A Dehydrogenation Route to Azomethine Ylides and Isoindoles

## Ronald Grigg * and Frances Heaney
Department of Chemistry, Queen's University, Belfast BT9 5AG, Northern Ireland

Dehydrogenation of methyl 1,2,3,4-tetrahydroisoquinolin-2-yl- and β-carbolin-9-yl-acetates with palladium black in dimethylformamide generates *anti*-azomethine ylides stereospecifically. The analogous reaction with methyl isoindolin-2-ylacetate gives the corresponding isoindole. Both types of product can be trapped by *N*-methylmaleimide. The mechanism of the dehydrogenation processes is discussed.

There has been a great resurgence of interest recently in new methods of generating azomethine ylides. Methods have been developed involving oxazolines,[1] desilylation of *N*-(silylmethyl)imines[2] and related precursors,[3] 1,2-prototropy in activated imines[4] and related metal ion catalysed processes,[5] decarboxylation of imines of α-amino acids,[6] tertiary amine oxides,[7] and deprotonation of intermediate iminium species.[8] We now report a further and radically different method, dehydrogenation, for the generation of these reactive intermediates.

A solution of compound (1) (1 mol) and *N*-methylmaleimide (NMM) (2 mol) when heated in dimethylformamide (DMF) at 110 °C for 18 h in the presence of palladium black afforded a 1:1 mixture of cycloadducts (2) and (3) in 65%

(1)

(2)

(3)

(4) **a** :   R = CO$_2$Me ,   R^1 = H

b :   R = H ,   R^1 = CO$_2$Me
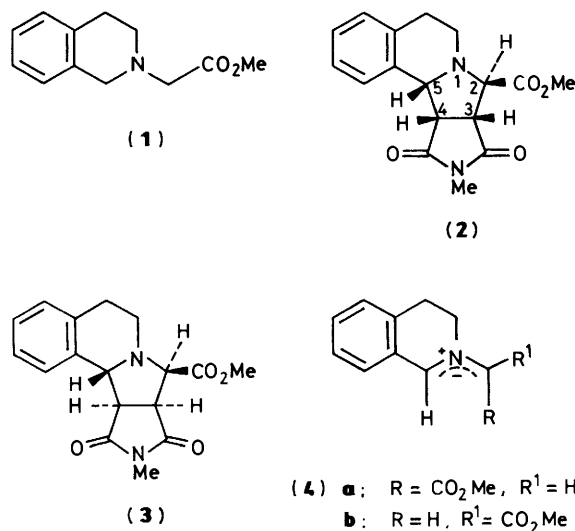
combined yield. Excess of NMM was used to regenerate the active palladium catalyst by acting as a recipient for the hydrogen removed from (1) in the dehydrogenation process. The stereochemistry of (2) and (3), which was established by n.O.e. experiments, indicates the *anti*-dipole (4a) is involved in

the cycloaddition process. No adducts arising from the *syn*-dipole (4b) were detected. Our wide experience with NMM as a dipolarophile indicates that its high reactivity ensures trapping of the dipole mixture produced under kinetic control,[6] *i.e.* before any equilibration (4a) $\rightleftharpoons$ (4b). Thus, the dehydrogenation results in stereospecific formation of (4a).

An analogous result was obtained with (5) which, under the same conditions, afforded a 1:1 mixture of (6) and (7), both of which are derived from the *anti*-dipole (8). No adducts arising from the corresponding *syn*-dipole were detected. Both (4a) and (8) can also be intercepted by dimethyl fumarate to give analogous adducts in 50—60% yield. In the case of (5) the reaction was noticeably slower and had proceeded to *ca.* 67% conversion after 40 h. Thus, (1) reacts with dimethyl fumarate and palladium black to afford a 1:1 mixture of (9) and (10) (50% combined yield) together with *ca.* 10% of a third, as yet unidentified, product.

An attempt to generate a dipole from (11) (NMM, DMF, 110 °C, 18 h) using palladium black led to the formation of (12) in *ca.* 60% yield. This result indicates that the initial dehydrogenation involves the benzylic methylene group, *i.e.* proceeds *via* (13), and that deprotonation leading to the isoindole (14) is preferred over deprotonation leading to dipole (15). Moreover, the acyclic tertiary amino acid ester (16) does not give a dipole under the same conditions.

Palladium catalysts have long been known to dealkylate tertiary amines *via* an intermediate iminium species followed by hydrolysis [Scheme 1 (a)].[9]

The failure of the acyclic substrate (14) to dehydrogenate under the same conditions† as (1), (5), and (11), and of the cycloadducts to further dehydrogenate, leads us to conclude that stereochemical factors are important in the dehydrogenation process. Hence we suggest co-ordination of palladium to the nitrogen atom facilitates insertion into the α-CH bond provided the dihedral angle between the α-CH and N–Pd bonds is near, or equal to, zero [Scheme 1(b)]. The iminium species
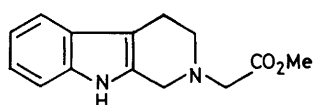
(5)
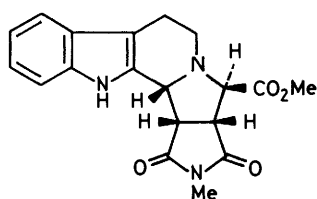
(6)

(7)

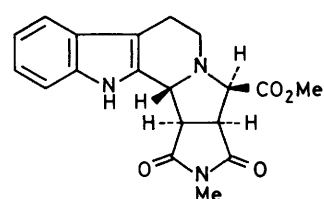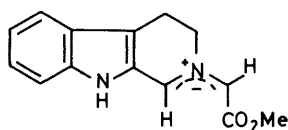(8)

(9)

(10)

(11)

(12)

(13)

(14)

(15)

(16)

(a)

(b)
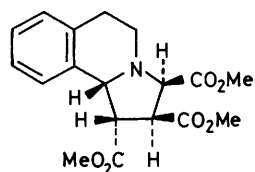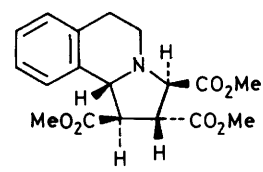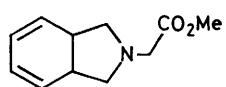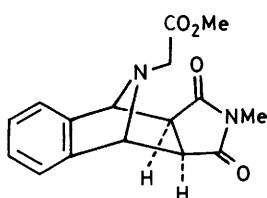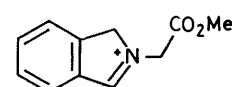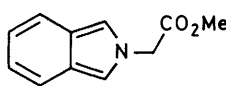
Scheme 1.

Scheme 2.

then undergoes deprotonation furnishing either the dipoles (4a) and (8) or the isoindole (14). A related dehydrogenation of hydroxylamines to nitrones has been reported.[10] Stereospecific formation of the *anti*-dipole suggest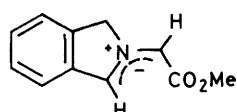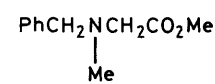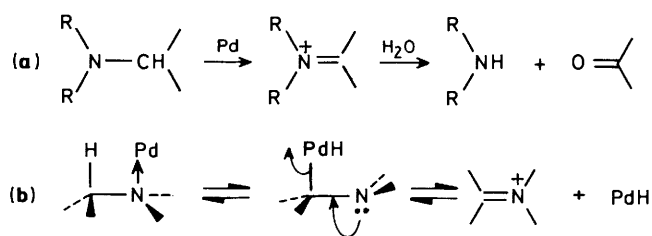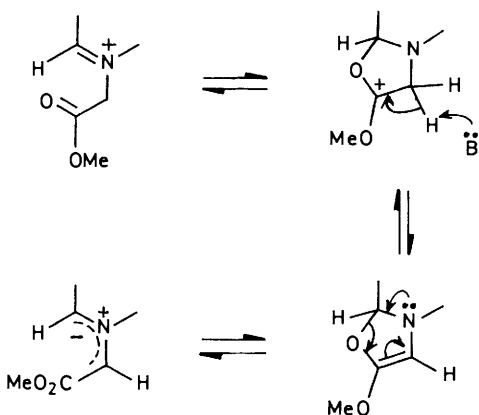s the intervention of an oxazoline intermediate (Scheme 2). Oxazolines are known to ring open to azomethine ylides.[1] Our previously reported generation of azomethine ylides from primary and secondary amines and bifunctional carbonyl compounds[8] also furnishes *anti*-dipole stereospecifically.

Experimental

Preparation of Cycloadducts (2) *and* (3).—A mixture of methyl 1,2,3,4-tetrahydroisoquinoline-2-ylacetate (2.05 g, 10 mmol), *N*-methylmaleimide (2.2 g, 20 mmol), and palladium black (200 mg, 2 mmol) in DMF (70 ml) was stirred and heated at 110 °C for 18 h. The reaction mixture was cooled, diluted with CHCl$_3$ (50 ml), and filtered. The solvent was removed under reduced pressure to leave a dark brown viscous oil whose ^{1}H n.m.r. spectrum showed it to comprise a 1:1 mixture of (2) and (3), together with a small amount of unchanged starting material. Purification by column chromatography on silica eluting with ether–light petroleum (b.p. 40—60 °C) (2:1, v/v) afforded (2) (1 g) and (3) (1 g) (65% combined yield) [Found (mixed isomers): C, 64.75; H, 5.85; N, 8.7. C$_{17}$H$_{18}$N$_2$O$_4$ requires C, 64.95; H, 5.75; N, 8.90%]; *m/z* (mixed isomers) 314 (M^+, 25%) and 255 (100%).

(2). Colourless hexagonal plates from ether–light petroleum

(b.p. 40—60 °C), m.p. 142—144 °C; δ(CDCl$_3$) 7.4, 7.2, and 7.1 (3 × m, 4 H, ArH), 4.51 (d, 1 H, J 7.3 Hz, 5-H), 4.23 (s, 1 H, 2-H), 3.76 (s, 3 H, OMe), 3.72 (t, 1 H, J 7.5 Hz, 4-H), 3.62 (d, 1 H, 3-H), 3.15—2.68 (m, 4 H, 2 × CH$_2$), and 2.85 (s, 3 H, NMe).

(**3**). Fine colourless needles from ether–light petroleum (b.p. 40—60 °C), m.p. 145—146 °C; δ(CDCl$_3$), 7.4, 7.2, and 7.1 (3 × m, 4 H, ArH), 4.84 (br s, 1 H, 5-H), 4.06 (d, 1 H, J 7.6 Hz, 2-H), 3.83 (s, 3 H, OMe), 3.57 (t, 1 H, 3-H), 3.49 (dd, 1 H, J 2.4 and 8.0 Hz, 4-H), 3.32 and 3.18 (2 × m, 2 × 1 H, NCH$_2$), 3.05 (s, 3 H, NMe), and 3.02 and 2.60 (2 × m, 2 × 1 H, ArCH$_2$).

Acknowledgements

References
1 E. Vedejs and J. Grissom, *J. Am. Chem. Soc.*, 1988, **110**, 3238; *J. Org. Chem.*, 1988, **53**, 1876.
2 E. Vedejs and G. R. Martinez, *J. Am. Chem. Soc.*, 1979, **101**, 6452; E. Vedejs and F. G. West, *Chem. Rev.*, 1986, **86**, 941; A. Mosonomi, Y. Sakata, and H. Sakurai, *Chem. Lett.*, 1984, 1117; K. Achiwa and M. Sekiya, *Heterocycles*, 1983, **120**, 167; W. K. Anderson and T. T. Dabrah, *Synth. Commun.*, 1986, **16**, 559; A. Padwa, P. Eisenbarth, M. K. Venkatramanan, and G. S. K. Wong, *J. Org. Chem.*, 1987, **52**, 2427.
3 E. Vedejs and F. G. West, *J. Org. Chem.*, 1983, **48**, 4773; A. Padwa, G. Haffmans and M. Thomas, *J. Org. Chem.*, 1984, **49**, 3314; O. Tsuge, S. Kanemasa, A. Hatada, and K. Matsuda, *Bull. Chem. Soc. Jpn.*, 1986, **59**, 2537.
4 R. Grigg, J. Komp, and N. Thompson, *Tetrahedron Lett.*, 1978, 2827; R. Grigg, H. Q. N. Gunaratne, V. Sridharan, and S. Thianpatanagul, *ibid.*, 1983, **24**, 4363; R. Grigg, *Chem. Soc. Rev.*, 1987, **16**, 89.
5 R. Grigg, H. Q. N. Gunaratne, and V. Sridharan, *Tetrahedron*, 1987, **43**, 5887; D. A. Barr, R. Grigg, H. A. N. Gunaratne, J. Kemp, P. McMeekin, and V. Sridharan, *ibid.*, 1988, **44**, 557; O. Tsuge, S. Kanemasa, and M. Yoshioka, *J. Org. Chem.*, 1988, **53**, 1384.
6 H. Ardill, R. Grigg, V. Sridharan, and S. Surendrakumar, *Tetrahedron*, 1988, **44**, 4953 and references therein.
7 J. Chastenet and G. Roussi, *J. Org. Chem.*, 1988, **53**, 3808.
8 H. Ardill, R. Grigg, V. Sridharan, S. Surendrakumar, S. Thianpatanagul, and S. Kanajun. *J. Chem. Soc., Chem. Commun.*, 1986, 602.
9 S.-T. Murahashi, T. Hirano, and T. Yano, *J. Am. Chem. Soc.*, 1978, **100**, 348; S.-I. Murahashi and T. Watanabe, *ibid.*, 1979, **101**, 7429.
10 S.-I. Murahashi, H. Mitsui, T. Watanabe, and S.-I. Zenki, *Tetrahedron Lett.*, 1983, **24**, 1049.