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STEREOSELECTIVE SYNTHESIS OF 1,2-DIAMINOINDANS: A NOVEL APPROACH TO VICINAL DIAMINES

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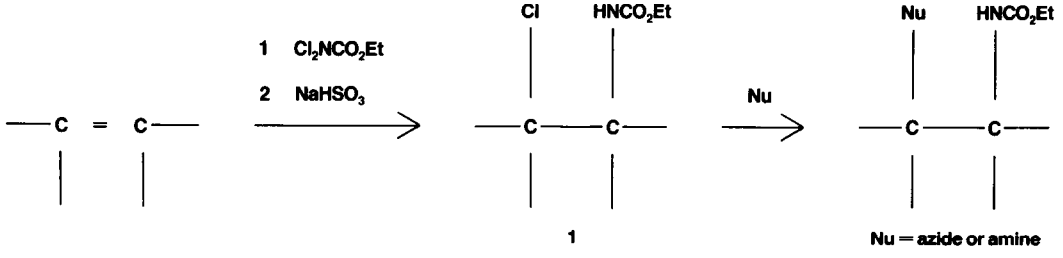
Summary: A new approach to the synthesis of unsymmetrical N-substituted vicinal diamines is illustrated by the stereospecific conversion of indene into *cis* and *trans* 1,2-diaminoindan derivatives.

Traditional approaches to vicinal diamines rely on the opening of epoxides[1] or aziridines[2] by suitable nucleophiles such as azide ion or amines. Direct amination procedures mediated by organometallic reagents e.g. $OsO(N\text{-}tBu)_3$[3], $PdCl_2(PhCN)_2$[4], HgO[5] and $Tl(OAc)_3$[6] have been used successfully for the conversion of olefins into vicinal diamines, but such methods appear to be limited to the introduction of identical amino groups. Recently Kohn[7] described a four stage sequence for preparing nitrogen unsubstituted vicinal diamines from olefins via imidazoline intermediates.

As an alternative to existing methodology, it was envisaged that olefins might serve as precursors for N-substituted 1,2-diamines via a two stage sequence involving addition of N,N-dichlorourethane followed by displacement using azide ion or an amine (Scheme 1). The reaction of olefins with N,N-dichlorourethane is well documented[8]. Regioselective addition usually occurs with unsymmetrical olefins[9]. Although the adduct (1) is often obtained as a mixture of stereoisomers, there are examples of stereospecific additions to cyclic olefins[9c]. This suggested that such an approach might be suited to the functionalisation of cyclic systems and raised the possibility of controlling overall stereochemistry by judicious choice of conditions at both stages of the process.



Scheme 1

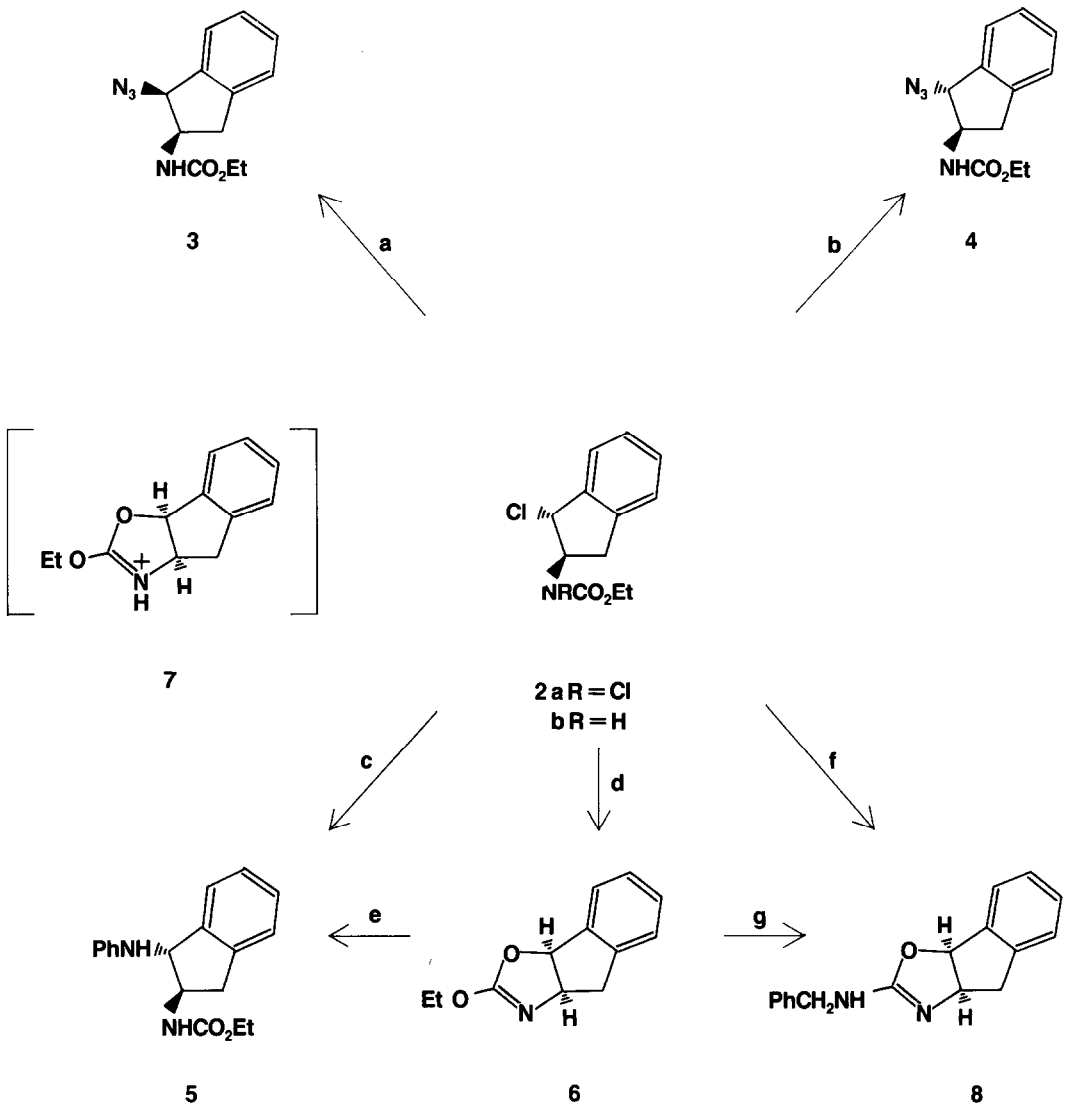
Application of this strategy is illustrated by the synthesis of 1,2-diaminoindan derivatives (Scheme 2). Addition of N,N-dichlorourethane to indene at ambient temperature followed by *in situ* reduction of the intermediate N-chlorourethane (2a) has been shown to give the *trans* adduct (2b)[9c]. Treatment of (2b) with sodium azide produced the *cis* azidoindan (3). The corresponding *trans*[10] isomer (4) was obtained from (2b) by reaction with sodium azide after *in situ* generation of the derived aziridine. Reduction of both *cis* and *trans* azides readily afforded the corresponding diamines.

The behaviour of (2b) towards amine nucleophiles proved sensitive to the basicity of the amine and the conditions employed. The reaction of aniline with (2b) gave the *trans*[10] diamine derivative (5) m.p. 131-2°. Optimal conditions involved warming (2b) with excess aniline and produced an 80% yield of (5). An acceptable yield (50%) also resulted from treatment of (2b) with one equivalent of aniline using $BaCO_3$ as a mild acid mop. When the reaction was performed in the presence of a stronger base such as K_2CO_3 the yield dropped to 25%. The crude material contained a second component which comprised 30% of the total and was identified as the oxazoline (6) m.p. 53-4°. Indeed the oxazoline (6) could be obtained in excellent yield (97%) by treatment of (2b) with K_2CO_3 in aqueous ethanol.

In order to clarify the role of the oxazoline (6) in the alkylation process its reactivity towards aniline was examined. Reaction proved sluggish and prolonged heating led to a mixture from which the *trans* diamine derivative (5) was isolated in low yield (20%). The addition of a catalytic amount of p-toluenesulphonic acid enhanced the rate considerably and resulted in a good yield (60%) of (5) under mild conditions. These observations are in line with reports of acid catalysed ring openings of simple 2-alkyl-2-oxazolines to give N-(2-aminoethyl) carboxamides[11], and point to the interm ediacy of the oxazolinium salt (7) in the facile reaction between aniline and the adduct (2b). Such a mechanism would account for the pH dependence of the reaction and the *trans* stereochemistry of the product. Further evidence for the pH dependent interconversion between (2b) and the oxazoline (6) was provided by the observation that the latter could readily be converted back into (2b) by treatment with ethereal HCl.

Treatment of (2b) with benzylamine produced a low yield of the 2-benzylamino-2-oxazoline (8)[12]. It is likely that this reaction proceeds via the oxazoline (6) since treatment of (6) with benzylamine readily afforded (8). The preference shown by benzylamine for attack at the 2-position of the oxazoline (6) was also observed in the presence of an acid catalyst. The reasons for the marked differences in reactivity displayed by the oxazoline (6) towards aniline and benzylamine remain to be elucidated.

In summary, addition of N,N-dichlorourethane to indene followed by displacement with aniline leads to a *trans* diamine derivative, whereas reaction with azide ion gives *cis* or *trans* diamine precursors depending on the conditions employed. This approach is currently being extended to include other arylamines as well as related cyclic olefins.



a) NaN_3/DMF/rt/24h (77%); b) NaH/DMF/40°/10h then NaN_3/NH_4Cl/55°/50 min (67%); c) $PhNH_2$/50°/4h (80%) or $PhNH_2$/$BaCO_3$/DMF/85°/10h (50%); d) K_2CO_3/EtOH-H_2O/rt/20h (97%); e) $PhNH_2$/p-toluenesulphonic acid/toluene/50°/0.5h (60%); f) $PhCH_2NH_2$/DMF-toluene/80°/6h (23%); g) $PhCH_2NH_2$/toluene/60°/20h (80%).

Scheme 2

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10. In 1,2 disubstituted indans the shift difference between protons at C-3 is generally smaller in the *cis* compound than in the corresponding *trans* isomer (see C.F. Huebner, E.M. Donoghue, C.J. Novak, L. Dorfman and E. Wenkert, *J. Org. Chem.*, 1970, *35*, 1149). These protons are observed at δ2.80 (dd, J=16Hz, 9Hz) and δ3.22 (dd, J=16Hz, 7Hz) in (3) whereas (4) gives signals at δ2.70 (dd, J=16Hz, 6Hz) and δ3.30 (dd, J=16Hz, 7Hz). In (5) the C-3 protons appear at δ2.80 (dd, J=16Hz, 6Hz) and δ3.38 (dd, J=16Hz, 6Hz). These assignments have been confirmed by X-Ray analysis on products derived from (3) and (5).
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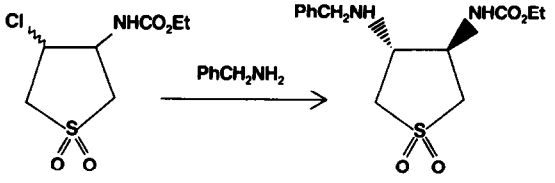
12. For comparison see K. Ohba, K. Mori, T. Kitahara, S. Kitamura and M. Matsui, *Agr. Biol. Chem.*, 1974, *38*, 1679.



In this case the intermediate is probably the unsaturated sulphone which can undergo a Michael reaction with benzylamine.

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