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AN EFFICIENT METHOD FOR THE SYNTHESIS OF *N*-ARYL SUBSTITUTED C1-FUNCTIONALIZED 1,2,3,4-TETRAHYDROISOQUINOLINES

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Abstract – An efficient and facile cyclic iminium-ion-based strategy has been developed for the synthesis of structurally diverse *N*-aryl substituted C1-functionalized THIQs. Cyclic iminium ions generated in situ from 2-(2-bromomethyl)benzaldehyde reacted with acetone to furnish ketone moiety at C-1 position in THIQs in moderate to good yields.

The 1,2,3,4-tetrahydroisoquinoline (THIQ) structural motif, especially C1-substituted THIQs, is active structural unit in natural products, pharmaceuticals, and exhibits a wide range of biological activities,[1] including anticancer activities,[2] anti-inflammatory,[3] antimicrobial,[4] and anti-plasmodial activities.[5] Representative examples (Figure 1) include (+)-dysoxyline (**A**), isolated from *Dysoxylum lenticellare*,[6] Praziquantel (**B**), a broad-spectrum antischistosomal agent,[7] and Lifitegrast (**C**), a novel integrin antagonist marketed in 2016 for the treatment of dry eye disease.[8] Moreover, drug candidate BMS-962212 (**D**), a reversible, direct, and highly selective small molecule inbibtor of factor XIa is in phase I clinical trials.[9]

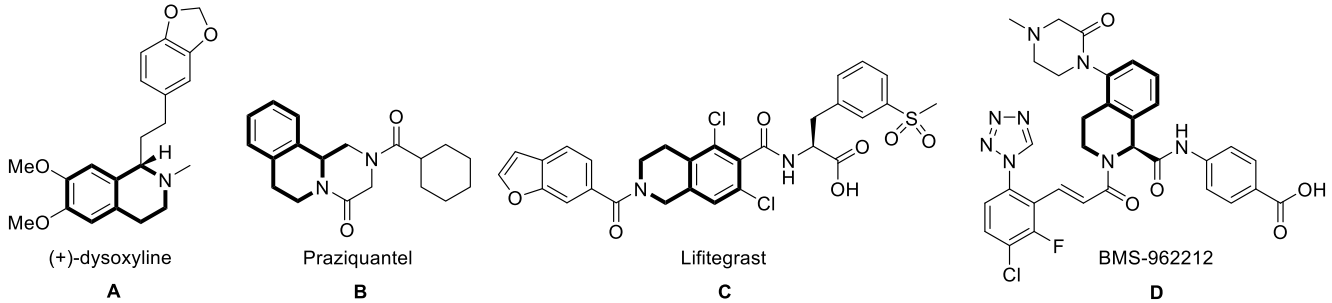
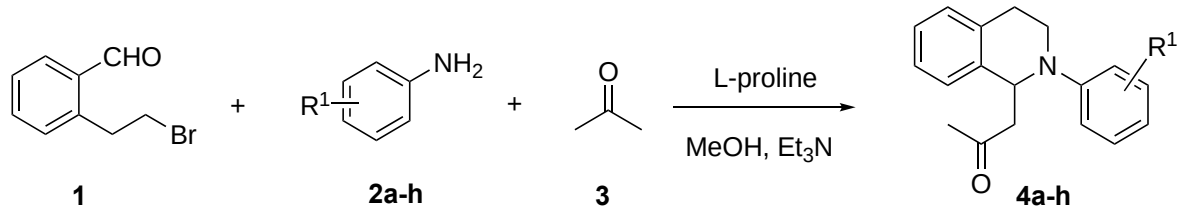


Figure 1. Examples of bioactive compounds containing a THIQ moiety

Due to the significant biological properties of THIQ derivatives, various methods have been reported for the synthesis of C1-substituted THIQs based on traditional synthetic methods (the sequential Bischler-Napieralski cyclization/reduction,[10] the Pictet-Spengler[11]) and nucleophilic addition to the preformed C=N$^+$ bond of cyclic precursors.[12] During the past decade, iminium ion has been used as a key intermediate in the synthesis of nitrogen-containing ring complex molecule, particularly in biologically important alkaloids through carbon-carbon and carbon-heteroatom bond-forming reactions.[13] The Mannich,[14] aza-Cope,[15] and Pictet-Spengler[16] reactions exemplify the significance of iminium ion chemistry in organic synthesis. Recently, an iminium-ion-based one-pot methodology for the synthesis of alkynyl THIQs using zinc acetylide as carbon nucleophile has been reported by Mukkanti and coworkers.[17] They did not further systematically study the diverse synthesis of THIQs. Proline catalyzed one-pot three component Mannich reactions have been used for the effective generation of amino ketones, which are further transformed to alkaloids, sugar derivatives, amino acids, and amino alcohols.[18] Despite this progress, we are interested to know if enolized ketones could be used as carbon nucleophiles to undergo nucleophilic attack to C, N-iminium ion at the C1-position, which will provide a new approach for the one-step synthesis of multifunctionalized THIQs (Scheme 1).



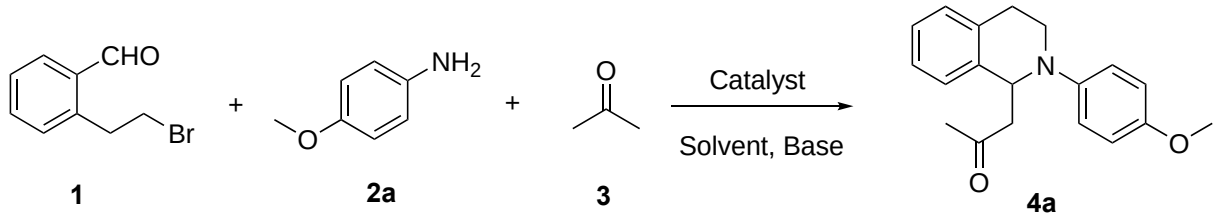
Scheme 1. Synthesis of *N*-aryl substituted C1-ketone THIQs

In order to find the most suitable one-pot reaction conditions, 2-(2-bromomethyl)benzaldehyde (**1**) with 4-methoxybenzeneamine (**2a**) and acetone (**3**) were chosen as model substrates for the preparation of 1-(2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)propan-2-one (**4a**) and the results are summarized in **Table 1**. Initially, the reaction of **1** (1.0 mmol), **2a** (1.1 mmol) and **3** (1.0 mmol) were performed in dichloromethane at room temperature for 16 h without any catalyst, affording the trace amounts of **4a** (Table 1, entry 1). When acetone acted as reagent and solvent,[19] the three-component reaction of **1** with **2a** promoted by L-proline at room temperature just afford trace amounts of the desired product **4a** at 16 h (Table 1, entry 2). When triethylamine (1.0 equiv.) was used to neutralize the HBr generated during the course of the reaction, it could access the corresponding product **4a** in 85% yield (Table 1, entry 3). In the absence of a base, HBr generated during the reaction maybe acidolysis of the intermediates. Optimization experiments revealed that triethylamine (1.0 equiv.) was a suitable base, beside DIPEA, DMAP were also effective (Table 1, entries 4 and 5). Screening of solvents showed that

methanol gave the best yield of the product (Table 1, entry 8). It was very disappointing that although L-proline or DL-proline for the reaction in terms of conversion could be attained, no selectivity was observed.[20]

With the optimized conditions in hand, we then extended the scope of substrates to different amines. The results at this scope are summarized in **Table 2**. Various anilines including aromatic mono-substituted aniline, aromatic di-substituted aniline **2h**, with **1**, and acetone could smoothly give the corresponding *N*-aryl substituted C1-ketone THIQs in moderate to good yields (Table 2, entries 1-8). However, no target product was obtained when 2-nitroaniline was used, possibly due to its poor nucleophilicity.

Table 1. Optimization of the reaction conditions for **1a**, **2a** and **3**[a]

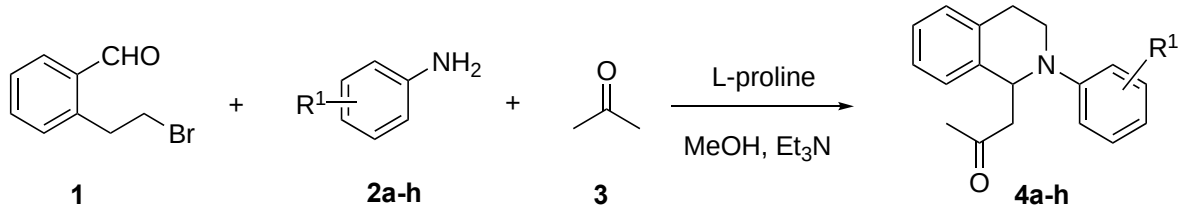


1 **2a** **3** **4a**

Entry	Catalyst[b]	Base	Solvent	Time/h	Yield[c]/%
1	none	none	CH_2Cl_2	16	trace
2	L-proline	none	acetone[d]	16	trace
3	L-proline	Et_3N[e]	acetone	2	85
4	-	Et_3N	acetone	2	trace
5	L-proline	DIPEA	acetone	2	78
6	L-proline	DMAP	acetone	2	75
7	L-proline	Na_2CO_3	acetone	2	45
8	L-proline	Et_3N	CH_2Cl_2	2	88
9	L-proline	Et_3N	MeOH	2	90
10	L-proline	Et_3N	THF	2	56
11	L-proline	Et_3N	MeCN	2	45
12	L-proline	Et_3N	toluene	2	67
13	DL-proline	Et_3N	acetone	2	82

[a] Reation condition: **1** (1.0 mmol), **2a** (1.1 mmol), **3** (1.0 mmol). [b] catalyst (10 mol%). [c] Yield of isolated products. [d] Acetone as reagent and solvent, 1.0 mL. [e] Base (1.0 mmol).

Table 2. Synthesis of *N*-substituted C1-ketone THIQs from **1** with amines **2a-h**, acetone **3**[a]

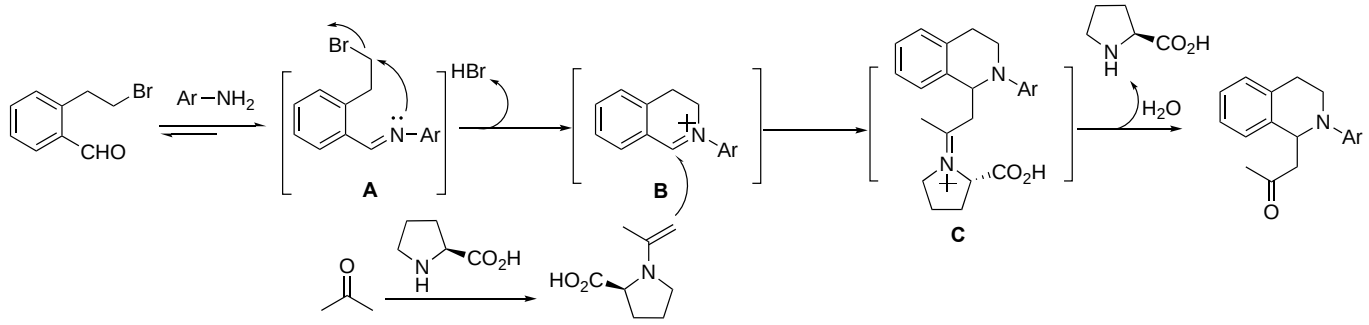


1 **2a-h** **3** **4a-h**

Entry	Amines	Yield (%)[b]	Time (h)[c]	Product
1	*p*-anisidine (**2a**)	90	2	**4a**
2	*o*-anisidine (**2b**)	81	2	**4b**
3	aniline (**2c**)	88	4	**4c**
4	*p*-toluidine (**2d**)	86	2	**4d**
5	*m*-toluidine (**2e**)	90	2	**4e**
6	*m*-chloroaniline (**2f**)	78	4	**4f**
7	*p*-bromoaniline (**2g**)	81	4	**4g**
8	3, 4-dimethylaniline (**2h**)	88	2	**4h**

[a] All reactions were performed with 1.0 mmol of **1**, 1.2 mmol of amine **2a-h**, 1.0 mmol of acetone, 1.0 mmol of Et_3N and 10 mol% of L-proline. [b] Isolated yield.

Based on the above result, a plausible mechanism is proposed for the formation of *N*-aryl substituted C1-functionalized THIQ derivatives under the proline catalyzed conditions (Scheme 2). Firstly, the reaction proceeds through the formation of an enamine derived from *p*-anisidine and 2-(2-bromomethyl)-benzaldehyde to give the iminium ion intermediate **A**. Secondly, the intermediate A cyclizes by intramolecular S_N2 displacement of the bromine group to form the electrophilic cyclic iminium ion **B**. Then, the α-carbon of enamine, which derived from acetone and L-proline, attacks at the cyclic iminium ion carbon with a Mannich-type reaction to give rise to the formation intermediate **C**. The intermediate **C** hydrolyzes to give the C1-functionalized THIQ derivatives and proline.



Scheme 2. Possible reaction mechanism for the formation of *N*-aryl substituted C1-ketone THIQs

In conclusion, we have developed an efficient and simple proline catalyzed one-pot three component Mannich-type reaction, using 2-(2-bromomethyl)benzaldehyde, amines, and acetone, which proceeds

through a cyclization to afforded a series of *N*-aryl substituted C1-ketone THIQs under Et_3N in moderate to good yields (78%~90%). This protocol provides a straightforward route to prepare variety of *N*-aryl substituted C1-functionalized THIQ derivatives.

EXPERIMENTAL

All reactions were monitored by thin layer chromatography (TLC) using commercial silica gel HSGF254 plates. TLC spots were viewed under ultraviolet light. All other reagents and solvents were purchased from Energy Chemical Company and used without any further purification. Product purification by gravity column chromatography was performed using commercial silica gel HG/T2354-92 (200-300 mesh). ^1H and ^{13}C NMR (600 and 125 MHz, respectively) spectra were recorded in $CDCl_3$, and TMS was used as an internal standard.

General procedure for the synthesis of *N*-aryl substituted C1-ketone THIQs (4a-h)

To a stirred solution of **1** (1.0 mmol) in MeOH (4 mL), amine **2** (1.0 mmol), acetone (1.0 mmol), L-proline (0.1 mmol) and Et_3N (1.0 mmol) were added successively. The solution was stirred well for about 2 h at room temperature. After the reaction finished, the solvents were removed under reduced pressure and the crude reaction mixture was purified through column chromatography (5:1 petroleum ether/EtOAc).

1-(2-(4-Methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)propan-2-one (**4a**), known compound[21]**:** Obtained as a yellow oil, yield 90%, ^1H NMR (600 MHz, $CDCl_3$) δ 7.17 – 7.12 (m, 3H), 7.12 – 7.07 (m, 1H), 6.93 – 6.87 (m, 2H), 6.83 – 6.76 (m, 2H), 5.27 – 5.21 (m, 1H), 3.73 (s, 3H), 3.56 – 3.52 (m, 1H), 3.46 – 3.42 (m, 1H), 3.05 – 2.95 (m, 2H), 2.78 – 2.68 (m, 2H), 2.04 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.60, 153.29, 143.65, 138.30, 134.38, 129.03, 126.88, 126.71, 126.25, 118.44, 114.64, 56.00, 55.62, 50.02, 42.84, 30.98, 26.74.

1-(2-(2-Methoxypheny)-1,2,3,4-tetrahydroisoquinolin-1-yl)propan-2-one (**4b**), known compound[21b]**:** Obtained as a syrup, yield 81%. ^1H NMR (600 MHz, $CDCl_3$) δ 7.07 (d, J = 4.0 Hz, 3H), 7.01 (d, J = 4.3 Hz, 1H), 6.90 (d, J = 7.3 Hz, 1H), 6.76 (dd, J = 14.4, 7.3 Hz, 3H), 5.31 (t, J = 6.2 Hz, 1H), 3.85 (s, 3H), 3.48 – 3.40 (m, 2H), 2.97 (dd, J = 15.5, 6.9 Hz, 2H), 2.73 – 2.60 (m, 2H), 1.98 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.48, 152.99, 139.73, 138.82, 134.28, 129.06, 126.83, 126.32, 126.02, 123.37, 121.42, 120.72, 111.78, 55.61, 55.41, 55.27, 49.82, 42.90, 30.47, 27.40.

1-(2-Phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)propan-2-one **(4c)**, known compound[21b]**:** Obtained as a yellow syrup, yield 88%, ^1H NMR (600 MHz, $CDCl_3$) δ 7.27 – 7.23 (m, 2H), 7.20 – 7.12 (m, 4H), 6.94 (d, J = 8.2 Hz, 2H), 6.78 (t, J = 7.2 Hz, 1H), 5.40 (t, J = 6.4 Hz, 1H), 3.67 – 3.63 (m, 1H), 3.55 – 3.51 (m, 1H), 3.10 – 3.00 (m, 2H), 2.84 – 2.80 (m, 2H), 2.08 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.53, 148.87, 138.28, 134.49, 129.41, 128.72, 126.88, 126.33, 118.27, 114.76, 54.80, 50.21, 42.05, 31.19,

27.19.

1-(2-(p-Tolyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)propan-2-one (**4d**), known compound[21]**:** Obtained as a yellow oil, yield 86%, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.11 – 7.05 (m, 3H), 7.03 (dd, J = 7.1, 2.9 Hz, 1H), 6.97 (d, J = 8.4 Hz, 2H), 6.78 (d, J = 8.4 Hz, 2H), 5.26 (t, J = 6.5 Hz, 1H), 3.54 (dt, J = 12.8, 5.0 Hz, 1H), 3.40 (ddd, J = 12.7, 9.7, 4.5 Hz, 1H), 2.96 (dd, J = 9.5, 5.9 Hz, 1H), 2.93 (d, J = 6.0 Hz, 1H), 2.75 – 2.65 (m, 2H), 2.16 (s, 3H), 1.98 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.59, 146.85, 138.32, 134.46, 129.90, 128.86, 128.00, 126.91, 126.76, 126.25, 115.68, 55.18, 50.08, 42.17, 31.11, 26.99, 20.40.

1-(2-(m-Tolyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)propan-2-one (**4e**), known compound[12a]**:** Obtained as a colorless oil, yield 90%. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.16 (dd, J = 12.9, 5.0 Hz, 5H), 6.77 (d, J = 8.1 Hz, 2H), 6.63 (d, J = 7.2 Hz, 1H), 5.41 (t, J = 6.3 Hz, 1H), 3.73 – 3.59 (m, 1H), 3.59 – 3.44 (m, 1H), 3.16 – 2.96 (m, 2H), 2.83 (dt, J = 16.0, 5.2 Hz, 2H), 2.33 (s, 3H), 2.09 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.34, 148.96, 139.01, 138.32, 134.46, 128.67, 126.81, 126.23, 119.23, 115.62, 111.98, 54.84, 50.20, 42.04, 31.11, 27.24, 21.92.

1-(2-(3-Chlorophenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)propan-2-one (**4f**), known compound[12a]**:** Obtained as a yellow oil, yield 78%, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.15 (qt, J = 8.2, 4.2 Hz, 5H), 6.88 (t, J = 2.2 Hz, 1H), 6.81 (dd, J = 8.4, 2.6 Hz, 1H), 6.72 (dd, J = 7.8, 2.0 Hz, 1H), 5.36 (dd, J = 7.3, 5.5 Hz, 1H), 3.59 (dt, J = 11.6, 5.6 Hz, 1H), 3.52 (ddd, J = 12.8, 8.5, 4.8 Hz, 1H), 3.08 – 3.00 (m, 2H), 2.84 (ddd, J = 16.6, 8.9, 3.6 Hz, 2H), 2.09 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.04, 149.84, 137.89, 135.20, 134.29, 130.34, 128.67, 127.08, 126.91, 126.49, 117.75, 113.94, 112.29, 54.53, 50.22, 42.14, 31.23, 27.16.

1-(2-(4-Bromophenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)propan-2-one (**4g**), known compound[12a]**:** Obtained as a colorless syrub, yield 81%. ^{1}H NMR (600 MHz,$CDCl_3$) δ 7.30 (d, J = 12.3 Hz, 2H), 7.16 (d, J = 5.2 Hz, 4H), 6.81 (d, J = 8.9 Hz, 2H), 5.35 (t, J = 6.2 Hz, 1H), 3.65 – 3.55 (m, 1H), 3.55 – 3.44 (m, 1H), 3.10 – 2.97 (m, 2H), 2.89 – 2.76 (m, 2H), 2.09 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.00, 147.79, 137.88, 132.01, 128.67, 126.97, 126.79, 126.40, 116.10, 110.05, 54.62, 50.11, 42.12, 31.13, 27.03.

1-(2-(3,4-Dimethylphenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)propan-2-one (**4h**), known compound[12a]**:** Obtained as a colorless oil, yield 88%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.14 (d, J = 10.5 Hz, 4H), 7.00 (d, J = 8.2 Hz, 1H), 6.77 (s, 1H), 6.70 (dd, J = 8.1, 2.2 Hz, 1H), 5.34 (t, J = 6.3 Hz, 1H), 3.73 – 3.57 (m, 1H), 3.57 – 3.40 (m, 1H), 3.04 (ddd, J = 16.0, 10.2, 5.8 Hz, 2H), 2.78 (ddd, J = 12.4, 9.5, 5.5 Hz, 2H), 2.23 (s, 3H), 2.17 (s, 3H), 2.07 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.39, 147.28, 138.32, 137.26, 134.41, 126.82, 126.78, 126.62, 126.12, 117.27, 113.08, 55.13, 50.05, 42.13, 30.98, 26.99, 20.28, 18.64.

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