ChemComm

Application of Baylis–Hillman methodology in a novel synthesis of quinoline derivatives

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Received (in Cambridge, UK) 27th May 1998, Accepted 8th October 1998

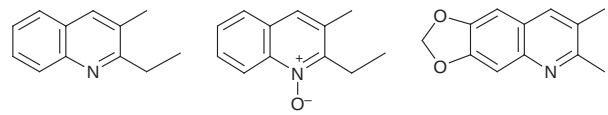
Reaction of 2-nitrobenzaldehyde with vinyl carbonyl compounds in the presence of 1,4-diazabicyclo[2.2.2]octane affords Baylis–Hillman products, catalytic reduction of which results in direct cyclisation to quinoline derivatives.

The Baylis–Hillman reaction has been the subject of two recent reviews[1,2] and continues to elicit attention.[3,4] We have demonstrated applications of this reaction in the synthesis of substituted indolizines from pyridine-2-carbaldehydes[5,6] and, in analogous reactions of salicylaldehydes, have uncovered a veritable cascade of transformations involving the formation of chromene and coumarin derivatives.[7,8] Extension of this general methodology to 2-aminobenzaldehydes was expected to provide access to quinoline derivatives.

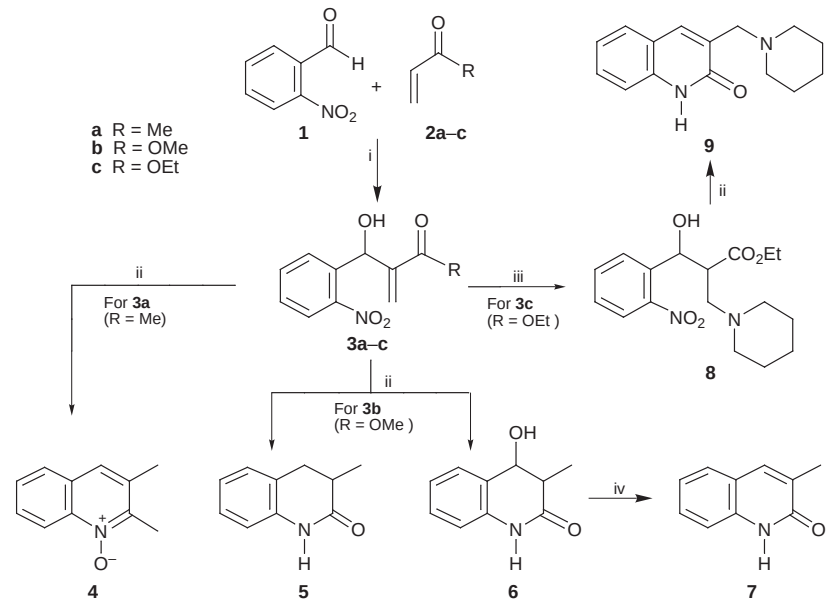
Numerous quinoline syntheses have been developed,[9] including the Friedlander synthesis (and modifications thereof) in which use is made of 2-aminobenzaldehydes. A limiting factor in the Friedlander methodology, however, is the relative inaccessibility of substituted 2-aminobenzaldehydes. This limitation, coupled with the fact that aldehyde electrophilicity is an important factor in Baylis–Hillman reactions,[10] prompted us to explore the use of 2-nitrobenzaldehyde as an activated alternative to 2-aminobenzaldehyde, subsequent reduction of the nitro group being expected to permit cyclisation *via* the resulting amine. Quinolines have, in fact, been obtained previously in yields of 27–30%, by passing mixtures of 2-nitrobenzaldehyde and various alcohols over a heterogeneous catalyst at elevated temperature (300–320 °C).[11] Here we report preliminary results which clearly illustrate the potential of the Baylis–Hillman approach to quinoline derivatives under remarkably mild conditions.

Treatment of 2-nitrobenzaldehyde **1** with methyl vinyl ketone (MVK) **2a**, methyl acrylate **2b** and ethyl acrylate **2c** in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) at, or below, room temperature† afforded the expected Baylis–Hillman products **3a–c** (Scheme 1) in moderate to good yield (68–85%). Several methods of reducing the nitro compounds **3a–c** were examined, the most efficient proving to be catalytic hydrogenation using a 10% palladium on carbon catalyst in EtOH.‡ Reduction of compound **3a** afforded, in 56% yield, a product initially presumed to be 2,3-dimethylquinoline but subsequently identified as the *N*-oxide **4**.§ Hydrogenation of the methyl ester **3b** afforded two cyclised products, *viz*. 3-methyl-2-oxo-1,2,3,4-tetrahydroquinoline **5** (22%) and the 4-hydroxy analogue **6** (59%), the latter as a diastereomeric pair, which could be readily dehydrated (in 70% yield) to the conjugated, achiral 3-methyl-2-quinolinone **7**. The α,β-unsaturated carbonyl moiety in the Baylis–Hillman products **3** is, of course, susceptible to conjugate addition, and treatment of the ethyl ester **3c** with piperidine¶ led to the diastereomers **8**, reduction of which afforded the 2-quinolinone derivative **9**;‖ in this case, cyclisation of the corresponding amino intermediate may only occur *via* acyl substitution. In principle, cyclisation of the reduced, or partially reduced, intermediates may be expected to involve *either* conjugate addition *or* nucleophilic attack at the carbonyl carbon. In practice, the latter path appears to be the dominant, if not exclusive, mode of cyclisation—somewhat surprisingly, given the lack of regioselectivity exhibited by salicylaldehyde analogues.[7,8]

Application of the methodology to the reaction of 2-nitrobenzaldehyde with ethyl vinyl ketone afforded *both* 2-ethyl-3-methylquinoline **10** (25%) *and* the *N*-oxide **11** (31%).



10 **11** **12**



Scheme 1 *Reagents and conditions*: i, DABCO, $CHCl_3$; ii, H_2, Pd-C, EtOH; iii, piperidine, THF; iv, TsOH, toluene, reflux.

Formation of the *N*-oxides **4** and **11** was established, in each case, by FAB MS analysis. Further extension of the procedure to the reaction of methyl vinyl ketone with 6-nitropiperonal gave, amongst other products, the corresponding quinoline **12** (26%).

In summary, application of the Baylis–Hillman reaction to 2-nitrobenzaldehydes provides convenient access to substituted quinoline derivatives which, in turn, constitute useful substrates for further elaboration. The results of ongoing studies, aimed at optimising reaction conditions for the selective formation of the quinolines or their *N*-oxides and exploring the generality of the method, will be reported fully in due course.

We thank the Foundation for Research Development (FRD) and Rhodes University for generous financial support, the University of Lagos, Nigeria, for study leave (to O. B. F.), Dr W. E. Molema for assistance with NMR analysis and Dr L. Fourie (University of Potchefstroom) for FAB MS data.

Notes and references

† In a typical Baylis–Hillman reaction, a solution of 2-nitrobenzaldehyde **1** (5.0 g, 33 mmol), methyl acrylate **2b** (2.95 g, 34.2 mmol) and DABCO (0.18 g, 1.6 mmol) was stirred in a stoppered flask for 3–7 d. [In the case of methyl vinyl ketone **2a**, the reaction was noticeably exothermic; use of CH_2Cl_2 as solvent and cooling the mixture (*ca*. 0 °C) during addition of the reactants resulted in a significantly cleaner product.] The solvent was evaporated *in vacuo* and the residue chromatographed [flash chromatography on silica; elution with hexane–EtOAc (3:1)] to give **3a** (6.78 g; 85%).

‡ Hydrogenation was effected in EtOH at atmospheric pressure using a 10% Pd-C catalyst (wet, Degussa type; as supplied by Aldrich Chemical Co.)

§ *Selected data* for **4**, mp 123–125 °C (Found, by FAB MS, MH^+: 174.09179. Calc. for $C_{11}H_{12}NO^+$, 174.09189.); δ_H(400 MHz; $CDCl_3$) 2.45 (3H, s, 3-Me), 2.68 (3H, s, 2-Me), 7.45 (1H, s, 4-H), 7.51 (1H, t, 6-H), 7.63 (1H, t, 7-H), 7.68 (1H, d, 5-H), 8.68(1H, d, 8-H); δ_C(100 MHz; $CDCl_3$) 14.7 (2-Me), 20.2 (3-Me), 119.6 (C-5), 125.1 (C-4), 127.1 (C-8), 127.7 (C-7), 128.1 (C-4a), 129.2 (C-6), 130.8 (C-3), 139.9 (C-8a), 146.4(C-2)].

¶ A mixture of **2c** (0.5 g), piperidine (0.5 ml) and THF (5 ml) was stirred in a stoppered flask for 24 h. Excess piperidine was evaporated *in vacuo* and the residue was chromatographed [flash chromatography on silica; elution with hexane–EtOAc (2:1)] to give **8** (0.61g, 85%).

‖ Compounds **6**, **8** and **9**, which appear to be new, and the known quinoline derivatives **4**, **5**, **7**, **10–12** were characterised by elemental (high resolution MS) and ^1H and ^{13}C NMR spectroscopic analyses.

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Communication 8/07827K