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Catalyst-free synthesis of octahydroacridines using glycerol as recyclable solvent

José E. R. Nascimento [a], Angelita M. Barcellos [a], Maraísa Sachini [a], Gelson Perin [a,*], Eder J. Lenardão [a], Diego Alves [a], Raquel G. Jacob [a,*], Fabiana Missau [b]

[a] Instituto de Química e Geociências, LASOL, Universidade Federal de Pelotas, UFPel, PO Box 354, 96010-900, Pelotas, RS, Brazil
[b] UNIPAMPA, Campus Itaqui, Itaqui-RS, Brazil

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ABSTRACT

We describe herein the use of glycerol as an efficient, safe and recyclable solvent in the one-pot hetero-Diels–Alder (HDA) reaction of (*R*)-citronellal with substituted arylamines. The catalyst-free reactions proceed easily using glycerol at 90 °C and the corresponding octahydroacridines (OHAs) were obtained in good to excellent yields by simply decantation of products. After removing the products, glycerol was directly reused for further HDA reactions without lost of activity.

Due to the extensive uses of solvents in nearly all industrial chemical processes and the limited sources of fossil petroleum[1] the use of solvents from renewable resources has gained much interest. The desired characteristics of such green solvents includes also low flammability, high availability, and biodegradability.[2] Due to its peculiar physical and chemical properties, such as polarity, low toxicity, biodegradability, high boiling point, and easy availability from renewable feedstocks,[3] glycerol has emerged as an economically and secure solvent for organic synthesis.[4–6] Recently the use of glycerol as solvent was described for Pd-catalyzed Heck,[5a–c] and Suzuki[5a] cross-couplings, copper catalyzed coupling,[4a] base[5b] and acid[4b] promoted condensations, catalytic hydrogenation,[5c,d] asymmetrical reduction[5c] and multicomponent reactions.[5e] Furthermore the electrophilic activation of carbonyl compounds in glycerol-promoted reactions allows eliminates the use of acidic catalysts.[4e,5f]

On the other hand, the Lewis-acid catalyzed intramolecular reaction of *N*-arylimines with non-activated alkenes, formally hetero-Diels–Alder (HDA) reaction of a 2-azadiene, is a powerful synthetic tool for the preparation of nitrogen containing six-membered heterocycles.[7] This efficient protocol has been recently used in the synthesis of several substituted hydroquinolines[8] and octahydroacridine (OHA) derivatives.[9] OHAs are a class of compounds with pharmacological interest, acting as a gastric acid secretion inhibitors.[10] There are a number of different methods to synthesize the OHA skeleton, such as acid catalyzed isophorone–aniline condensation,[11] Beckmann rearrangement of oxime sulfonate,[12] catalytic hydrogenation of acridine[13] and amino-Claisen rearrangement of geranyl aniline.[14] The imine-Diels–Alder reaction catalyzed by a Lewis-acid is the most atom-economic method, furnishing OHAs in high yields and, in some cases, with 100% of stereoselectivity.[15] Based on our studies of the electrophilic activation of carbonyl compounds in the reaction of thiols with aldehydes and ketones,[4e] we will describe here the use of glycerol as solvent in the catalyst-free HDA-reaction of (*R*)-citronellal with substituted arylamines to octahydroacridines (Scheme 1).

In a first assay the reaction of (*R*)-citronellal **1** and aniline **2a** (R = H) in glycerol as solvent to access the OHAs **3a** and **4a** was studied at different temperatures. At room temperature, no reaction was observed after stirring for 24 h. Increase of the reaction temperature to 60 °C in an oil bath, gave a mixture of **3a** and **4a** in poor yield. However, after 7 h at 90 °C the respective OHAs **3a** and **4a** were obtained with a yield of 96% yield (Table 1, entry 1). As the formed products are insoluble in glycerol they can be easily removed from the reaction medium by decantation. When the reaction was performed in different solvents, such as DMSO, MeCN and EtOH, only traces of OHAs **3a** and **4a** were obtained. A decrease in the yield of OHAs **3a** and **4a** was observed when the reaction was realized in H_2O (62%). Thus, in an optimized reaction, (*R*)-citronellal **1** (1.0 mmol) was dissolved in glycerol (3 mL) and reacted with aniline **2a** (1.0 mmol) at 90 °C during 7.0 h, yielding **3a** + **4a** in 96% yield.[16]

In order to explore the scope and limitations of this new protocol, a range of differently substituted anilines were reacted with citronellal **1** under these optimized conditions. As it can be seen

* Corresponding authors. Tel./fax: +55 53 32757533.
E-mail addresses: gelson_perin@ufpel.edu.br (G. Perin), raquel.jacob@ufpel.edu.br (R.G. Jacob).

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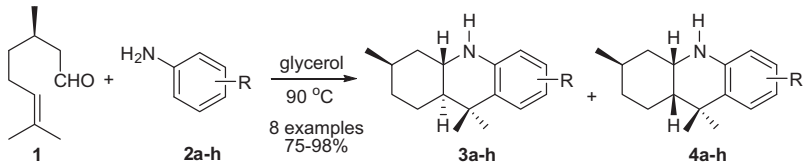
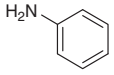
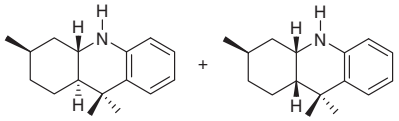
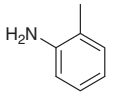
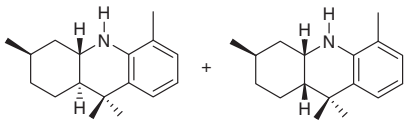
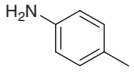
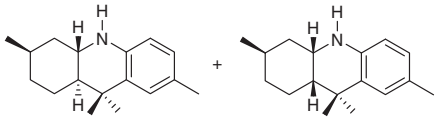
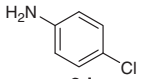
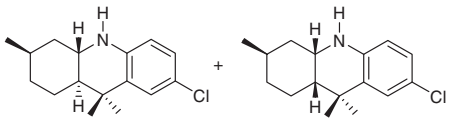
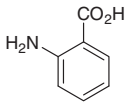
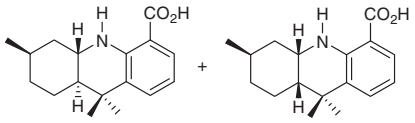
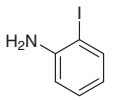
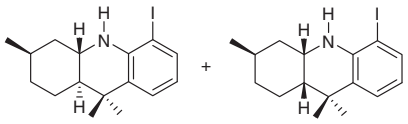
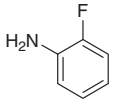
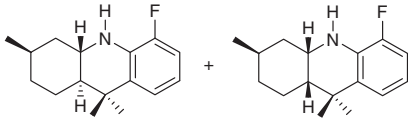
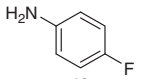
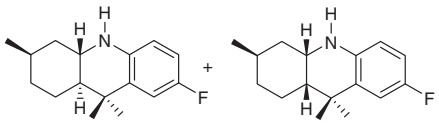


Scheme 1. Synthesis of octahydroacridines using glycerol.

Table 1
Catalyst-free synthesis of octahydroacridines using glycerol

Entry	Arylamine **2**	Products **3** + **4**	Reaction time[a] (h)	Yield[b] (%)	Ratio [c] **3**:**4**
1	 **2a**	 **3a** **4a**	7	96	46:54
2	 **2b**	 **3b** **4b**	18	94	41:59
3	 **2c**	 **3c** **4c**	16	87	47:53
4	 **2d**	 **3d** **4d**	12	75	44: 56
5	 **2e**	 **3e** **4e**	21	98	21:79
6	 **2f**	 **3f** **4f**	15	90	23: 77
7	 **2g**	 **3g** **4g**	20	76	32:68
8	 **2h**	 **3h** **4h**	16	98	44:56

[a] The reaction progress was followed by TLC.
[b] Yields after purification by column chromatography.
[c] Determined by ^{1}H NMR of the crude reaction mixture and compared after purification.

from Table 1, most of the substrates gave good yields of the corresponding octahydroacridines. As it was determined by ^{1}H NMR, all studied anilines **2a**–**h**, gave mixture of the *cis* and *trans* OHAs. Due to the higher polarity of the *trans*-isomer they could be easily separated by column chromatography. The *o*-substituted anilines containing electron withdrawing groups, such as, *o*-aminobenzoic acid **2e**, *o*-iodoaniline **2f** and *o*-fluoroaniline **2g** formed selectively the respective OHAs, with an enhanced selectivity towards the *cis*