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Three component synthesis of oxa-bridged tetracyclic tetrahydroquinolines

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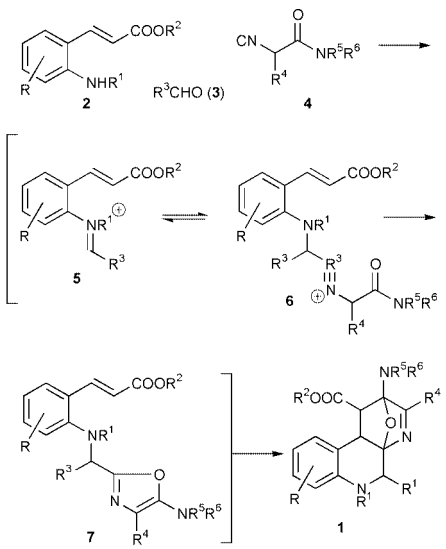
Received (in Cambridge, UK) 16th May 2001, Accepted 11th July 2001
First published as an Advance Article on the web 16th August 2001

Bridged tetracyclic tetrahydroquinoline is synthesized by a novel one-pot three component condensation of an *ortho*-amino cinnamate, α-isocyano acetamide and an aldehyde.

Maximizing synthetic efficiency by designing complexity-generating multicomponent domino processes is gaining more and more importance in organic synthesis and in drug discovery endeavour.[1–4] In connection with our ongoing project, a novel one-pot three component synthesis of tetracyclic tetrahydroquinoline[5] was envisaged. The sequence of events, hinged upon our recently developed synthesis of 5-aminooxazole,[6] is outlined in Scheme 1. Thus, reaction of an aniline, an aldehyde and an α-isocyano acetamide should give the aminooxazole *via* an iminium, then a nitrilium ion intermediate. Cycloaddition of oxazole as an aza-diene with a properly predisposed dienophile would then produce a bridged tetrahydroquinoline-containing polycycle that, *a priori*, would undergo further fragmentation to provide phenanthroline.[7] While domino Ugi/Diels–Alder cycloadditions starting from diene- and dienophile-containing building blocks have been elegantly developed,[8] the multi-component reaction (MCR)/cycloaddition sequence involving *en route* generation of a transient diene, to the best of our knowledge, was unknown.[9] The realization of this concept as well as the documentation of the remarkable thermostability of cycloadduct **1** is the subject of this communication.

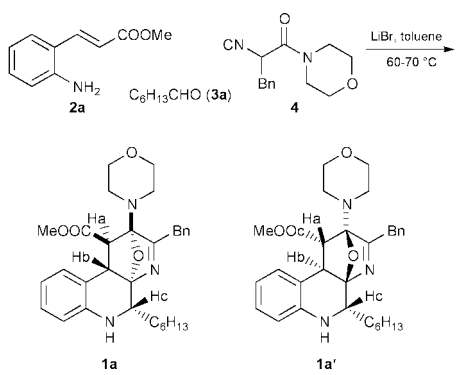
Using *ortho*-amino methyl cinnamate (**2a**), heptanal (**3a**) and α-isocyano α-benzyl acetamide (**4a**) as inputs, reaction conditions were surveyed varying the solvent (MeOH, CF_3CH_2OH, benzene, toluene), the temperature (rt to 110°C), and the promotor (LiBr, $BF_3{\cdot}OEt_2$, $Yb(OTf)_3$, $Sc(OTf)_3$, $MgSO_4$). After a considerable number of experiments, conditions were worked out for the domino 3 component reaction (3CR)/intramolecular Diels–Alder cycloaddition process. Thus, under the optimal conditions (**2a** and **3a**, LiBr, in toluene, 2h then **4a**, 70 °C), tetracyclic tetrahydroquinoline **1** was isolated in 94% yield as a mixture of two separable diastereomers (ratio of **1a**:**1a′** = 3:1, Scheme 2). Without LiBr, **1a** and **1a′** were isolated in less than 6% yield under otherwise identical conditions.[10] The identification of 5-aminooxazole intermediate **7** (where NR^5R^6 = NEt_2) provided evidence that the reaction indeed proceeded as programmed. It is worthy of note that one C–N, one C–O and three C–O bonds were formed with the concomitant creation of five asymmetric centers in this one-pot process. The efficiency of this reaction was thus truly remarkable if one looks at the yield per bond formation.



Scheme 1

The stereochemistry of compound **1a** and **1a′** was deduced from both mechanistic consideration and NMR studies. The observed coupling constant between H_a and H_b ($J_{Ha\text{-}Hb}$ = 4.6 Hz for **1a** and 4.4 Hz for **1a′**) indicated a *gauche* relationship of these two protons in both compounds. For the inherent ring strain imposed by the connecting bridge, only the aryl-*exo*-ester-*endo* mode of cycloaddition was possible leading to the observed compounds. This model of ring formation is also indicative of a concerted rather than a stepwise process, since one could expect the formation of aryl-*exo*-ester-*exo* diastereomers if the latter mechanism was operating. The relative stereochemistry of the major adduct **1a** was deduced from the observation of a strong NOE cross peak between H_b and H_c in its NOESY spectrum and corroborated by X-ray analysis (Fig. 1).‡

Control experiments showed that the observed stereoselectivity was a thermodynamically controlled process. Indeed, re-submitting the diastereomerically pure compound **1a** to the reaction conditions led to the formation of a mixture of **1a** and **1a′** with the ratio identical to that resulting from the reaction mixture. The same is true for **1a′**. While the thermo-equilibrium can be interpreted by a sequence of heterocycloreversion/



Scheme 2

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 DOI: 10.1039/b104317j

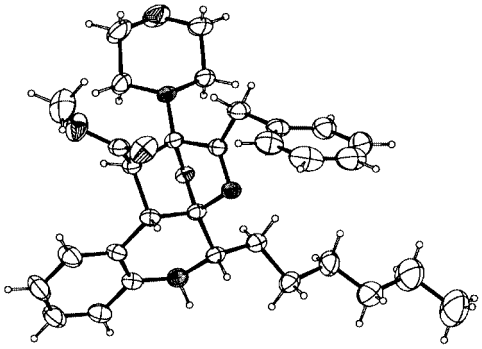

Fig. 1 X-ray structure of **1a**.

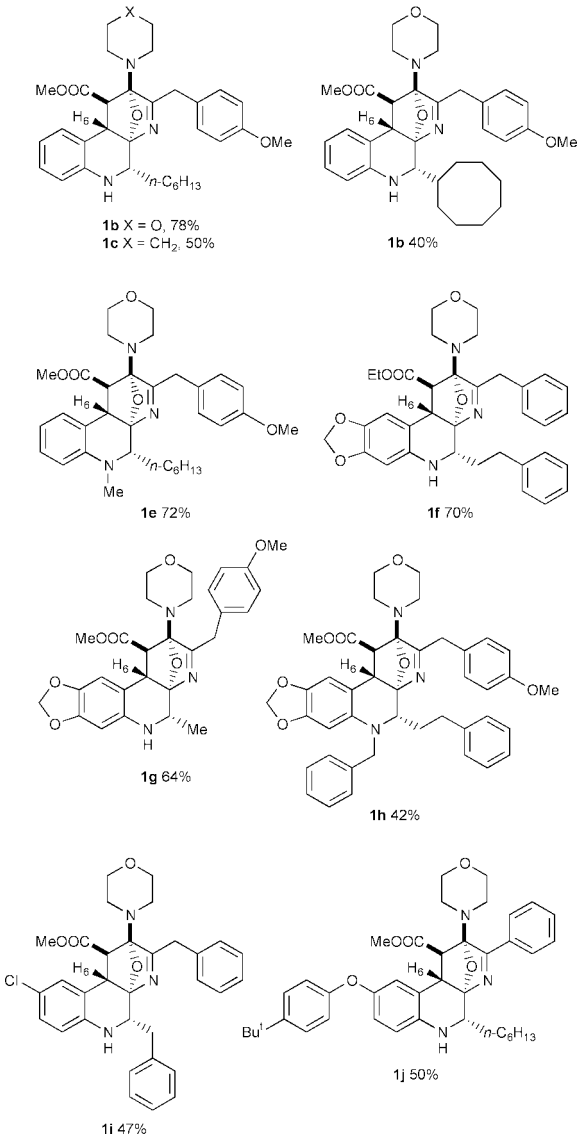

Fig. 2 Selected tetrahydroquinolines synthesized.

cycloaddition, the relatively high stability of compound **1** with a strained aminal function was nevertheless intriguing.

Selected structures synthesized in this preliminary study are listed in Fig. 2.§ The reaction conditions have not been individually optimized. As is seen, all substituents at the periphery of the tetracyclic ring system can be varied. The *ortho*-amino cinnamate with either electron donating or electron withdrawing group participated in the reaction, as did the *N*-alkylated derivatives. The α-branched aldehydes, as well as the α-alkyl and α-aryl substituted α-isocyano acetamides took part in this reaction. When cyclooctyl aldehyde was used, a single diastereomer was isolated. Since the nitrogen bearing the asymmetric center was the one that controlled the facial selectivity of the subsequent aza-Diels–Alder cycloaddition, the observation is thus understandable. As expected for Ugi type reaction, racemic tetrahydroquinoline was obtained even when enantiomerically pure isonitrile **4** (R = Bn, or phenyl) was used as input. At this stage of the development, the failure of aromatic aldehyde to enter the reaction cascade constituted the limitation of the present methodology.

In conclusion, we have developed a novel multicomponent domino process for the synthesis of oxa-bridged tetrahydroquinoline starting from simple and readily accessible linear precursors. Besides its synthetic efficiency and potential application in diversity oriented synthesis, we demonstrated, to the best of our knowledge, for the first time that Ugi-type condensations can be performed in toluene in the presence of LiBr without concurrent occurrence of a Passerini-type reaction.

Financial support from CONACYT (E. G.-Z.) and CNRS are gratefully acknowledged. We thank Mr M. De Paolis for helpful discussion.

Notes and references

‡ *Crystal data for* **1a**: pale yellow crystal (0.32 × 0.37 × 0.40 mm). $C_{31}H_{39}N_3O_4$, M_w = 517.65. Monoclinic system, space group $P2_1/n$, Z = 4, a = 14.049 (5), b = 9.982 (5), c = 20.886 (8) Å, β = 97.64 (3)°, V = 2903 Å^3, D_C = 1.184 g cm^{-3}, $F(000)$ = 1112, λ(Mo Kα) = 0.71073 Å, T = 293 K, μ = 0.08 mm^{-1}; 8306 data measured (θ range: 2.12 to 27.47°) on a Nonius Kappa-CCD area-detector diffractometer. Refinement with *SHELXL93*. $R_1(F)$ = 0.0755 for the 3303 $F_o \geq 4\,\sigma(F_o)$ and $wR_2(F^2)$ = 0.2294 for all the 4665 unique data. *GOF S* = 1.101. Residual electron density between −0.24 and 0.71 e Å^{-3}. CCDC 164901. See http://www.rsc.org/suppdata/cc/b1/b104317j/ for crystallographic data in .cif or other electronic format.

§ For the sake of convenience, only one diastereomer is shown.

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5 A broad range of bioactivities have been described for quinoline derivatives. For recent syntheses by MCR, see: (*a*) P. A. Grieco and A. Bahsas, *Tetrahedron Lett.*, 1988, **29**, 5855; (*b*) J. M. Mellor and G. D. Merriman, *Tetrahedron*, 1995, **51**, 6115; (*c*) S. Kobayashi and S. Nagayama, *J. Am. Chem. Soc.*, 1996, **118**, 8977; (*d*) B. Crosse, J. P. Bégué and D. Bonnet-Delpon, *J. Org. Chem.*, 2000, **65**, 5009.

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10 As a mild Lewis acid, lithium bromide may activate the imine intermediate and thus facilitating the subsequent nucleophilic attack. Control experiements showed that the strong Lewis acids such as $BF_3{\cdot}OEt_2$ decomposed both the tetrahydroisoquinoline and the amino-oxazole intermediate.