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An Efficient Three-Component One-Pot Approach to the Synthesis of 2,3,4,5-Tetrahydro-1*H*-2-benzazepines by Means of Rhodium-Catalyzed Hydroaminomethylation†

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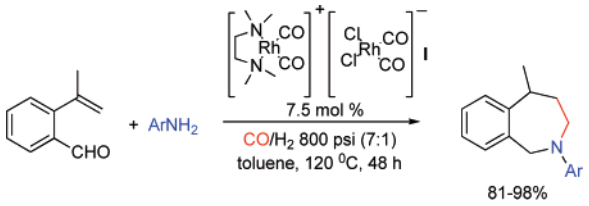
ABSTRACT



We have developed a novel and efficient three-component one-pot, catalytic approach for the synthesis of 2,3,4,5-tetrahydro-1*H*-2-benzazepines, using a rhodium catalyst that does not require phosphine. The isolated yields are excellent and the protocol tolerates anilines of diverse basicity.

Significant efforts have been made to develop new methods for the preparation of heterocyclic compounds.[1] A particularly interesting class of heterocycles are the seven-membered ring benzazepines. The 2-benzazepine moiety constitutes the core structure of a number of pharmacologically important

† In memoriam of Prof. Helena M. C. Ferraz (1948−2007).

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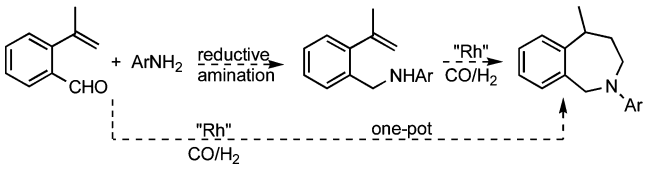
compounds.[2] Several members of this class have exhibited hypotensive, analgesic, anticonvulsant, antiarrhythimic activities, and have also proved to be useful for the treatment of mental disorders and hypoxia.[3,4] Quite recently, 2-benzazepines were found to be antagonists of $\alpha_v\beta_3$ integrin—a receptor of glycoproteins assumed to play a pivotal role in cell−cell adhesion, signaling, and apoptosis.[5] Therefore, the development of simple and convenient procedures for the synthesis of such subunits is a challenging endeavor in synthetic organic chemistry.[6]

Carbonylation strategies to heterocycles have attracted considerable attention in recent years, and several creative applications have been described in the literature.[7] Furthermore, as the hydroformylation reaction represents an industrially applicable methodology, extension of this technique toward multistep one-pot transformations is particularly appealing. A powerful example is the hydroaminomethylation reaction[8]—an elegant and important industrial process for the preparation of secondary and tertiary amines. This is a highly atom economical process that consists of a tandem hydroformylation reaction followed by reductive amination.[9,10] Thus, this catalytic reaction is consistent with the goals of "green" chemistry.

Inspired by our recent results concerning the synthesis of 1,2,3,4-tetrahydroquinolines,[10a] we wondered whether 2-benzazepine motifs could be pursued through Rh-catalyzed hydroaminomethylation (Scheme 1). *Herein, we report a*

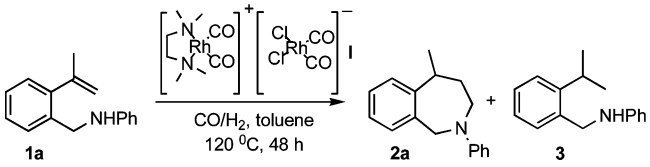
Scheme 1. Envisioned Route for the Synthesis of 2-Benzazepines



novel and efficient one-pot catalytic approach for the synthesis of 2,3,4,5-tetrahydro-1H-2-benzazepines, using a rhodium catalyst that does not require phosphine.

To check the feasibility of the proposed protocol, a few experiments were performed using the amine **1a** as the substrate. At higher H_2 pressures, hydrogenation of the substrate occurred in up to 20% yield (Table 1, entry 1). However, after optimization by use of a 7:1 ratio of CO/H_2, **2a** could be obtained as the only product, although using a higher catalyst concentration (Table 1, entry 5).

Table 1. Screening for the Hydroaminomethylation of **1a**[a]

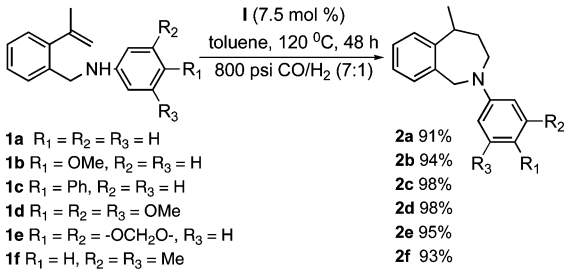


entry	*I* (mol %)	CO/H_2 (psi)	conv (%)	**2a** (%)	**3** (%)
1	5.0	700/300	>98	80	20
2	5.0	700/200	>98	90	10
3	5.0	700/100	80	>98	
4	6.0	700/100	90	>98	
5	7.5	700/100	>98	>98	

[a] All reactions were performed on a 0.5 mmol scale in 2.5 mL of toluene. The percent conversion and the product ratio were determined by ^1H NMR on the crude product mixture.

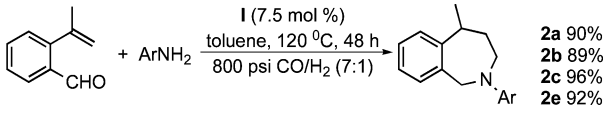
Having found the optimum conditions, a number of substrates were used, with different substitution patterns at the nitrogen. The 2-benzazepines were isolated in excellent yields (Scheme 2).

Scheme 2. Hydroaminomethylation of a Series of Isopropenylamines



The route presented in Scheme 1 begins and ends with reductive amination. Although the protocol developed thus far is very attractive, we were interested in determining whether we could combine the preparation of the starting materials and the hydroaminomethylation itself into a one-pot sequential process. Thus, by mixing 2-isopropenylbenzaldehyde, aniline, and the rhodium catalyst, under the conditions previously optimized, we were gratified to isolate **2a** in 90% yield. To contrast the two methods, the benzazepines **2b**,**c**,**e** were also prepared, through the multicomponent approach, and the high isolated yields were comparable (Scheme 3).

Scheme 3. One-Pot Synthesis of 2-Benzazepines



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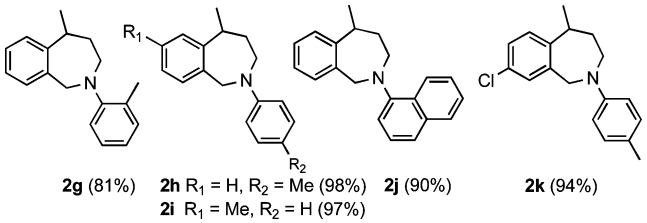

Figure 1. Other 2-benzazepines prepared by the three-component one-pot approach. All reactions were performed by using 0.50 mmol each of aldehyde and aniline, 7.5 mol % of **I**, 2.5 mL of toluene, under 800 psi CO/H_2 (7:1), at 120 °C, for 48 h. Isolated yields are shown.

The scope of the reaction was further investigated by the preparation of several other 2-benzazepines, through this multicomponent alternative method, in excellent yields (Figure 1). The protocol proved to be general and highly efficient for the diverse nature of benzaldehydes and anilines.

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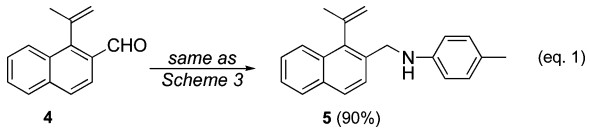
The hydroaminomethylation reaction is a well-known protocol, and its mechanism has been previously established.[9] However, for our three-component multistep approach, it is not possible to be certain of the order of the events. Intuitively, one would anticipate that the initial reductive amination should happen first, and the hydroformylation of a trisubstituted double bond should be the rate-determining step. Some indication of this pathway comes from the use of **4** as the reactant, which only formed the amine **5** in 90% yield (eq 1). The reaction stopped after the first reductive amination, and the hydroformylation could not take place, probably due to steric hindrance.



4 **5** (90%)

In conclusion, we have discovered a novel and highly atom economical protocol for the one-pot synthesis of 2-benzazepines. Notable features include the following: (a) the air-stable catalyst does not require added phosphine; (b) the ease of access of substrates and; (c) the high product yields. This strategy opens new opportunities for the synthesis of a wide variety of 2-benzazepines, and to the possibility of building libraries of pharmaceutically important moieties.

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Supporting Information Available: Experimental procedures and full characterization of new compounds are reported, as well as the NMR spectra for the precursor amines and the 2-benzazepines prepared. This material is available free of charge via the Internet at http://pubs.acs.org.

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