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Tetrahedron Letters
Tetrahedron Letters 47 (2006) 6899–6902

Preparation of substituted 1,2,3,4-tetrahydroquinoxalines and 2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepines from catalytic Cp*Ir hydrogen transfer N-heterocyclization of anilino alcohols

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Received 16 June 2006; revised 6 July 2006; accepted 8 July 2006
Available online 4 August 2006

Abstract—The $[Cp^*IrCl_2]_2/K_2CO_3$ catalyzed hydrogen transfer N-heterocyclization on a series of anilino alcohols has been investigated. The catalyst (20% loading) converts anilino alcohols to 1,2,3,4-tetrahydroquinoxalines and 2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepines in 30–84% isolated yield.

We recently became interested in new methods for the synthesis of substituted 1,2,3,4-tetrahydroquinoxalines as part of a medicinal chemistry program. Compounds containing these heterocyclic cores have demonstrated a wide range of biological activities. Some 1,2,3,4-tetrahydroquinoxaline containing structures (Fig. 1) have been pursued as prostaglandin D2 receptor[1] antagonists (**1**) and vasopressin V2 receptor antagonists (**2**).[2]

At present, there are a limited number of methods for preparing 1,2,3,4-tetrahydroquinoxalines. A common strategy involves the reduction of quinoxalines.[3] This requires that the starting aromatic quinoxaline be appropriately substituted so that it is reduced to the desired tetrahydro species and does not allow for the formation of quaternary centers. An alternate strategy involves the metal-mediated reaction of 1,2 dianilines with 1,4 butene diol and acetate derivatives to form 2-vinyl 1,2,3,4-tetrahydroquinoxalines.[4] Although the 2-vinyl 1,2,3,4-tetrahydroquinoxalines are formed in high yield, this method is limited to symmetrically substituted dianilines to avoid mixtures of regioisomers. Additional methods to prepare 1,2,3,4-tetrahydroquinoxalines involve intermolecular Michael additions,[5] tandem reduction–reductive amination reactions[6] and the reduction and S_N2 cyclization of nitroarenes with leaving groups.[7,8]

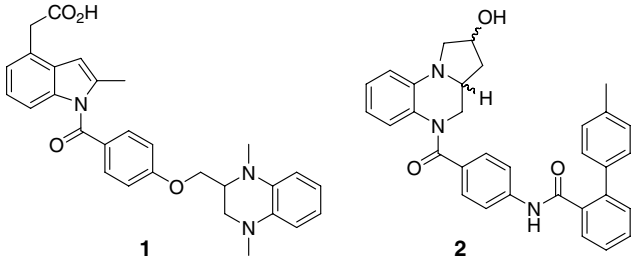
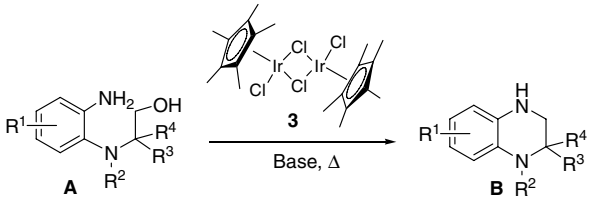


Figure 1. Biologically active 1,2,3,4-tetrahydroquinoxalines.

Recent reports of the Cp*Ir-complex hydrogen transfer N-heterocyclization[9] to form indoles,[4] tetrahydroquinolines,[10] and lactams[11] prompted us to investigate this transformation as a new method to form 1,2,3,4-tetrahydroquinoxalines from anilino alcohols (Scheme 1).



Scheme 1.

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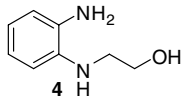
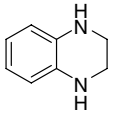
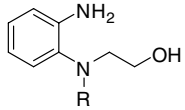
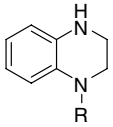
0040-4039/$ - see front matter © 2006 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2006.07.033

This approach would allow direct preparation of 1,2,3,4-tetrahydroquinoxalines (**B**) from anilino alcohols (**A**) in a catalytic and regioselective fashion that would allow for the incorporation of quaternary centers. The required substrates are easily prepared from substituted ethanolamines and *ortho*-nitro aryl fluorides via S_NAr reactions[12] and the catalyst (**3**) is now commercially available. The proposed mechanism[9,10] for N-heterocyclization is thought to begin with initial Oppenauer-type oxidation of the alcohol followed by cyclization and reduction of the imine intermediate by the catalyst system.

One of the first systems studied was 3-(2-aminophenylamino) ethanol (**4**), which should undergo hydrogen transfer to produce 1,2,3,4-tetrahydroquinoxaline (Table 1). Conditions similar (10% **3**, 10% K_2CO_3, toluene sealed tube 110 °C) to those used by Fujita and Yamaguchi[10] were utilized to study the transformation. These conditions failed to produce the desired 1,2,3,4-tetrahydroquinoxaline even after several days of heating. Catalyst (**3**) loading was increased to 25% and the solvent was switched to xylenes, in order to increase the temperature of the reaction, and the product was formed in 30% yield after five days.

Since the hydrogen atom transfer reaction on substrate **4** was sluggish compared to the simpler published systems,[10] we decided to study the effect of substitution on N1. The extra heteroatom in our substrates may allow bis coordination with iridium and render catalyst turnover less efficient. The N-methylated substrate **5** produced the desired 1,2,3,4-tetrahydoquinoxaline in modest yield after eight days with 10% of **3**. Increasing the catalyst loading to 25% also increased the yield to 80% with the reaction being complete after 17 h. We also investigated N-heterocyclization for *N*-benzyl substrate **6**, which was converted to product in low yield with

Table 1.[a]

Substrate	Product	Catalyst (**3**) (%)	Time	Yield[b] (%)
 **4**		10	4 d	NR
		25	5 d	30[c]
 **5** R = Me, **6** R = Bn, **7** R = Ts		10	8 d	52
		25	17 h	80
		20	4 d	19
		20	4 d	NR

[a] Reactions performed in a sealed tube at ~120 °C in toluene at 0.25 M with K_2CO_3 content equal to catalyst.
[b] All yields based upon isolated material after chromatography.
[c] Xylene was used as a solvent and the reaction was run at 140 °C.

Table 2.

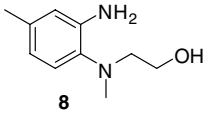
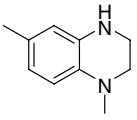
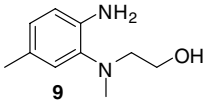
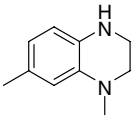
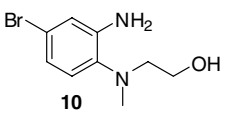
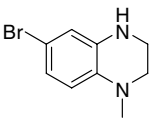
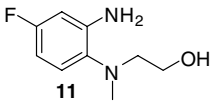
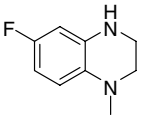
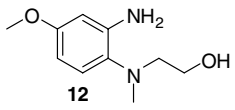
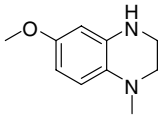
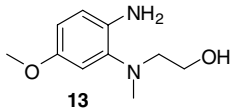
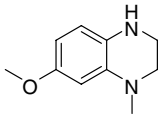
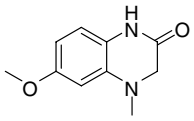
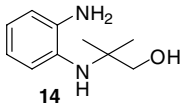
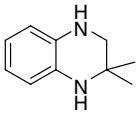
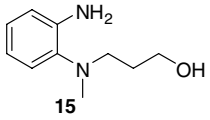
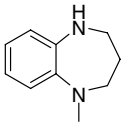
Substrate	Product	Catalyst (%)	Time	Yield (%)
 **8**		20	2 d	64
 **9**		20	2 d	59
 **10**		20	3 d	62
 **11**		20	3 d	64

Table 2 (*continued*)

Substrate	Product	Catalyst (%)	Time	Yield (%)
 **12**		20	3 d	61
 **13**		20	3 d	42
				18
 **14**		20	1 d	84
 **15**		20	7 d	68

some debenzylated material produced. No desired product was isolated when N-heterocyclization was attempted on tosyl protected aniline **7**. After several days, ~80% of the starting material was recovered.

After our initial experiments, we decided to investigate a series of substrates with 20% catalyst (**3**) loading under our standard conditions.[13] We chose a series of N1 methyl substrates (**8**–**13**) with various aromatic substitutions along with a 2,2-dimethyl substrate (**14**) and homologated substrate (**15**). In general, yields were ~60% regardless of substitution with electron donating or withdrawing groups. The weakly donating methyl groups for substrates **8** and **9** produced marginally faster reactions. The strong electron donating groups in **12** and **13** did not increase the reaction rate. Substrate **13** with the methoxy *para* to the aniline nitrogen underwent a side reaction to produce significant amounts of the 3,4-dihydroquinoxalin-2(1*H*)-one (18%). This byproduct was observed in low (1–5%) amounts for several of the substrates studied.[11] The 2,2-branched free aniline **14** produced the highest yield of product with the shortest reaction time. Since **14** is sterically hindered around N1, the nitrogen's ability to bis coordinate iridium may be attenuated producing a faster transformation and/or the dimethyl substituents may produce a more favorable conformation for cyclization.[14] We were pleased to observe cyclization of **15**[15] to the 7-membered 1-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepine. The extended reaction time needed is likely due to the less favorable 7-endo cyclization mode (Table 2).

In summary, we have described a new and convenient method to prepare 1,2,3,4-tetrahydroquinoxalines and 2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepines directly from anilino alcohols using catalytic amounts of **3**. This reaction allows for the incorporation of quaternary centers in a regioselective manner. Reaction times vary from one to seven days using 20% catalyst loading with yields averaging 63%. Substrates that are sterically hindered at the 2-position, or alkylated at N1, produce higher N-heterocyclization yields with shorter reaction times.

References and notes

1. Torisu, K.; Kobayashi, K.; Iwahashi, M.; Nakai, Y.; Onoda, T.; Nagase, T.; Sugimoto, I.; Okada, Y.; Matsumoto, R.; Nanbu, F.; Ohuchida, S.; Nakai, H.; Toda, M. *Bioorg. Med. Chem.* **2004**, 5361–5378.
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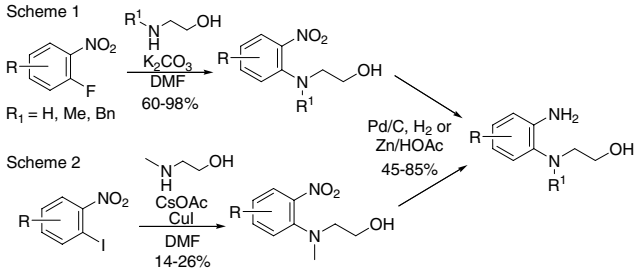
9. Fujita, K.; Yamaguchi, R. *Synlett* **2005**, 560–571.
10. Fujita, K.; Yamamoto, K.; Yamaguchi, R. *Org. Lett.* **2002**, *16*, 2691–2694.
11. Fujita, K.; Takahashi, Y.; Owaki, M.; Yamamoto, K.; Yamaguchi, R. *Org. Lett.* **2004**, *6*, 2785–2788.
12. Substrates **4**–**6** and **8**–**11** were prepared as shown in Scheme 1. Substrates **12** and **13** were prepared as described in Scheme 2.



Substrate **7** was prepared from 4-methyl-*N*-(2-nitrophenyl)benzenesulfonamide and 2-bromethanol utilizing sodium hydride as base (43%). The nitro group was then reduced with Zn as shown above (77%). Substrate **14** was prepared as shown above in Scheme 1 using methyl 2-amino-2-methylpropanoate (77%). The resulting ester was then reduced with $LiBH_4$ (22%) to the alcohol followed by nitro reduction Pd/C, H_2 (60%) as shown above.
13. General experimental: Substrate (1.0 equiv), **3** (0.2 equiv), and base (0.2 equiv) were suspended in toluene (0.25 M) in a pressure tube under a nitrogen atmosphere. The vessel was sealed and heated to 110 °C with magnetic stirring. The reaction was followed by TLC, HPLC, and LCMS. The reactions generally took between 1 and 4 days depending on the substrate. Once complete, the cooled reaction mixture was purified directly via flash chromatography (1:1 hexanes/EtOAc to 100% EtOAc).
14. Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc.* **1915**, 1080.
15. Hussenether, T.; Hübner, H.; Gmeiner, P.; Troschütz, R. *Bioorg. Med. Chem.* **2004**, *12*, 2625–2637, Substrate **15** was prepared from LAH carboxylic acid reduction (29%) and subsequent nitro reduction (Pd/C, 94%) of 3-(methyl-(2-nitrophenyl)amino)propanoic acid.