Catalysis Letters, Vol. 117, Nos. 3–4, September 2007 (© 2007)
DOI: 10.1007/s10562-007-9127-4

A new, simple synthesis of 1,2-dihydroquinolines *via* cyclocondensation using zeolite catalyst

Adrienn Hegedüs,[a] Zoltán Hell,[a,*] Tamás Vargadi,[a] Attila Potor,[a] and Iván Gresits[b]

[a]*Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, H-1521Budapest, Hungary*
[b]*Department of Chemical and Environmental Process Engineering, Budapest University of Technology and Economics, H-1521Budapest, Hungary*

Received 12 April 2007; accepted 12 April 2007

A new, environmentally-friendly synthesis of dihydroquinolines from aniline and ketones using a small pore size zeolite as catalyst is described. This method is simple, cheap and gives the dihydroquinolines in high yield.

KEY WORDS: dihydroquinolines; zeolite; green chemistry.

1. Introduction

Dihydroquinolines and their derivatives are an important class of substances in organic and medicinal chemistry. They are found as core units in many natural products [1–4]. 2,2,4-Trisubstituted dihydroquinolines are found to exhibit a wide range of biological activities, such as antibacterial [5], antidiabetic [6] and anti-inflammatory [7] properties. These compounds have also been shown to act as lipid peroxidation inhibitors [8], HMG-CoA reductase inhibitors [9] and progesterone agonists [10] and antagonists [11].

In the literature numerous methods are described for the synthesis of dihydroquinolines [12–16], but these methods have several disadvantages, such as long reaction times, strong reaction conditions or the formation of tarry byproducts. A possible way for the preparation of 1,2-dihydroquinolines is the reaction of aromatic amines with different compounds such as glycerine (Skraup synthesis [17]), β-diketones (Combes synthesis [18]), α,β-unsaturated carbonyl compounds (Doebner–Miller reaction [19]) or ketones [20] in the presence of an acid catalyst. Newer synthetic methodes were also studied e.g. the reaction of aromatic amines with ketones using $Sc(OTf)_3$ as catalyst under microwave irradiation in the modified Skraup synthesis [21].

Ersorb-4 (E4) is a weakly acidic (pH $\sim$ 5.5) clinoptilolite-type zeolite adsorbent with 4 Å pore size. It can adsorb only small molecules such as water, hydrochloric acid, ammonia, methanol. The commercially also available E4a is a modification of E4 with enhanced acidity (pH $\sim$ 3, the modification is a protected procedure of the manufacturer, details are not given) [22,23]. The acidity of E4 and E4a were determined by pyridine adsorption method. Thus, in E4 the amount of Lewis and Brønsted acid sites are 14 and 16 μmol/g, respectively, while in E4a the corresponding values are 17 and 25 μmol/g, respectively. Recently we reported, that E4 showed good activity in different condensation reactions such as synthesis of oxazoline derivatives from β-aminoalcohols and carboxylic acids [24], preparation of 2-arylimidazolines and 2-aryl-benzoxazoles [25], and tetrahydropyranylation of alcohols and phenols [26]. E4a has been found to be good catalyst in the preparation of 1-substituted tetrahydroisoquinolines *via* the Pictet-Spengler reaction [27], in the oxa-Pictet-Spengler reaction [28], in the synthesis of 3,4-dihydro-pyrimidin-2(1*H*)-ones [29] or in the synthesis of 1,5-benzodiazepines [30]. Because of the pore size of these zeolites these reaction can take place on the outer surface of the mineral while the water formed can be adsorbed in the pores.

2. Results and discussion

In continuation of our work we examined further the application of modified Ersorb adsorbents as catalysts in the preparation of heterocycles under mild reaction conditions. The reaction of aniline with acetophenone in the presence of E4a in toluene gave the appropriate 2,4-diphenyl-2-methyl-1,2-dihydroquinoline with high conversion (figure 1). The optimal reaction conditions were determined in this reaction. The results are summarized in table 1. The yields are based on the ^{1}H NMR spectra of the reaction mixture (signal of the 3-H proton of the quinoline at 5.1–5.3 ppm).The reaction required 5 equivalents of ketone for the good result. Less amount of ketone resulted no reaction. The weaker acidic E4

---

*To whom correspondence should be addressed.
E-mail: zhell@mail.bme.hu

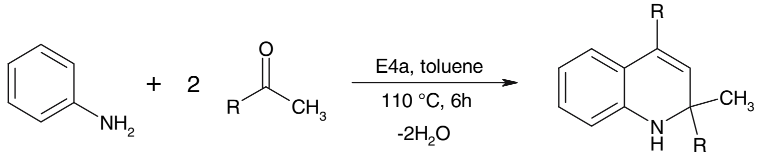

Figure 1.

Table 1
Reaction of aniline with acetophenone[a]

Entry	Catalyst	Amount of catalyst (g)	Reaction time (h)	Yield[b] (%)
1	E4a	0.8	8	88
2	E4	0.8	8	—
3	—	—	8	—
4	E4a	0.5	8	91
5	E4a	0.3	8	60
6	E4a	0.5	10	90
7	E4a	0.5	6	92
8	E4a	0.5	5	74

[a] 2 mmol aniline, 10 mmol acetophenone, 10 ml toluene, 110 °C.
[b] Based on the ^{1}H NMR spectra.

showed no activity, and no reaction was obtained without catalyst either. The optimal reaction time was 6 h in toluene at 110 °C. The required amount of catalyst was 0.5 g for 2 mmol aniline.

Under these optimal reaction conditions we examined the reaction of aniline with different aromatic and aliphatic ketones. The results are summarized in table 2. There was no significant substituent effect observed in the reactions, in all cases the appropriate dihydroquinolines were obtained in high yield. The workup of the reaction mixture was easy, the catalyst was simply filtered out and the solvent was evaporated. The catalyst was washed with acetone, dried at 120 °C for 2 h and then reused without significant loss of activity (table 2, entries 1, 4 and 9). The efficiency of the known solid acid K10 was checked in the reaction of aniline and acetone at 60 °C for 6 h (table 2, entry 9). No appreciable amount of product was obtained.

Table 2
Reaction of aniline with ketones in the presence of E4a[a]

Entry	R	Yield[b] (%)
1	C_6H_5	92 (90[c], 90[d], 89[e])
2	4-Cl–C_6H_4	88
3	4-CH_3–C_6H_4	94
4	4-CH_3O–C_6H_4	87 (87[c], 83[d])
5	3-CH_3O–C_6H_4	83
6	2-CH_3–C_6H_4	79
7	2-Cl–C_6H_4	84
8	2-CH_3O–C_6H_4	76
9	CH_3	96 (95[c], 95[d], 94[e], –[f])[g]
10	CH_3–CH_2	90[h]
11	$(CH_3)_2CH$–CH_2	87[h]

[a] 2 mmol aniline, 10 mmol ketone, 0.5 g E4a, 10 ml toluene, 110 °C, 6 h.
[b] Based on the ^{1}H NMR spectra.
[c] Recycled E4a.
[d] Third use of E4a.
[e] Fourth use of E4a.
[f] K10 montmorillonite instead of E4a.
[g] Excess acetone as solvent, 60 °C.
[h] Reaction temperature 80 °C.

This way a new, simple preparation of 1,2-dihydroquinolines from aniline and ketones was developed *via* a simple cyclocondensation. The method is simple, environmentally-friendly, and the catalyst can be easily recycled without any loss of activity.

3. Experimental

The commercial starting materials were purchased from Merck-Hungary Ltd. except of E4a and E4, which are the products of Erdőkémia-ker Ltd., Hungary.

Pretreatment of the catalyst: before the experiments sample of E4a was powdered and heated at 120 °C for 2 h.

General procedure for the preparation of dihydroquinolines: a mixture of 2 mmol of aniline, 10 mmol of ketone and 0.5 g E4a in 10 ml toluene was heated at 110 °C for 6 h. The solid was then filtered out, the filtrate was evaporated and the residue characterized.

All products have satisfactory spectral data (IR, ^{1}H NMR). The spectral data of the known compounds were identical with those reported in the literature. Representative spectroscopical data for 2,2,4-trimethyl-1,2-dihydroquinoline (table 2, entry 9): colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz): 1.23 (s, 6H, CH_3), 1.96 (s, 3H, CH_3), 3.6 (s, 1H, NH), 5.28 (s, 1H, CH), 6.41 (t, 1H, Ar CH), 6.61 (t, 1H, Ar CH), 6.94 (t, 1H, Ar CH), 7.02 (t, 1H, Ar CH); IR (film): 3367 cm^{-1}.

Acknowledgments

This work was supported by the Hungarian Research Fund Programs (OTKA Grant No. T 037757) and the common EU-Hungarian G.V.O.P. project Nr 3.2.1-2004/0346. The authors are grateful to Dr Laurence Pirault-Roy and the staff of Laboratoire de Catalyse en Chimie Organique of Université de Poitiers for the determinations of the acid sites.

References

[1] A. Balayer, T. Sevenet, H. Schaller, A. Hamid, A. Hadi, A. Chiaroni, C. Riche and M. Pais, Nat. Prod. Lett. 2 (1993) 61.

[2] W. Doepke and G. Fritsch, Pharmazie 24 (1969) 782.

[3] J. Parello, Bull. Soc. Chim. Fr. 3 (1968) 1117.

[4] F. Abe, T. Yamauchi, H. Shibuya, I. Kitagawa and M. Yamashita, Chem. Pharm. Bull. 46 (1998) 1235.

[5] J.V. Johnson, J. Med. Chem. 32 (1989) 19429.

[6] T. Aono, T. Doi and K. Fukatsu, JP 042823701992 A2 (1992).

[7] G. de Nanteuil, J. Duhault, D. Ravel and Y. Herve, EP 528734 (1993).

[8] B.C. Pearce and J.J. Wright, US 5411969 (1995).

[9] T.K. Jones, D.T. Winn, L. Zhi, L.G. Hamann, C.M. Tegley and C.L.F. Pooley, US 5688808 (1997).

[10] T.K. Jones, M.E. Goldman, C.L.F. Pooley, D.T. Winn, J.E. Edwards, S.J. West, C.M. Tegley, L. Zhi and L.G. Hamann, WO 9619458 (1996).

[11] M.J. Coughlan, S.W. Elmore, M.E. Kort, P.R. Kym, J.L. Moore, J.K. Pratt, A.X. Wang, J.P. Edwards and T.K. Jones, WO 9941256 (1999).

[12] J. Cossy, C. Poitevin, D. Gomez Pardo, J.-L. Peglion and A. Dessinges, Tetrahedron Lett. 39 (1998) 2965.

[13] K. Kobayashi, M. Kawakita, O. Morikawa and H. Konishi, Chem. Lett. 7 (1995) 575.

[14] H. Walter and J. Schneider, Heterocycles 41 (1995) 1251.

[15] J.P. Edwards, J.D. Ringgenberg and T.K. Jones, Tetrahedron Lett. 39 (1998) 5139.

[16] A. Arduini, F. Bigi, G. Casiraghi, G. Casnati andG. Sartori Synthesis (1981) 975.

[17] Z.H. Skraup, Berichte 13 (1880) 2086.

[18] A. Combes, Bull. Soc. Chim. France 49 (1888) 89.

[19] O. Doebner and W.v. Miller, Chem. Ber. 16 (1883) 2464.

[20] D. Craig, J. Am. Chem. Soc. 60 (1938) 1458.

[21] M.-E. Theoclitou and L.A. Robinson, Tetrahedron Lett. 43 (2002) 3907.

[22] G. Klopp, Ph.D. Thesis, Budapest (1975).

[23] The characterization of the Ersorb products was described elsewhere, see e.g. Ref. 30. Furthermore, tablets (diameter: 10 mm, mass: 0,3 g, pression: 100 bar for 1 min) from the powdered material were subjected to isotopic excited X-ray fluorescence analysis. Three toroid exciting sources were used: ^{55}Fe, ^{125}I and ^{241} Am for the determination of the elements of groups A, B, and C, respectively. In group A near the major components Al, Si, K, Ca, and Mg the minor elements P, Cl, and Ti were found in an amount less than 50 ppm. In group B near the larger amount of Fe, Rb and Sr were detected in the 40–120 ppm range, while Cr, Mn, Ni, Cu, Zn, Mo, Pd, and Ag were found as minor components. In group C Cs and Ba were found as minor constituents.

[24] A. Cwik, Z. Hell, A. Hegedüs, Z. Finta and Z. Horváth, Tetrahedron Lett. 43 (2002) 3985.

[25] A. Hegedüs, I. Vígh and Z. Hell, Heteroatom Chem. 15 (2004) 428.

[26] A. Hegedüs, I. Vígh and Z. Hell, Synth. Commun. 32 (2004) 4145.

[27] A. Hegedüs and Z. Hell, Tetrahedron Lett. 45 (2004) 8553.

[28] A. Hegedüs and Z. Hell, Org. Biomol. Chem. 4 (2006) 1220.

[29] A. Hegedüs, Z. Hell and I. Vígh, Synth. Commun. 36 (2006) 129.

[30] A. Hegedüs, Z. Hell and A. Potor, Catal. Lett. 105 (2005) 229.