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A MILD AND EFFICIENT $Ga(OTf)_3$-CATALYSED FRIEDLÄNDER REACTION FOR THE SYNTHESIS OF QUINOLINES

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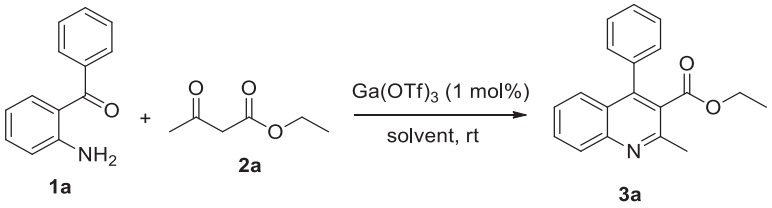
Abstract – The application of gallium triflate [$Ga(OTf)_3$] for the synthesis of quinolines *via* the Friedländer reaction is described. This mild and straightforward method employed only 1 mol% of $Ga(OTf)_3$ to deliver the quinoline products in excellent yields, demonstrating the high catalytic activity of this rare earth metal triflate.

Quinolines are an important class of compounds owing to their presence in biologically active natural products and synthetic molecules.[1] The quinoline ring system is a privileged scaffold that exhibits a wide range of pharmacological properties such as antimalarial,[2] antibacterial,[3] antitubercular,[4] and anticancer activities.[5] A variety of synthetic methods have been developed for the construction of the quinoline heterocycle such as the Doebner–Miller, Friedländer, Skraup, and Combes reactions as well as various other approaches.[6] Among these methods is the Friedländer annulation which is one of the most convenient and simple strategies for the synthesis of quinoline derivatives. Acid catalysts are more effective than base catalysts for the Friedländer annulation and a variety of acid-catalysed protocols have been developed.[7] Although valuable, some of the current methods have shortcomings such as high catalyst loading, drastic reaction conditions, extended reaction times, and convenience.

Metal triflates such as $Bi(OTf)_3$,[8] $Y(OTf)_3$,[9] and $Yb(OTf)_3$[10] have also been reported; however, in each of these methods at least 5 mol% catalyst was required. Therefore, the development of new and simple synthetic methods that requires low catalyst loading for the synthesis of quinolines through the Friedländer annulation is highly desirable. Gallium triflate [$Ga(OTf)_3$] is a recyclable, water-tolerant, and stable Lewis acid that has been extensively used in various organic reactions, requiring low catalyst loading in many transformations.[11] In continuation of our interest in metal-catalysed reactions for the synthesis of molecules of interest,[12-15] herein we report a practical and efficient method for the synthesis of quinolines through the Friedländer annulation using $Ga(OTf)_3$ as a highly efficient Lewis acid catalyst.

We commenced our investigation on the use of $Ga(OTf)_3$ as a catalyst for the Friedländer annulation by selecting 2-aminoaryl ketone **1a** and *β*-ketoester **2a** as the model reaction to find optimal conditions. From the outset, we reacted **1a** with **2a** using low catalyst loading (1 mol%) of $Ga(OTf)_3$ in various solvents at room temperature (Table 1). Pleasingly, when the reaction was performed in acetonitrile (MeCN) the desired quinoline product **3a** was formed in 93% yield. Other tested solvents such as dichloromethane, THF, EtOH, and DMF were inferior to MeCN as the yields were much lower. Thus, MeCN was the best solvent that gave the optimal yield for the reaction.

Table 1. Screening various solvents for the Friedländer reaction under $Ga(OTf)_3$ catalysis

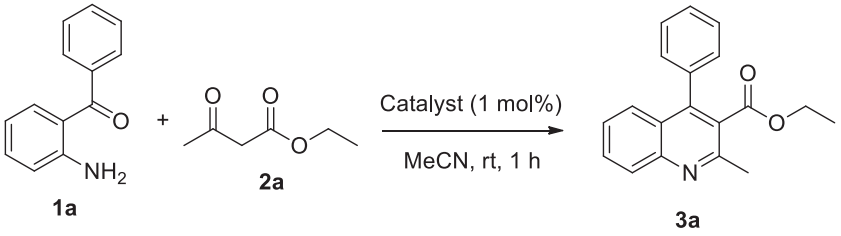


Entry	Solvent	Yield (%)[a]
1	CH_2Cl_2	45
2	MeCN	93
3	THF	41
4	EtOH	15
5	DMF	36

[a]All reactions were performed using 2-aminoaryl ketone **1a** (1 mmol), *β*-ketoester **2a** (1.2 mmol), $Ga(OTf)_3$ (1 mol%), and solvent at room temperature for 1 h.

We then decided to test the synthesis of quinoline **3a** using $Yb(OTf)_3$, $Y(OTf)_3$, and $Bi(OTf)_3$ in independent reactions at 1 mol% catalyst loading with MeCN as the solvent (Table 2). From the obtained results, we found $Ga(OTf)_3$ to be superior to the other tested metal triflates as it displayed a high level of activity and provided the best yield of the quinoline product **3a** (93%).

Table 2. Comparison of $Ga(OTf)_3$ with other metal triflate catalysts in the Friedländer reaction at 1 mol% catalyst loading



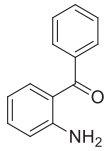
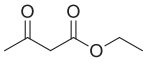
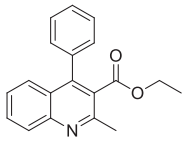
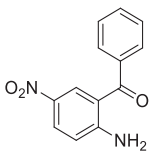
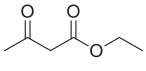
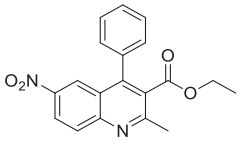
1a + **2a** → **3a**

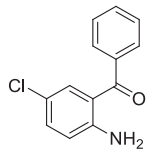
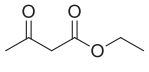
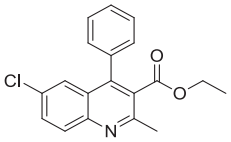
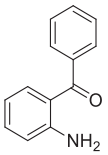
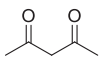
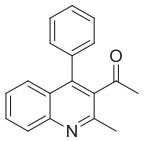
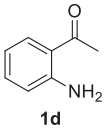
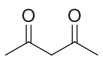
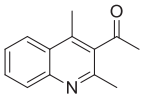
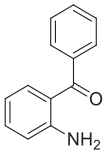
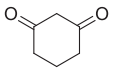
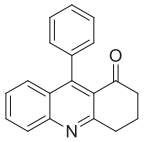
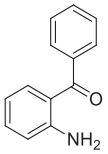
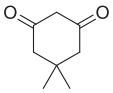
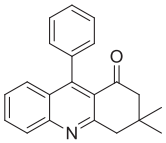
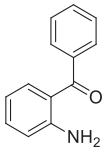
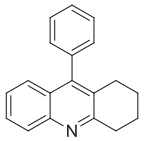
Entry	Metal triflate	Yield (%)[a]
1	$Ga(OTf)_3$	93
2	$Yb(OTf)_3$	31
3	$Y(OTf)_3$	22
4	$Bi(OTf)_3$	trace

[a]All reactions were carried out using 2-aminoaryl ketone **1a** (1 mmol), *β*-ketoester **2a** (1.2 mmol), catalyst (1 mol%), and MeCN at room temperature for 1 h.

The scope of this method was then explored using various 2-aminoaryl ketone substrates with acyclic and cyclic ketones which afforded the desired quinoline products **3a**–**3h** in yields ranging from 83–95% (Table 3). Under the reaction conditions, the acyclic and cyclic ketones proceeded smoothly to give quinolines **3a**–**3h**. Interestingly, the cyclic ketone **2e** (cyclohexanone) also underwent smooth condensation to provide quinoline **3h** in 86% yield.

Table 3. $Ga(OTf)_3$-catalysed synthesis of quinolines **3a**–**3h** *via* the Friedländer reaction

Entry	2-Aminoaryl ketone	Ketone	Product	Yield (%)
1	 **1a**	 **2a**	 **3a**	93
2	 **1b**	 **2a**	 **3b**	91

3	 **1c**	 **2a**	 **3c**	95
4	 **1a**	 **2b**	 **3d**	85
5	 **1d**	 **2b**	 **3e**	83
6	 **1a**	 **2c**	 **3f**	92
7	 **1a**	 **2d**	 **3g**	89
8	 **1a**	 **2e**	 **3h**	86

This method tolerated 2-aminoaryl ketone substrates bearing an electron withdrawing group (**1b**) or a halogen (**1c**) to afford the quinoline products **3b** and **3c** in 91% and 95% yield, respectively. In all reactions, the transformation to quinolines progressed smoothly at room temperature with impressive efficiency.

In summary, we have described a mild and highly efficient method for the synthesis of quinolines *via* the Friedländer reaction employing $Ga(OTf)_3$ as the catalyst. This environmentally benign method required only 1 mol% of catalyst loading to provide the quinoline products in excellent yields.

EXPERIMENTAL

General experimental

Melting points were determined using a Gallenkamp melting point apparatus and are uncorrected.

Chemical reactions were carried out under a nitrogen atmosphere with anhydrous MeCN. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm silica gel plates with fluorescent indicator (254 nm) and visualised using UV irradiation and/or staining with aqueous basic solution of potassium permanganate. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker 400 MHz spectrometer using $CDCl_3$ as the solvent and calibrated using residual undeuterated solvent as an internal reference. Chemical shifts and coupling constants (*J* values) are reported in parts per million (ppm) and Hertz (Hz), respectively. The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, triplet = t, quartet = q, quintet = quin, and m = multiplet. High resolution mass spectrometry was conducted using a Micromass Q-ToF mass spectrometer.

General procedure for the preparation of quinolines 3a–3h (Friedländer reaction):

A mixture of 2-aminoaryl ketone substrate (1 mmol), ketone substrate (1.2 mmol) and $Ga(OTf)_3$ (1 mol%) in MeCN was stirred at rt for 1 h. Water (10 mL) was added and the crude product was extracted with EtOAc (three times). The combined organic layers were dried over $MgSO_4$, filtered, and the solvent was evaporated in vacuo. Purification by silica gel column chromatography afforded the quinoline products.

Ethyl 2-methyl-4-phenylquinoline-3-carboxylate (3a).[9] White solid, 93% yield; mp 91–93 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, *J* = 8.2 Hz, 1H), 7.69 (t, *J* = 8.2 Hz, 1H), 7.56 (d, *J* = 7.4 Hz, 1H), 7.48–7.45 (m, 3H), 7.41–7.36 (m, 1H), 7.35–7.34 (m, 2H), 4.05 (q, *J* = 7.4 Hz, 2H), 2.78 (s, 3H), 0.93 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 154.6, 147.7, 146.2, 135.7, 130.2, 129.3, 128.8, 128.4, 128.2, 127.4, 126.5, 126.4, 125.1, 61.3, 23.8, 13.6; HRMS (ESI) calcd for $C_{19}H_{18}NO_2$ $[M+H]^+$ 292.1338, found 292.1329.

Ethyl 2-methyl-6-nitro-4-phenylquinoline-3-carboxylate (3b).[16] Yellow solid, 91% yield; mp 138–140 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.52–8.51 (m, 1H), 8.45 (dd, *J* = 9.0, 2.4 Hz, 1H), 8.17 (d, *J* = 9.0 Hz, 1H), 7.54–7.51 (m, 3H), 7.36–7.34 (m, 2H), 4.07 (q, *J* = 7.2 Hz, 2H), 2.81 (s, 3H), 0.95 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 158.9, 149.8, 148.0, 145.6, 134.2, 130.8, 129.5, 129.3, 129.2, 128.8, 124.6, 123.8, 123.6, 61.9, 24.3, 13.7; HRMS (ESI) calcd for $C_{19}H_{17}N_2O_4$ $[M+H]^+$ 337.1188, found 337.1185.

Ethyl 6-chloro-2-methyl-4-phenylquinoline-3-carboxylate (3c).[17] Yellow solid, 95% yield; mp 105–107 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, *J* = 8.7 Hz, 1H), 7.60 (d, *J* = 9.2 Hz, 1H), 7.51–7.45 (m, 4H), 7.33–7.30 (m, 2H), 4.04 (q, *J* = 7.3 Hz, 2H), 2.74 (s, 3H), 0.91 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 155.1, 146.1, 145.5, 135.1, 132.4, 131.2, 130.6, 129.4, 128.8, 128.5, 128.2, 126.0, 125.3, 61.5, 23.8, 13.7; HRMS (ESI) calcd for $C_{19}H_{17}ClNO_2$ $[M+H]^+$ 326.0948, found 326.0947.

1-(2-Methyl-4-phenylquinolin-3-yl)ethenone (3d).[9] White solid, 85% yield; mp 109–110 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, *J* = 8.4 Hz, 1H), 7.72 (t, *J* = 8.4 Hz, 1H), 7.62 (d, *J* = 8.4 Hz, 1H),

7.52–7.50 (m, 3H), 7.44 (t, *J* = 7.1 Hz, 1H), 7.37–7.34 (m, 2H), 2.70 (s, 3H), 2.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.9, 153.6, 147.6, 144.0, 135.3, 134.9, 130.2, 130.1, 129.0, 128.9, 128.8, 126.6, 126.3, 125.1, 32.1, 24.0; HRMS (ESI) calcd for $C_{18}H_{16}NO$ $[M+H]^+$ 262.1232, found 262.1230.

1-(2,4-Dimethylquinolin-3-yl)ethenone (3e).[17] Yellow oil, 83% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.4 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.66 (t, *J* = 7.6 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 1H), 2.60 (s, 3H), 2.55 (s, 3H), 2.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.7, 152.7, 146.9, 138.7, 135.8, 129.9, 129.3, 126.5, 125.9, 123.7, 32.7, 23.6, 15.3; HRMS (ESI) calcd for $C_{13}H_{14}NO$ $[M+H]^+$ 200.1075, found 200.1073.

9-Phenyl-3,4-dihydroacridin-1(2*H*)-one (3f).[8] White solid, 92% yield; mp 157–159 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, *J* = 8.4 Hz, 1H), 7.75 (t, *J* = 8.3 Hz, 1H), 7.50–7.45 (m, 4H), 7.41–7.37 (m, 1H), 7.18–7.16 (m, 2H), 3.37 (t, *J* = 6.6 Hz, 2H), 2.70 (t, *J* = 6.6 Hz, 2H), 2.24 (quin, *J* = 6.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.9, 162.2, 151.4, 148.6, 137.6, 131.7, 128.4, 128.2, 128.1, 128.0, 127.5, 127.4, 126.4, 123.8, 40.6, 34.5, 21.3; HRMS (ESI) calcd for $C_{19}H_{16}NO$ $[M+H]^+$ 274.1232, found 274.1222.

3,3-Dimethyl-9-phenyl-3,4-dihydroacridin-1(2*H*)-one (3g).[9] Yellow solid, 89% yield; mp 239–241 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (d, *J* = 8.4 Hz, 1H), 7.79–7.61 (m, 1H), 7.53–7.48 (m, 4H), 7.43–7.39 (m, 1H), 7.20–7.18 (m, 2H), 3.28 (s, 2H), 2.58 (s, 2H), 1.17 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.1, 161.2, 151.1, 149.1, 137.7, 131.8, 128.6, 128.4, 128.2, 128.1, 127.7, 127.5, 126.6, 122.8, 54.2, 48.4, 32.3, 28.4; HRMS (ESI) calcd for $C_{21}H_{20}NO$ $[M+H]^+$ 302.1545, found 302.1539.

9-Phenyl-1,2,3,4-tetrahydroacridine (3h).[9] White solid, 86% yield; mp 139–141 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.5 Hz, 1H), 7.62−7.58 (m, 1H), 7.54−7.45 (m, 3H), 7.34−7.29 (m, 2H), 7.24 (d, *J* = 6.8 Hz, 2H), 3.21 (t, *J* = 6.5 Hz, 2H), 2.61 (t, *J* = 6.5 Hz, 2H), 1.97 (quin, *J* = 6.5 Hz, 2H), 1.79 (quin, *J* = 6.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 146.5, 146.4, 137.2, 129.1, 128.6, 128.4, 128.3, 127.8, 126.7, 125.8, 125.4, 34.3, 28.1, 23.1, 23.0; HRMS (ESI) calcd for $C_{19}H_{18}N$ $[M+H]^+$ 260.1439, found 260.1431.

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