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LETTERS

Lewis-acid Catalyzed Reaction of 2-Isopropenylaniline with Ketones: Improved Synthesis of 2,2,4-Trisubstituted 1,2-Dihydroquinolines

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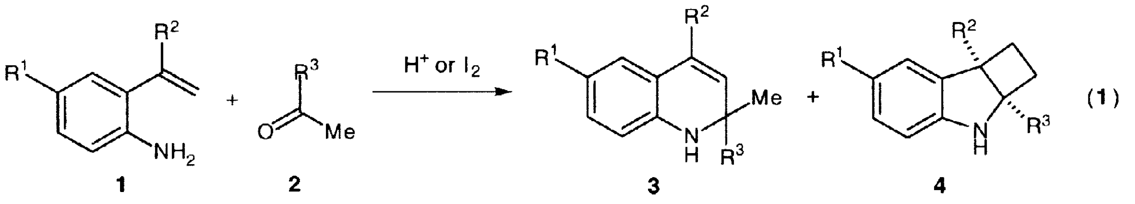
***Abstract*:** The $BF_3 \cdot OEt_2$-mediated reaction of 2-isopropenylaniline with a variety of ketones to form 2,2,4-trisubstituted 1,2-dihydroquinolines was studied. Treatment of 2-isopropenylaniline with a number of different ketones in the presence of $BF_3 \cdot OEt_2$ in toluene at elevated temperatures afforded cleanly and in moderate to excellent yields the requisite 2,2,4-trisubstituted dihydroquinolines. Sterically hindered and/or cyclopropyl ketones failed to afford the desired products. © 1998 Elsevier Science Ltd. All rights reserved.

INTRODUCTION

The utility of 2,2,4-trisubstituted 1,2-dihydroquinolines as feed additives, dyes, and pharmaceuticals is well-documented.[1] The most expedient route to this structure is the reaction of an aniline with a ketone in the presence of a catalyst such as iodine, a process first described by Reddelien[2] and recognized as a variant of the Skraup reaction.[3] In practice, the Skraup reaction to form 2,2,4-trialkyl-1,2-dihydroquinolines is generally limited to the use of acetone as the ketone and problems of regioselectivity and reactivity with higher ketones have been noted. The copper-mediated cyclization of 1,1-disubstituted propargylanilines[4] is of general utility, but precludes substitution at C(3) and substitution at C(4) is problematic, since the most efficient synthesis of propargylanilines is limited to terminal acetylenes.[5] Other routes are of limited utility.[6] We were attracted to recent reports from Walter and co-workers who described the reaction of *o*-aminostyrenes with ketones in the presence of *p*-toluenesulphonic acid or iodine, affording in moderate yields the requisite 2,2,4-trisubstituted 1,2-dihydroquinolines **3** (Eq 1).[7]



Unfortunately, the reaction can often take an alternate course affording indoline derivatives **4**, particularly for isopropenyl anilines (R^2 = Me). Only α-substituted *o*-aminostyrenes (R^1 = Me or Ph) were examined, the phenyl-substituted analog providing the most generality and highest yields. An earlier report by Qiang and Baine described similar reactions of *o*-aminostyrenes with aryl aldehydes affording, after oxidation of the initially-formed dihydroquinolines, substituted quinolines;[8] the reaction fails with aliphatic aldehydes. These reports prompted us

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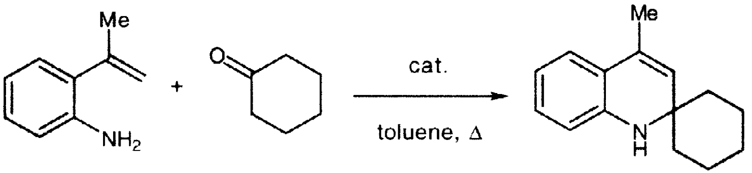
to investigate the reaction between *o*-aminostyrenes and ketones with the aim of improving the generality and efficiency of this potentially powerful dihydroquinoline synthesis. Initial efforts to optimize the reaction of 2-isopropenylaniline with a variety of ketones to afford 1,2-dihydroquinolines are discussed below.

RESULTS

Orienting experiments with 2-isopropenylaniline (**5**) were performed with cyclohexanone (**6a**) as the ketone component (Eq 2). Treatment of **5** with two equivalents of **6a** and 10 mol% *p*-toluenesulphonic acid hydrate (p-TSA·H_2O) in refluxing toluene afforded the dihydroquinoline **7a** in 30-35% yields, consistent with the original observation of Walter and co-workers.[7a, 9]



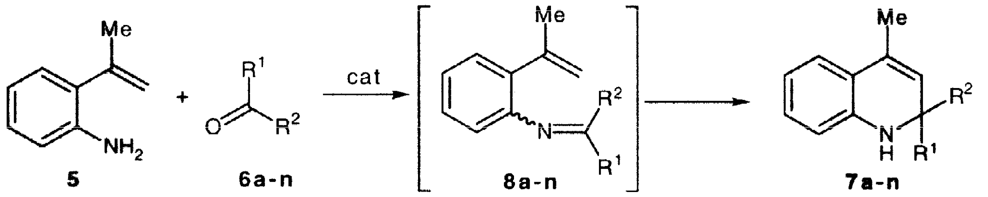
5 **6a** **7a** (**2**)

Since formation of the undesired indolines **4** is postulated to involve cationic intermediates,[7c] we sought to slow this alternate pathway by replacing the p-TSA·H_2O with a Lewis acid. This substitution gave encouraging yields of **7a**: 6 mol% $Sc(OTf)_3$ hydrate (50%); 20 mol% $Zn(OTf)_2$ (40%); 50 mol% $ZnCl_2$ (47%); 10 mol% $BF_3·OEt_2$ (80%). The use of more polar solvents (dioxane, 1,2-dichloroethane) gave similar results but offered no advantage. The $BF_3·OEt_2$-mediated reaction was not only higher yielding but also qualitatively faster and cleaner, so the use of this Lewis acid in toluene was examined with a range of ketone substrates.

The results of a survey of the reaction of 2-isopropenylaniline with 14 different ketones under $BF_3·OEt_2$-catalysis are depicted in Table 1. As noted, cyclohexanone was an excellent substrate for the cyclization reaction, affording the dihydroquinoline **7a** in 80% yield using 5 mol% $BF_3·OEt_2$. Likewise, 4-*tert*-butylcyclohexanone afforded **7b** in 82% yield as a 7:1 mixture of diastereomers favoring the cis isomer.[10] Cyclopentanone reacted far more sluggishly, affording only a 29% yield of **7c**, which decomposed on standing. In general, straight-chain ketones and methyl ketones afforded moderate to good yields of the dihydroquinolines **7**; sterically hindered ketones (**6f**, **6g**, **6j**) did not participate in this reaction and methyl cyclopropyl ketone (**6i**) afforded a rearranged product.[11] Both 3-pentanone (**6d**) and 4-heptanone (**6e**) provided acceptable (57-67%) yields of **7d** and **7e**, but neither diisopropyl ketone (**6f**) nor dicyclopropylketone (**6g**) yielded dihydroquinoline under these conditions. Under forcing conditions (25 mol% $BF_3·OEt_2$, 130 °C, sealed tube), treatment of **5** with **6f** produced a complex reaction mixture. Steric effects were playing a major role in this reaction, either in the putative formation of imines **8** or in the cyclization to form **7**. This was confirmed by comparing the results of the reactions using methyl ketones **6h** and **6j**: although two α-methyl substituents did not interfere with formation of **7h** (60% yield), three α-methyl substituents severely slowed the reaction (<5% yield of **7j**). The cationic nature of some step along the reaction pathway was suggested by the isolation of a rearrangement product from reaction of methyl cyclopropyl ketone **6i** with **5**.[11]

A particularly stringent test of this process involves the use of acetophenone derivatives, as these ketones are poor substrates under acid-catalyzed conditions.[7] Reaction of **6k-m** with **5** afforded moderate (29-49%) yields of **7k-m**: however, these yields compare very favorably with the acid-catalyzed reactions, which afford only poor (20-25%) yields of inseparable mixtures of **3** and **4**.[7c] The attempted preparation of 2,2-diphenyl derivative **7n** gave an inseparable 1.6:1 mixture of **7n** and the imine **8n** (39% combined). Significant amounts of cyclobutane side-products (e.g, **4**) were not detected in any of these reactions and unchanged starting material was generally the only other major product recovered.

Table 1. Formation of 2,2-Dialkyl-1,2-dihydro-4-methylquinolines **7a-n** from 2-Isopropenylaniline **5**[a]



Product	R^1	R^2	Amount of $BF_3 \cdot OEt_2$ (mol%)	Reaction time (h)	Yield (%)
7a	spirocyclohexyl		5	8.5	80
7b	spiro-4'-*tert*-butylcyclohexyl		10	3.5	82[b]
7c	spirocyclopentyl		10	12.5	29
7d	Et	Et	5	8	57
7e	*n*-Pr	*n*-Pr	10	20	67
7f	*i*-Pr	*i*-Pr	10	14	0
7g	*c*-Pr	*c*-Pr	10	24	0
7h	Me	*i*-Pr	10	11	60
7i	Me	*c*-Pr	10	7	0[c]
7j	Me	*t*-Bu	10	24	<5
7k	Me	Ph	20	3	49
7l	Me	4'-Fluorophenyl	10	17	46
7m	Me	4'-Methoxyphenyl	20	4	29
7n	Ph	Ph	20	8	24[d]

[a] All reactions were run in toluene at 95-100 °C for the time indicated. Yield refers to homogeneous material isolated by silica gel chromatography.

[b] 7:1 cis / trans ratio of diastereomers.

[c] A product arising from apparent rearrangement of the cyclopropyl ring was isolated but not fully characterized. See Footnote 10.

[d] Isolated as a 39% yield of a 1.6:1 mixture with the corresponding imine **8n**.

CONCLUSION

These results demonstrate that the Lewis acid mediated reaction of 2-isopropenylaniline (**5**) with certain ketones is a powerful method for the construction of 2,2,4-trisubstituted dihydroquinolines, affording a number of derivatives in useful yields. This process represents a significant improvement over the Brønsted acid catalyzed reaction, given the consistently higher chemical yields. In addition, the successful use of acyclic aliphatic ketones in this transformation has been demonstrated for the first time. It is noteworthy that reactions of the acetophenone derivatives **6k-m** with **5** afforded useful yields of **7k-m**, as these substrates had previously been demonstrated to provide very poor yields of impure dihydroquinolines using Brønsted acid catalysis. This reaction is certain to benefit from further study, particularly the survey of a wider range of Lewis acids and examination of *o*-aminostyrenes with varied substitution patterns.

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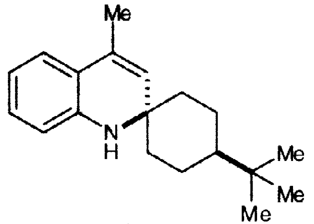
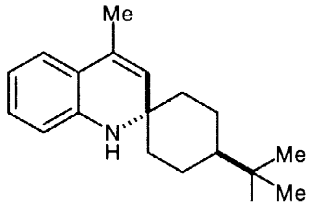
9. The yield of dihydroquinoline from isopropenyl aniline and 3-methylcyclohexanone under these conditions is reported to be 38%; see Ref. 7a.
10. The relative stereochemistry of the minor (trans) diastereomer of **7b** was unambiguously assigned by ^{1}H-^{1}H decoupling and n.O.e. experiments.



7 **a**-major



7 **b**-minor

11. This product could not be isolated in pure form due to decomposition and has been tentatively assigned a pyrrolidine structure based on ^{1}H NMR data: