Diastereoselective synthesis of dihydroquinolines and tetrahydroquinolines from Morita Baylis-Hillman adducts

Manoel T. Rodrigues Jr., Andre Capretz Agy, Danilo Machado Lustosa and Fernando Coelho*

Laboratório de Síntese de Produtos Naturais e Fármacos, Instituto de Química, Universidade Estadual de Campinas-UNICAMP, Caixa Postal 6154, 13083-970, Campinas-SP-Brazil

*coelho@iqm.unicamp.br

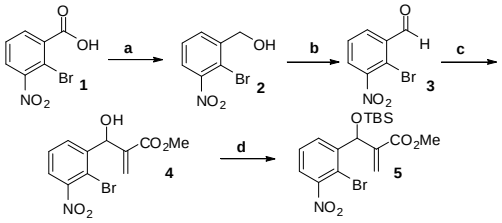
Keywords: Morita-Baylis-Hillman Reaction, dihydroquinolines and tetrahydroquinolines.

INTRODUCTION

The quinolone, dihydroquinolines and tetrahydroquinolines unities are present in many natural and synthetic compounds. These nuclei exhibit a wide spectrum of medicinal properties, such as antimalarial, antitumor, antibacterial, anti-thrombin, and many others.[1] Due to this biological profile several synthetic approaches have been known for the preparation of these heterocycles.[2] In this work we disclosed a facile method to prepare quinolines derivatives through a Morita-Baylis-Hillman adduct. Our approach is based on a tandem sequence involving a Michael addition reaction and a S_NAr reaction.

RESULTS AND DISCUSSION

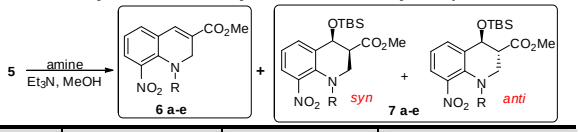
2-Bromo-3-nitrobenzaldehyde (**3**) was prepared according to a procedure described in literature. Acid **1** was reduced in the presence of $BH_3.SMe_2$ to afford alcohol **2** (Scheme 1). Oxidation of the alcohol **2** to aldehyde was accomplished using PCC, in 91% overall yield (2 steps). MBH adduct **4** was prepared using a protocol developed by our group.[3] In brief, aldehydes were treated with methyl acrylate to provide the corresponding MBH adduct in 98% yield. Compound 4 was therefore silylated in the presence of TBSOTf to give silylated derivative **5**, in 95% yield (Scheme 1).



Scheme 1. Preparation of aldehyde **3** and MBH adduct **4** and silylation of the MBH adduct. a) BH_3. SMe_2, rt, 12h; b) PCC, CH_2Cl_2, rt, 12h (91% - 2 steps); c) Methyl acrilate, DABCO,))), 24h, 98%; d) TBSOTf, CH_2Cl_2, rt, 2h, 95%.

A solution of the silylated MBH adduct **5** in methanol was treated, under reflux, with amine (1.2 eq.) in the presence of triethylamine (acting as a base) to give the substituted quinolines derivatives in good syn diastereoselectivity (*syn/anti*) and yields (Table 1).

Table 1. Synthesis of dihydro- and tetrahydroquinolines



Entry	R	6a-e Yield[a] %	7a-e Yield % (*syn:anti*)[b]
1	CH_2Ph	6a, 35	7a, 60 (11:1)
2	$(CH_2)_2$indoyl	6b, 42	7b, 53 (13:1)
3	$(CH_2)_2C_6H_4OMe$	6c, 43	7c, 53 (12:1)
4[c]	$CH_2Ph(OMe)_3$	6d, 48	7d, 35 (11:1)
5	$CH_2CH=CH_2$	6e, 43	7e, 52 (13:1)

[a]Yields refer to isolated purified products. [b]Diastereoselectivity was determined by ^{1}H NMR, by measuring the coupling constant of the carbinolic proton.[c] Entry 4: we observe a product degradation.

The formation of compounds **6a-e** can be explained by a S_N2' displacement reaction of silylated MBH **5** with amine followed by cyclization. Otherwise, the high diastereoselectivity attained in the preparation of compounds **7a-e** can be explained by the control exerted by the voluminous silyl group. Previous results described by our group support this proposition. Unfortunately all chromatographic attempts to separate the diastereoisomers failed.[4]

CONCLUSION

In summary, we have demonstrated that dihydro- and tetrahydroquinolines can be easily prepared in good yields and diastereoselectivity from MBH adducts.

ACKNOWLEDGEMENTS

We thank FAPESP, CNPq and CAPES for financial support.

REFERENCES

[1] Kaur, K.; Jain, M.; Reddy, R. P.; Jain, R. *Eur. J. Med. Chem.* **2010**, *45*, 3245. [2]Madapa, S.; Tusi, Z.; Batra, S. *Curr. Org. Chem.* **2008**, *12*,1116. [3] Coelho, F.; Almeida, W. P.; Mateus, C. R.; Feltrin, M.; Costa, A. M. *Tetrahedron* **2001**, *57*, 6901. [4]. Rodrigues Jr., M. T.; Gomes, J. C.; Smith, J.; Coelho, F. *Tetrahedron Lett.* **2010**, *51*, 4988.