Organic & Biomolecular Chemistry

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/obc

Journal Name

RSCPublishing

COMMUNICATION

An Intermolecular C-H Functionalization Method for the Synthesis of 3-Hydroxy-2-oxindoles

Cite this: DOI: 10.1039/x0xx00000x

Jinsen Chen, Chao Song, Pei Chen and Jin Zhu*[a]

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

An intermolecular C-H functionalization method has been developed for the synthesis of 3-hydroxy-2-oxindoles. Rh(III)-catalyzed *N*-nitroso-directed C-H addition to ethyl 2-oxoacetate allows subsequent denitrosation-triggered cyclization construction of 3-hydroxy-2-oxindoles. The method features a broad substrate scope and its synthetic utility is demonstrated on the synthesis of target compounds bearing functional groups (hydroxyl, bromo) amenable to further elaboration.

3-Hydroxy-2-oxindole scaffold represents a core unit of structurally diverse medicinal agents (e.g., convolutamydines,[1] maremycins,[2] donaxaridine,[3] and SM-130686[4]) with a wide spectrum of biological activities (e.g. antioxidant,[5] anticancer,[6] anti-HIV,[7] and neuroprotective properties[8]). In spite of tremendous progress in the development of synthetic tools for this important scaffold, an efficient and general protocol is still in demand.[4e, 9] Traditional methods for the generation of 3-hydroxy-2-oxindoles include those starting from isatins and 2-oxindoles, and recently, protocols via intramolecular cyclization routes.[10] The classical isatin and 2-oxindole synthetic methods (Sandmeyer, Stolle, Gassman, and Hinsberg protocols) either are limited in substrate scope or require the use of specially designed reagents. In addition, environmentally toxic side products (HCN) and reactants (HgO) can be involved.[10a, 10b] The intramolecular cyclization methods need the pre-installation of reactive functional groups. We envisioned a more straightforward protocol for the synthesis of 3-hydroxy-2-oxindoles through an intermolecular C-H functionalization process. Such a protocol is especially useful considering recent discovery of nucleophilic, enantioselective reactivity of hydroxyl-bearing C3 for the construction of tetrasubstituted stereogenic centers directly from 3-hydroxy-2-oxindoles.[4b, 11] We recently reported the Rh(III)-catalyzed *N*-nitroso-directed C-H addition to ethyl 2-oxoacetate, which has a broad functional tolerance as well as easily removable directing group (eq. 1),[12] and with C-H functionalization products **1a-1w** in hand, we envisaged, upon the denitrosation of *N*-nitroso group, a synthetically viable route to 3-hydroxy-2-oxindoles through an intramolecular ester-amide exchange process.[13]

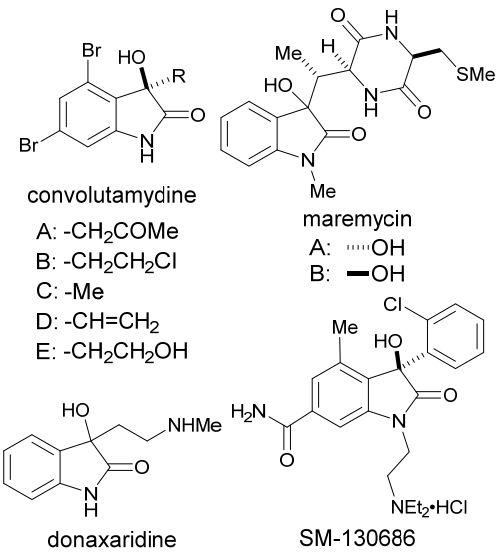
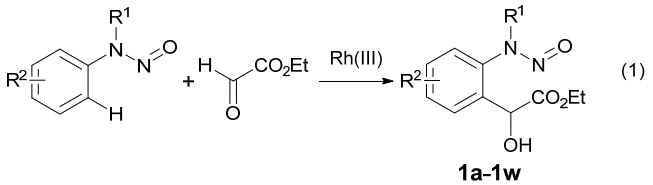


Figure 1 The structures of convolutamydines, maremycins, donaxaridine, and SM-130686

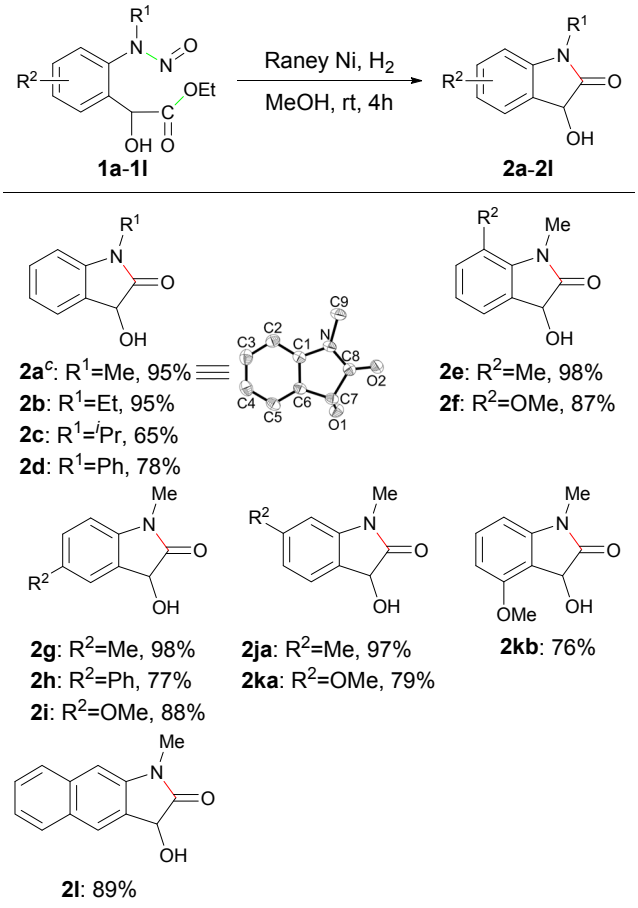


(1)

Denitrosation has been previously demonstrated on *N*-nitroso-directed olefination products under a variety of experimental conditions (e.g., $NiCl_2 \cdot H_2O/NaBH_4$, $Fe(CO)_5$, Raney Ni/H_2, CuCl/HCl).[13] Among those, only Raney Ni/H_2 can effect the high-yield (95%) transformation of **1a** into 3-hydroxy-1-methylindolin-2-one (**2a**, as confirmed by single-

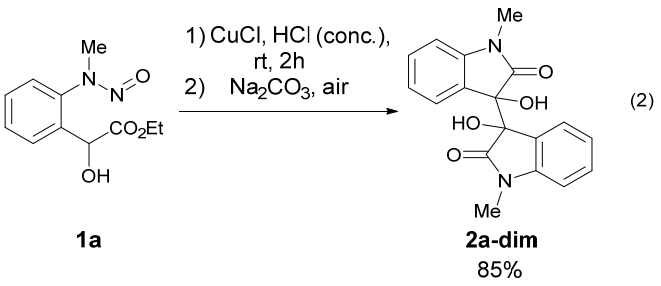
crystal analysis, Table 1), at rt. A substrate scope investigation indicates that the Raney Ni/H_2 condition is compatible with a pool of the C-H functionalization products. The steric hindrance of the substituent on the *N* atom affects the conversion efficiency. Thus, substrates bearing less hindered Me and Et groups can be transformed with product yields of 95%, substrates with larger ^{i}Pr and Ph groups only furnish products with yields of 65% and 78%, respectively (**2a-2d**, Table 1). And the conversion of a substrate with the Me group on the *ortho*, *para*, or *meta* position is almost quantitative (98%, 98%, and 97% respectively, **2e**, **2g**, and **2ja**, Table 1). For a substrate bearing an *ortho*- or *para*-substituted OMe group, the product yield is slightly lower (**2f**: 87%; **2i**: 88%). The substitution of a OMe group on the *meta* position provides a less effective substrate (**2ka**: 79%; **2kb**: 76%). A yield of 77% was obtained when the substrate possessing a large Ph group (**2h**) on the *para*-position was subjected to this reaction condition. Furthermore, for the disubstituted arenes **2l**, a good yield (89%) was also observed.

Table 1 Substrate scope under Raney Ni/H_2 condition[a,b]

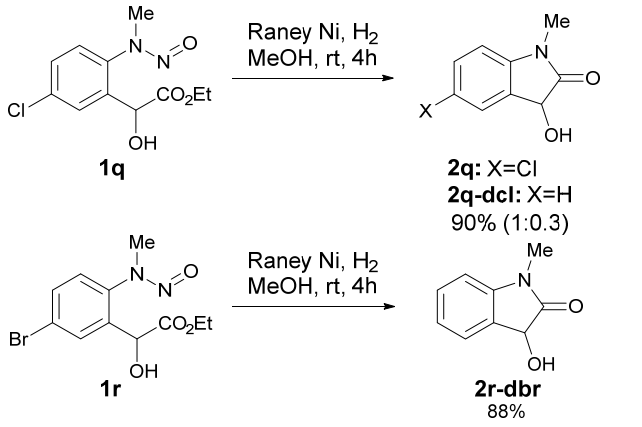


[a]Conditions : **1a-1l** (0.2 mmol), Raney Ni (4 mmol), H_2 (1 atm), MeOH (2 mL). [b]Isolated yields. [c]CCDC-1016276, thermal ellipsoid plot drawn at the 30% probability level and Hydrogen atoms omitted for clarity.

In contrast, with **2a** as the model substrate, a reaction in CuCl/HCl and a subsequent workup by neutralization with Na_2CO_3 affords an undesired dimeric product (**2a-dim**, eq. 2). Under this condition, denitrosation reaction occurred, but this was quickly followed by a dimerization process. The dimerization proceeds presumably, with oxygen as the initiator, through a radical pathway as reported previously.[4b, 14]



Further inspection of the substrate scope revealed that halogen substituents were not tolerated on account of their susceptibility to cleavage by hydrogenolysis. Thus, a chloro-bearing substrate (e.g., **1q**) furnishes a mixture of chloro-retained **2q** and chloro-removed **2q-dcl** products (with a combined total yield of 90%, 1:0.3, Scheme 1); and a higher reactivity for the bromo group (e.g., **1r**) results in its complete removal (with a yield of 88%, Scheme 1).



Scheme 1 Denitrosation reactions under Raney Ni/H_2 condition for substrates bearing Cl and Br substituents

Since *N*-nitrosamines could be prepared by amines with an acidic nitrosation reagent, HNO_2 (an instable species generated with $NaNO_2$ and HCl), we envisioned that denitrosation could be effected, analogously through a reverse process, by the utilization of an acid for the cleavage of N-N bond (eq. 3).[15] To enable the occurrence of such a hydrolysis process, a strong acid should be used in combination with a relatively strong nucleophile, such as Cl^-. In addition, the use of a "trap" for the hypothetical species HNO_2 would be advantageous for driving the reaction toward the denitrosation direction,[15c] as such a chemical equilibrium between *N*-nitrosamines and amines should favor the amine products.[16] After the screening of many kinds of "traps" for HNO_2 (Fe(II)-EDTA, Ni(II), Co(II), Cu(I), Ag(I), H_2NSO_3H, and H_2NCONH_2) we were lucky to found that a switch of reaction condition to HCl/H_2NSO_3H (with H_2NSO_3H as a HNO_2 trap)[15c] allows the circumvention of this constraint and renders halogen substituents compatible. Thus, substrates bearing halogen substituents (F, Cl and Br) on the *ortho* position of arene were successfully converted into 3-

hydroxy-2-oxindoles with yields of 68%, 97%, and 67%, respectively (**2m-2o**, Table 2). When F and Br are on the *para* position, the conversion was even better (95% and 96% for **2p** and **2r**, respectively). However, a Cl substituent on such a *para* position provides a less effective substrate (**2q**: 82%). And the yields for the substrates with substituents on the *meta* position are also generally good (76%, 85%, and 81% for **2t-2va**, respectively). It is worthwhile pointing out that a substrate bearing a nitro (**1s**) or an acetal (**1w**) group can also undergo the transformation smoothly under this condition, albeit with moderate yields (56% and 45%, respectively).

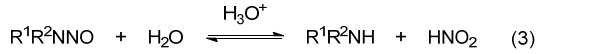
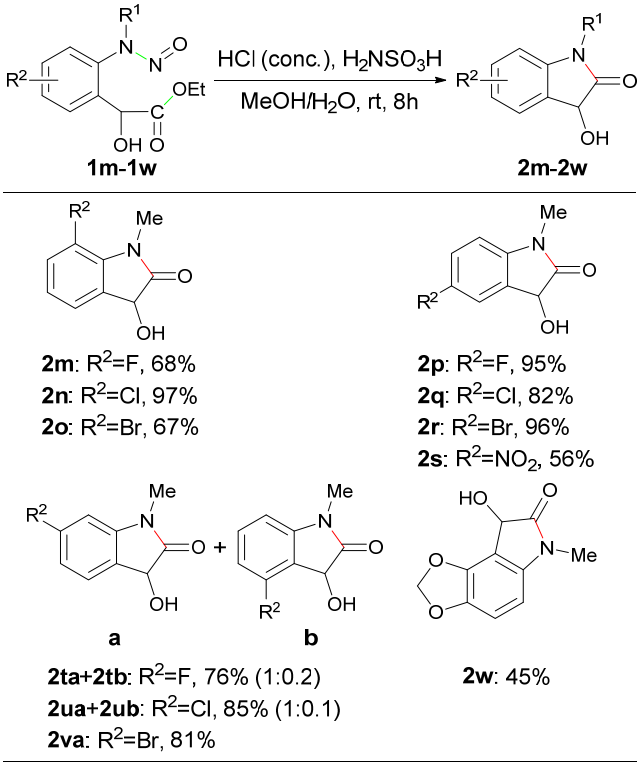


Table 2 Substrate scope under HCl/H_2NSO_3H condition[a,b]

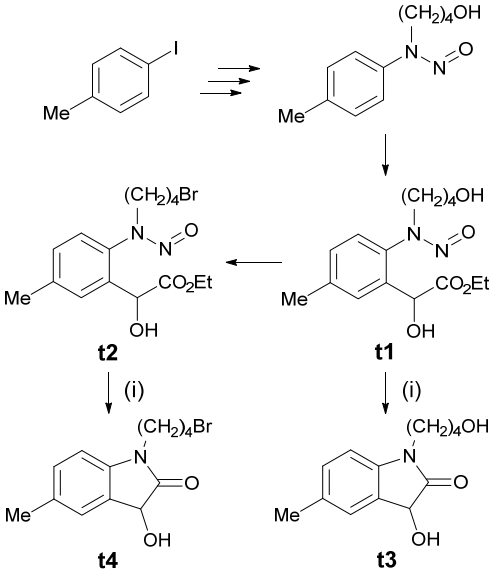


[a]Conditions : **1m-1w** (0.2 mmol), HCl (conc., 1 mL), H_2NSO_3H (1 mmol), MeOH (1 mL), H_2O (1 mL). [b]Isolated yields.

With the substrate scope examined, we next turned to the evaluation of the synthetic utility of this 3-hydroxy-2-oxindole synthesis protocol. To demonstrate this, two 3-hydroxy-2-oxindole compounds bearing functional groups (OH and Br) at the *N*-alkyl chain ends, which are amenable to a variety of transformations, were selected as targets (Scheme 2). Starting from the simple compound 4-iodotoluene, **t1** and **t2** can be obtained effectively,[12] and under the HCl/H_2NSO_3H developed herein, **t3** and **t4** can be furnished in 54% and 61% yields, respectively. Significantly, both OH and Br groups are robustly retained through this cyclization process.

Conclusions

In conclusion, we have developed a two step synthetic method that permits straightforward access to 3-hydroxy-2-oxindoles scaffold through an intermolecular C-H functionalization process. *N*-nitroso-directed C-H addition to ethyl 2-oxoacetate allows the construction of a molecule containing reactive directing group and installed group, which, under denitrosation condition, enables the synthesis of cyclized target product. Given the functional group tolerance of this protocol, we expect that the method can be applied in the synthesis of structurally complex molecules and used for structure-activity relationship studies.



Scheme 2 Synthetic utility of the developed protocol

Conditions: (i) **t1** (or **t2**) (1.0 mmol), HCl (5 mL), NH_2SO_3H (5.0 mmol), MeOH (5 mL), H_2O (5 mL), rt, 24 h; (**t3**, 51%; **t4,** 64%).

Acknowledgements

J.Z. gratefully acknowledges support from the National Natural Science Foundation of China (21274058) and the National Basic Research Program of China (2013CB922101, 2011CB935801).

Notes and references

[a] Department of Polymer Science and Engineering, School of Chemistry and Chemical Engineering, State Key Laboratory of Coordination Chemistry, Nanjing National Laboratory of Microstructures, Nanjing University, Nanjing 210093, China.

† Electronic Supplementary Information (ESI) available. See DOI: 10.1039/c000000x/. CCDC-1016276 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.

1. (a) Y. Kamano, A. Kotake, H. Hashima, I. Hayakawa, H. Hiraide, H.-p. Zhang, H. Kizu, K. Komiyama, M. Hayashi and G. R. Pettit, *Collect. Czech. Chem. Commun.*, 1999, 64, 1147-1153. (b) Y. Kamano, H.-p. Zhang, Y. Ichihara, H. Kizu, K. Komiyama and G. R. Pettit, *Tetrahedron Lett.*, 1995, 36, 2783-2784. (c) H.-p. Zhang, Y. Kamano, Y. Ichihara, H. Kizu, K. Komiyama, H. Itokawa and G. R. Pettit, *Tetrahedron*, 1995, 51, 5523-5528. (d) H.-p. Zhang, H.

Shigemori, M. Ishibashi, T. Kosaka, G. R. Pettit, Y. Kamano and J. i. Kobayashi, *Tetrahedron*, 1994, 50, 10201-10206.
2. W. Balk-Bindseil, E. Helmke, H. Weyland and H. Laatsch, *Liebigs Ann.*, 1995, 1291-1294.
3. K. A. Ubaidullaev, R. Shakirov and S. Y. Yunusov, *Chem. Nat. Compd.*, 1976, 12, 499-500.
4. (a) S. Peddibhotla, *Curr. Bioact. Compd.*, 2009, 5, 20-38. (b) G. Bergonzini and P. Melchiorre, *Angew. Chem. Int. Ed.*, 2012, 51, 971-974. (c) T. Bui, N. R. Candeias and C. F. Barbas, *J. Am. Chem. Soc.*, 2010, 132, 5574-5575. (d) T. Tokunaga, W. E. Hume, J. Nagamine, T. Kawamura, M. Taiji and R. Nagata, *Bioorg. Med. Chem. Lett.*, 2005, 15, 1789-1792. (e) T. Tokunaga, W. E. Hume, T. Umezome, K. Okazaki, Y. Ueki, K. Kumagai, S. Hourai, J. Nagamine, H. Seki, M. Taiji, H. Noguchi and R. Nagata, *J. Med. Chem.*, 2001, 44, 4641-4649.
5. T. Takao, F. Kitatani, N. Watanabe, A. Yagi and K. Sakata, *Biosci. Biotechnol. Biochem.*, 1994, 58, 1780-1783.
6. (a) A. K. Franz, P. D. Dreyfuss and S. L. Schreiber, *J. Am. Chem. Soc.*, 2007, 129, 1020-1021. (b) K. A. Marx, P. O'Neil, P. Hoffman and M. Ujwal, *J. Chem. Inform. Comput. Sci.*, 2003, 43, 1652-1667. (c) V. Schulz, M. Davoust, M. Lemarié, J.-F. Lohier, J. Sopkova de Oliveira Santos, P. Metzner and J.-F. Brière, *Org. Lett.*, 2007, 9, 1745-1748. (d) S. R. Yong, A. T. Ung, S. G. Pyne, B. W. Skelton and A. H. White, *Tetrahedron*, 2007, 63, 5579-5586. (e) V. Kumar, S. Mukherjee, A. K. Prasad, C. E. Olsen, S. J. Schäffer, S. K. Sharma, A. C. Watterson, W. Errington and V. S. Parmar, *Tetrahedron*, 2005, 61, 5687-5697. (f) V. Sharma, S. Peddibhotla and J. J. Tepe, *J. Am. Chem. Soc.*, 2006, 128, 9137-9143.
7. N. Boechat, W. B. Kover, V. Bongertz, M. M. Bastos, N. C. Romeiro, M. L. Azevedo and W. Wollinger, *Med. Chem.*, 2007, 3, 533-542.
8. (a) H. Kobayashi, K. Shin-Ya, K. Nagai, K. Suzuki, Y. Hayakawa, H. Seto, B. S. Yun, I. J. Ryoo, J. S. Kim, C. J. Kim and I. D. Yoo, *J. Antibiot.* , 2001, 54, 1013-1018. (b) H. Kobayashi, K. Shin-Ya, K. Furihata, K. Nagai, K.-i. Suzuki, Y. Hayakawa, H. Seto, B.-S. Yun, I.-J. Ryoo and J.-S. Kim, *J. Antibiot.*, 2001, 54, 1019-1024.
9. (a) P. Hewawasam, N. A. Meanwell, V. K. Gribkoff, S. I. Dworetzky and C. G. Boissard, *Bioorg. Med. Chem. Lett.*, 1997, **7**, 1255-1260. (b) P. Hewawasam, M. Erway, S. L. Moon, J. Knipe, H. Weiner, C. G. Boissard, D. J. Post-Munson, Q. Gao, S. Huang, V. K. Gribkoff and N. A. Meanwell, *J. Med. Chem.*, 2002, **45**, 1487-1499. (c) A. Kumar and S. S. Chimni, *RSC Adv.*, 2012, **2**, 9748-9762.
10. (a) J. F. Da Silva, S. J. Garden and A. C. Pinto, *J. Braz. Chem. Soc.*, 2001, **12**, 273-324. (b) J. J. Li and E. J. Corey, in *Name Reactions in Heterocyclic Chemistry II*, eds. J. J. Li and E. J. Corey, John Wiley & Sons, Inc., Hoboken, NJ, USA., 2011, pp. 83-212. (c) T. Shirai, H. Ito and Y. Yamamoto, *Angew. Chem., Int. Ed.*, 2014, **53**, 2658-2661. (d) A. Kumar, J. Kaur, P. Chauhan and S. Singh Chimni, *Chem. - Asian J.*, 2014, **9**, 1305-1310. (e) Y.-L. Liu, B.-L. Wang, J.-J. Cao, L. Chen, Y.-X. Zhang, C. Wang and J. Zhou, *J. Am. Chem. Soc.*, 2010, **132**, 15176-15178. (f) G.-W. Wang, A.-X. Zhou, J.-J. Wang, R.-B. Hu and S.-D. Yang, *Org. Lett.*, 2013, **15**, 5270-5273. (g) J. C. Gomes, J. Sirvent, A. Moyano, M. T. Rodrigues, Jr. and F. Coelho, *Org. Lett.*, 2013, **15**, 5838-5841. (h) R. Niu, J. Xiao, T. Liang and X. Li, *Org. Lett.*, 2012, **14**, 676-679. (i) D. Monge, A. M. Crespo-Pena, E. Martin-Zamora, E. Alvarez, R. Fernandez and J. M. Lassaletta, *Chem. - Eur. J.*, 2013, **19**, 8421-8425. (j) K. Kumari, B. K. Allam and K. N. Singh, *RSC Adv.*, 2014, **4**, 19789-19793.
11. (a) D. Sano, K. Nagata and T. Itoh, *Org. Lett.*, 2008, **10**, 1593-1595. (b) M. Retini, G. Bergonzini and P. Melchiorre, *Chem. Commun.*, 2012, **48**, 3336-3338.
12. J. Chen, P. Chen, C. Song and J. Zhu, *Chem. - Eur. J.*, 2014, In Press.
13. B. Liu, Y. Fan, Y. Gao, C. Sun, C. Xu and J. Zhu, *J. Am. Chem. Soc.*, 2013, **135**, 468-473.
14. G. A. Russell, C. L. Myers, P. Bruni, F. A. Neugebauer and R. Blankespoor, *J. Am. Chem. Soc.*, 1970, **92**, 2762-2769.
15. (a) A. Fridman, F. Mukhametshin and S. S. Novikov, *Russ. Chem. Rev.*, 1971, **40**, 34. (b) R. F. Eizember, K. R. Vogler, R. W. Souter, W. N. Cannon and P. M. Wege, *J. Org. Chem.*, 1979, **44**, 784-786. (c) B. C. Challis and J. A. Challis, in *Amino, Nitrosco and Nitro Compounds and Their Derivatives (1982)*, John Wiley & Sons, Ltd., 1982, pp. 1151-1223.
16. (a) I. D. Biggs and D. L. H. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1975, 107-111. (b) J. T. Thompson and D. L. H. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1977, 1932-1937. (c) D. L. H. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1976, 1838-1841.