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Novel facile synthesis of 2,2,4 substituted 1,2-dihydroquinolines via a modified Skraup reaction

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Abstract—A variety of 2,2,4 substituted 1,2-dihydroquinolines were synthesized from substituted anilines or aminoheterocycles and the corresponding ketones in good yield via the use of lanthanide catalysts and microwave technology. This method can be readily applied to the general synthesis of combinatorial libraries of dihydroquinolines.

Dihydroquinoline moieties can be found in a variety of natural products[8–11] and in a large number of compounds which display biological activity. For example, 2,2,4 substituted 1,2-dihydroquinolines have been used to produce potent compounds that possess antibacterial,[1] antidiabetic[2] and anti-inflammatory[3] activities. Compounds possessing this motif have also been shown to act as lipid peroxidation inhibitors,[4] HMG-CoA reductase inhibitors,[5] ileal bile acid transporter inhibitors[12] and progesterone agonists[13] and antagonists.[6]

Dihydroquinolines of the type shown in Fig. 1, have been synthesized in the past via a variety of methods.[14–21] Typically these routes have been low yielding[14–17] or have required very detailed synthesis of the precursors.[18–21] The best method used to date, has been the Skraup cyclization,[7] which involves reaction of the respective aniline and acetone (or the desired ketone), in the presence of iodine, at 145°C under pressure for 2–3 days.

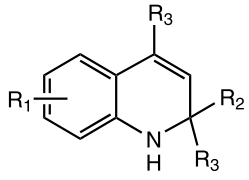
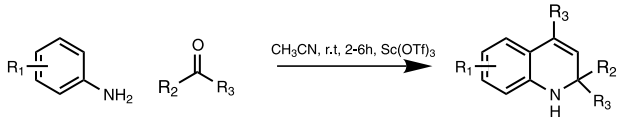


Figure 1. 2,2,4 Substituted 1,2-dihydroquinoline.

We were interested in synthesizing 2,2,4 substituted 1,2-dihydroquinolines in a combinatorial library format and determined that these literature procedures, involving lengthy periods at high temperatures, were not amenable to library synthesis. To circumvent these problems, we investigated the use of microwaves as a means to accelerate the reaction and improve yields. Through the use of the Personal Chemistry Smith Synthesizer™[25] microwave system, the yields of the Skraup cyclization were only increased slightly (i.e. 45–55%), in the best of conditions. However, the reaction times were shortened from 60 to 1 h (140°C).

In our effort to adapt and broaden the scope of the Skraup synthesis further, we investigated the use of lanthanide catalysts at room temperature. In reference to Scheme 1, where $R_1 = H$ and $R_2, R_3 = Me$, scandium-, indium- and ytterbium-trifluoromethane sulphonates gave yields of 65, 63 and 60%, respectively. These yields and reaction times once compared to those mentioned by the traditional Skraup route and the improved microwave technique, above indicated to us that lanthanide catalysts were extremely useful in this type of synthesis. Neither of the lanthanide catalysts offered any significant advantage over each other and hence further reactions were all carried out with the use of scandium trifluoromethane sulphonate. Yields obtained by the use of this catalyst will be quoted throughout for reference (Table 1).



Scheme 1. Synthesis of 2,2,4 substituted 1,2-dihydroquinolines.

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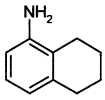
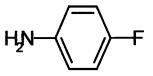
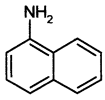
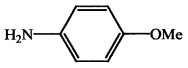
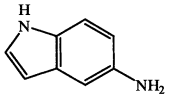
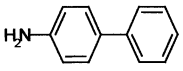
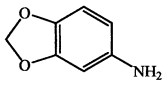
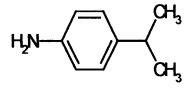
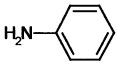
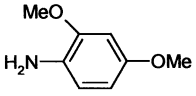
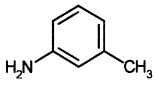
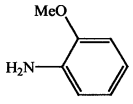
Table 1. Yields of 2,2,4-methyl 1,2 dihydroquinoles synthesized

Aniline used for R_1	R_2	R_3	Yield*	Aniline used for R_1	R_2	R_3	Yield*
	Me	Me	63%		Me	Me	76%
	Me	Me	78%		Me	Me	98%
	Me	Me	95%[a]		Me	Me	59%
	Me	Me	82%[b]		Me	Me	90%
	Me	Me	65%		Me	Me	90%
	Me	Me	88%		Me	Me	85%

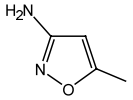
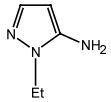
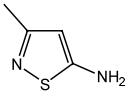
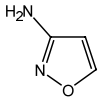
*Cases where two regioisomers are observed, the yield of the major isomer is quoted

[a]:-^{1}H NMR ($CDCl_3$)δ 10.01 (s, 1H), 7.07 (s, 1H), 7.01 (d, 1H), 6.98 (s, 1H), 6.61 (s, 1H), 6.23 (d, 1H), 5.30 (s, 1H), 1.98 (s, 3H), 1.15 (s, 3H), 1.10 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 141.40, 133.45, 129.02, 128.45, 127.01, 125.21, 119.62, 106.21, 103.32, 99.07, 72.84, 31.46, 29.53, 20.10 [b]:-^{1}H NMR ($CDCl_3$)δ 6.82 (s, 1H), 6.23 (s, 1H), 5.83 (s, 2H), 5.23 (s, 1H), 4.70 (bs, 1H), 1.85 (s, 3H), 1.18 (s, 3H), 1.15 (s, 3H) ; ^{13}C NMR ($CDCl_3$) δ 146.56, 144.05, 142.82, 133.34, 132.45, 121.81, 98.72, 94.71, 90.92, 72.17, 31.06, 29.96, 20.02

The cyclization reaction of a variety of anilines with acetone in the presence of scandium trifluoromethane sulphonate, proceeded very smoothly at room temperature[22] to give the desired products in yields of 59–98% (Scheme 1). In certain cases two regioisomeric products were isolated, as is commonly seen in the Skraup cyclization. The products were purified via a PE Sciex LC/MS system with mass triggered fraction collection.[26–28] Secondary anilines were also tested, but these reactions proceeded in 10–15% yield at room temperature. Elevated temperatures did not produce significantly higher yields. The method was extended to incorporate a variety of aminoheterocycles, resulting in a synthesis of several interesting fused bicyclic heterocycles (Table 2) in moderate yields.

Due to the success of the modified conditions with acetone, we explored incorporation of other ketones. Consequently, reactions were carried out with 2-butanone, acetophenone[24] and a variety of other ketones. While the reactions with more hindered ketones (e.g. 2-butanone) appeared to proceed well[23] (Table 3), albeit in lower yields than their acetone counterparts (minor amounts (2%) of 2-ethyl-2,3,4-trimethyl-1,2-dihydroquinoline were isolated), the reactions with e.g. acetophenone did not proceed at all at room temperature. It can be envisioned that compounds of this nature would be significantly sterically hindered and hence the synthesis of the cyclized products would be more difficult. Increasing the tempera-

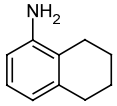
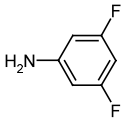
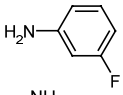
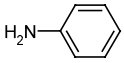
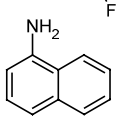
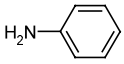
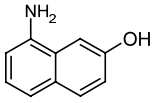
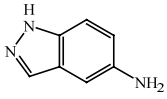
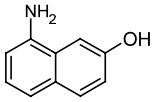
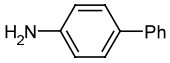
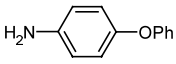
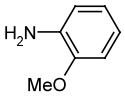
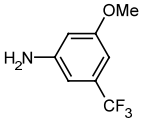
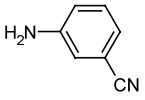
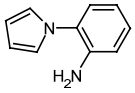
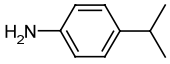
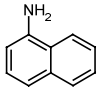
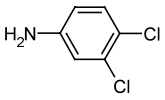
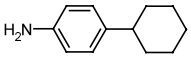
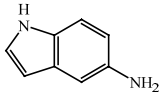
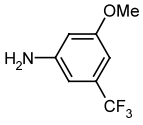
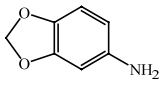
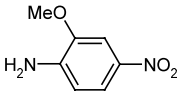
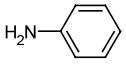
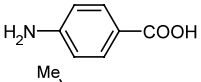
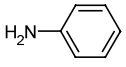
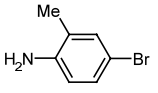
Table 2. Product yields with aminoheterocycles

Aminoheterocycle	R_2	R_3	Yield
	Me	Me	50%
	Me	Me	45%[a]
	Me	Me	49%[b]
	Me	Me	62%

[a]:-^{1}H NMR ($CDCl_3$)δ 7.01 (s, 1H), 5.28 (s, 1H), 5.01 (bs, 1H), 4.13 (q, J=7Hz, 2H), 2.30 (s, 1H), 1.28 (t, J=7Hz, 3H), 1.15 (s, 1H), 1.10 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 139.40, 137.45, 119.02, 113.45, 110.01, 57.21, 42.62, 31.21, 30.32, 20.87, 13.84

[b]:-^{1}H NMR ($CDCl_3$)δ 6.12 (bs, 1H), 5.23 (s, 1H), 2.33 (s, 3H), 2.23 (s, 3H), 2.30 (s, 1H), 1.25 (s, 3H), 1.15 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 185.56, 139.25, 124.82, 119.45, 116.01, 57.02, 31.71, 30.32, 20.17

Table 3. Yields of 2,2,4-methyl 1,2 dihydroquinolines synthesized

Aniline used for R_1	R_2	R_3	Yield*	Aniline used for R_1	R_2	R_3	Yield*
	Me	Et	81%		Me	3-F-Ph	78%
	Me	Et	79%		Me	2-thiophene	42%
	Me	Et	98%		Me	4-pyridine	35%
	Me	Et	65%		Me	3-Cl-Ph	60%[29]
	Me	Et	79%		Me	Ph	45%
	Me	Et	61%		Me	Ph	45%
	Me	Et	90%		Me	4-MeO-Ph	72%
	Me	Et	68%		Me	Ph	52%
	Me	Et	85%		Me	3,4-Cl-Ph	78%
	Me	Et	76%		Me	Ph	73%
	Me	Et	95%		Me	3,4-Cl-Ph	68%
	Me	Et	71%		Me	Ph	49%
	Me		30%		Me	Ph	63%
	Me	iPr	45%		Me	Ph	52%

*Cases where two regioisomers are observed, the yield of the major isomer is quoted

ture, in the presence of scandium triflate, to 80°C overnight gave the desired cyclized products, from acetophenone, in 23% yield.

We then decided to limit the reaction times by reacting the components using a Personal Chemistry SmithSynthesizer™.[24] Optimal yields were obtained when the reaction mixtures were microwaved at 150°C for 50 min (Table 3). Secondary anilines were also evaluated, but these reactions, once again, were either very low yielding (8–12%) or produced no product at all at room temperature.

The work presented here demonstrates a straightforward and mild procedure for the efficient synthesis of 2,2,4 substituted 1,2 dihydro-quinolines using scandium triflate catalysis. A variety of anilines and unsymmetrical ketones can be used to expand the scope of the substituents, particularly five-membered ring heterocycles to yield a variety of fused dihydropyridines. Compounds that were almost impossible to synthesize via the standard routes have also been produced in reasonable yields via the use of microwave technology. The mild conditions developed make this procedure especially amenable to combinatorial library synthesis.

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22. Experimental: 0.5 mmol of the desired aniline were dissolved in 3 mL anhydrous acetone. To this solution was added scandium triflate (0.1 equiv.; 0.05 mmol; 25 mg). The reaction mixture was shaken for 2 h at rt. After reaction was complete, by LC/MS monitoring, the mixture was evaporated to dryness, resuspended in 1:1 DMSO:CH_3CN, and filtered. Purification was carried out on a semipreparative YMC ODS-A reverse phase column (20×50 mm, particle size S-5) via use of a 10–99% gradient of 0.05% TFA in water/0.035% TFA in acetonitrile (flow rate 35 ml/min) on a Shimadzu HPLC system with an API150EX single quadropole mass spectrometer.
23. Experimental: 0.5 mmol of the desired aniline were dissolved in 3 mL anhydrous acetonitrile. To this solution was added scandium triflate (0.1 equiv.; 0.05 mmol; 25 mg) and 2-butanone (5 equiv.; 2.5 mmol; 223 μL). The reaction mixture was shaken for 6 h at rt. The workup was identical to that of Ref. 22.
24. Experimental for lanthanide catalyst reaction with Personal Chemistry SmithSynthesizer™ microwave: 0.5 mmol of the desired aniline were dissolved in 3 mL anhydrous acetonitrile. To this solution was added scandium triflate (0.1 equiv.; 0.05 mmol; 25 mg) and acetophenone (5 equiv.; 2.5 mmol; 291 μL). The reaction mixture was microwaved for 50 min at 150°C using a Smith Personal Workmate. The workup was identical to that of Ref. 22.
25. Experimental for Skraup conditions with Personal Chemistry SmithSynthesizer™ microwave: 0.5 mmol of the desired aniline were dissolved in 3 mL anhydrous acetone. To this solution was added iodine (0.1 equiv.; 0.05 mmol; 12.7 mg) and the reaction mixture was microwaved for 1 h at 140°C using a Smith Personal Workmate. The workup was identical to that of Ref. 22.
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29. ^{1}H NMR ($CDCl_3$): δ 8.01–7.38 (m, 6H), 7.28–6.89 (m, 7H), 6.18–6.12 (two bs, 2H), 5.73 (s, 1H), 1.80 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 149.40, 144.45, 140.72, 139.45, 136.41, 134.21, 133.62, 133.21, 131.32, 130.87, 129.84, 129.20, 128.94, 127.99, 127.98, 127.45, 126.54, 126.30, 126.23, 124.74, 122.99, 118.65, 116.45, 110.93, 53.50, 28.58.