1-methyl-2-oxoindolin-3-ylidene)malonate **2a** as a red solid (61 mg, 61%).

11 Running the reactions with more equivalents of silver salt and iodine did not lead to noticeable increases in yield.

12 CCDC 828908 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Notes and references

1 C. Sánchez, C. Méndez, J. A. Salas, *Nat. Prod. Rep.*, 2006, **23**, 1007.
2 T. Kawasaki, K. Higuchi, *Nat. Prod. Rep.*, 2005, **22**, 761.
3 R. J. Sundberg, *Indoles*; Academic Press: London, U.K., 1996.