IJASRM

International Journal of Advanced Scientific Research and Management, Volume 4 Issue 4, April 2019

www.ijasrm.com

ISSN 2455-6378

Alpha Functionalization of Aliphatic Amines – A Facile Approach

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Abstract

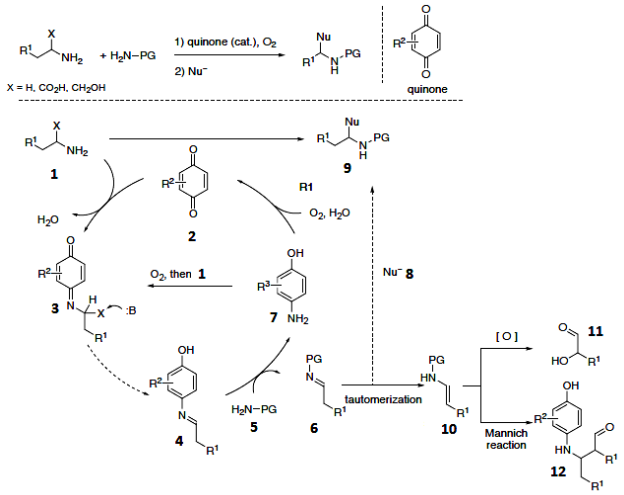
Amines are one of the most useful classes of molecules across a variety of scientific disciplines. For the synthesis of amines, the majority of well-established methods focus on C–N bond formation. In recent years, emerging α-functionalization of amine-containing compounds offers a new opportunity for efficient access to valuable amine molecules. So far, we have successfully developed quinone-catalyzed α-functionalization of activated amine-containing molecules. Unfortunately, aliphatic amine-containing molecules have failed to provide the desired reactivity under previously optimized conditions. To establish a general methodology of quinone-catalyzed α-functionalization of amine-containing molecules, this limitation must be overcome. In this paper, reaction development, optimization and scope study of quinone-catalyzed α-functionalization of aliphatic amine-containing compounds are detailed.

Keywords: *Amines, Oxidation, Nucleophilic Addition, C-H functionalization*

1. Introduction

Synthesis of aliphatic amines, α-amino acids and β-amino alcohols observed as significant challenges to the oxidative functionalization through quinone catalysis.[1-3] Under optimized conditions for the corresponding aromatic substrates, the aliphatic substrates failed to show any productive reactivity for quinone-catalyzed oxidation. It is a matter of the fact that functionalization of an alkylimine intermediate is less abundant than its aromatic counterpart. Synthetically useful alkylimines are generally conjugated, *e.g.* glyoxylate imines.[4-9] To develop an efficient protocol to expand the synthetic utility of alkylimines, we decided to revisit the role of aliphatic amine-containing molecules for quinone-catalyzed oxidative functionalization. The proposed mechanism of quinone-catalyzed α-functionalization of aliphatic amine-containing compounds is by the sequential oxidation/nucleophilic addition mechanisms for corresponding aromatic substrates as below (**Scheme 1**). In this mechanism, the aliphatic amine-containing substrate when X = H, α-amino acid when X = CO_2H, β-amino alcohol when X = CH_2OH) and a quinone catalyst are condensed together to yield an iminoquinone. This intermediate then undergoes oxidation to generate N-aryl imine which in turn participates in synthetic transformation with a protective amine to furnish N-protected imine. The oxidation is promoted by quinone.

Scheme 1: **Proposed Mechanism**



Actually, the higher transition state energy for the aliphatic amine containing substrates in the established protocols challenges quinone-catalyzed oxidative functionalization. Therefore, to facilitate the reactions with aliphatic substrates, the building negative charge should be stabilized so that the transition state energy could be lowered.

2. Results and Discussions

To execute quinone-catalyzed aliphatic amine functionalization, we initially studied the effects of Brønsted and Lewis acids. We expected that the

IJASRM
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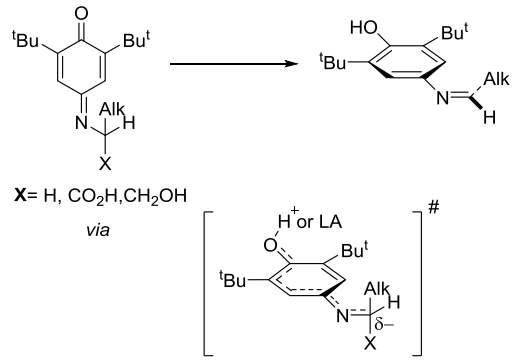
www.ijasrm.com
ISSN 2455-6378

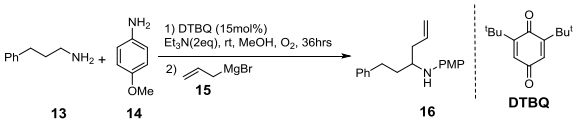
addition of acids could be a straightforward approach to stabilizing the negative charge in the transition state (**Scheme 2**). However, these attempts ended up with complex reaction mixtures, probably due to background acid-base interactions between the acid and the amino group in the substrates.

Scheme 2: **Stabilization of the transition state with Brønsted or Lewis acid**



It was noticed that the yield of the imine product could not be accurately measured by NMR experiments. This is probably due to hydrolysis or tautomerization of the imine product during the workup process. Therefore, the sequential quinone-catalysed oxidation/allylation reaction of 3-phenyl-1-propanamine (**13**) with allyl magnesium bromide (**15**) was chosen as the model reaction.

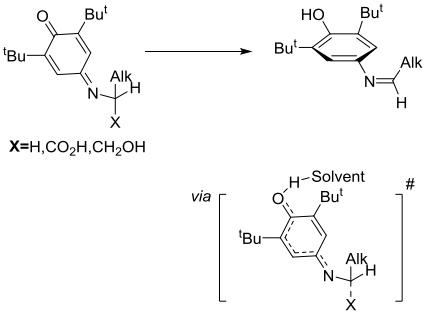
Table 1: Optimization of Quinone-catalyzed Oxidation/allylation[10]



Entry	Solvent	Temp (^{0}C)	Base	Yield (%)
1	PhMe	80	Et_3N	0
2	EtOH	70	Et_3N	0
3	EtOH	40	Et_3N	0
4	EtOH	rt	Et_3N	45
5	EtOH	0	Et_3N	19
6	MeOH	40	Et_3N	57
7	MeOH	rt	Et_3N	62
8	MeOH	0	Et_3N	50
9	MeOH	rt	None	36
10	MeOH	rt	DABCO	52
11	MeOH	rt	Hünig's base	35
12	MeOH	rt	DBU	15
13	^{i}PrOH	rt	Et_3N	5
14	^{t}BuOH	rt	Et_3N	0

Lowering temperature to room temperature (**Table 1**, entry **4**) provided the allylated amine **16** in 44% yield. This result suggested that possible tautomerization of the imine intermediate occurred at elevated temperatures. Lowering reaction temperature could kinetically prevent or slow down the tautomerization and following side reactions to allow the imine intermediate to participate in productive nucleophilic addition with allyl magnesium bromide. It was found that in the absence of a base additive, the reaction efficiency decreased to 36% yield (entry **9**). Additionally, none of the other organic bases (entry 10−12) provided better results in comparison to triethylamine. The difference in the reaction efficiency between ethanol and methanol is due to their ability to function as hydrogen bond donor, the physical parameter indicating a solvent's ability to act as a hydrogen bond donor to a solute[11]. Since methanol is a stronger hydrogen bond donor than ethanol, good yield with methanol as the solvent could be explained through better stabilization of the negative charge in the transition state through hydrogen bonding (**Scheme 3**). Lowering in the energy of the π* orbitals of the quinone moiety in the transition state could be explained by the interaction between the hydrogen bond donor and the iminoquinone oxygen, therefore lowering the energy gap between these π* orbitals and the σ(C–H) orbitals, thus ultimately promoting the oxidation step.

Scheme 3: **Effect of H-bonding on the stabilization of the transition state**



We also explored the scope of quinone-catalyzed oxidation/allylation sequence of aliphatic amine-containing molecules (**Table 2**). A number of aliphatic amines as well as natural amino acids were subjected to this reaction. While 3-phenyl-1-propanamine produced 60% of the allylated product (**19a**), 3-(4-methylphenyl)-1-propanamine afforded the product (**19b**) in 45% yield only. The methoxy derivative provided poor reaction efficiency (25% yield, **19c**).

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International Journal of Advanced Scientific Research and Management, Volume 4 Issue 4, April 2019
www.ijasrm.com
ISSN 2455-6378

Table 2: **Quinone-catalyzed Oxidation/allylation for Aliphatic Amines**

Compd.	When **R**=	Compd.	When **R**=
19a	(60% yield)	**19g**	(53% yield)
19b	Me (45% yield)	**19h**	(55% yield)
19c	MeO (25% yield)	**19i**	(28% yield)
19d	F 51% Yield	**19j**	(62% yield)
19e	(82% yield)	**19k**	Me (33% yield)
19f	(71% Yield)		

We also studied a series of cyclic methanamines. Out of them, cyclopropanemethanamine provided the allylated amine (**19e**) in excellent yield (82% yield). However, the analysis of the result indicates that decreasing yields are obtained with increasing the ring size of the cyclic substituents. Presumably, the larger ring size of the substituent would thermodynamically favor tautomerization of the N-PMP imine intermediate instead of nucleophilic addition since the corresponding enamine suffers less angle strain[12].

3. Materials and Methods

3.1 General Experimental Information.

Purification of reaction products was carried out by flash chromatography using 230-400 Mesh silica gel. UV-active TLC silica gel plate (GH_{254}) purchased from Merck was used for TLC monitoring purpose. Infrared (IR) spectra were recorded on Shimadzu FTIR-8400S. ^{1}H-NMR spectra were recorded on Bruker 400 MHz or Bruker 500 MHz spectrometers.

3.2 General Experimental Procedures for Oxidation Addition.

The amine or amino acid (2.5 mmol) was added to a well stirred solution of DTBQ (110 mg, 0.5 mmol), p-anisidine (615 mg, 5 mmol) and Et_3N (700.0 µL, 5 mmol) in dry methanol solvent (16 mL). The reaction flask was purged with oxygen and the reaction mixture was allowed to stir under aerobic condition at room temperature for next 24 hrs. The solvent was removed under reduced pressure and the oxidative decarboxylation product was further pumped for 1h with a high-vacuum pump.

3.3 General procedure for the synthesis alpha-substituted amines using allylmagnesium bromide through nucleophilic addition.

At 0°C, the reaction flask containing the oxidized product of amine was added to anhydrous THF (16.0 mL) and purged with argon. The nucleophile (10 mmol) was added dropwise under N_2 with vigorous stirring. After stirring at 0°C for 1.5h, the reaction mixture was removed from ice-bath and allowed to warm to room temperature. The reaction mixture was then quenched by slow addition of saturated aq. Solution of NH_4Cl (10 mL) followed by saturated aq. $NaHCO_3$ (50 mL). The resulting mixture was extracted with Et_2O (3x50 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Pure functionalized amines were obtained by using flash chromatography technique on silica gel.

3.4 Characterization Data of the Reported Compounds

19a: Flash chromatography on silica gel (5% ethyl acetate in hexanes) provided the product **19a** as a red-orange oil. **IR**: 3394, 3026, 2951, 1208 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) 7.31 – 7.25 (m, Ar H, obscured by $CDCl_3$), 7.22 – 7.15 (m, 3H), 6.83 – 6.70 (m, 2H), 6.58 – 6.45 (m, 2H), 5.81 (ddt, *J* = 16.8, 10.6, 7.2 Hz, 1H), 5.13 – 4.98 (m, 2H), 3.75 (s, 3H), 3.40 – 3.34 (m, 1H), 2.85 – 2.63 (m, 2H), 2.34 – 2.29 (m, 1.3 Hz, 2H), 1.93– 1.70 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) 152.1, 142.2, 141.9, 134.9, 128.6, 128.5, 126.0, 117.9, 115.1, 115.0, 56.0, 53.0, 38.7, 36.2, 32.5; HRMS (ESI): Exact mass calcd for $C_{19}H_{24}NO$ [M+H$^+$], 282.1863. Found 282.1788.

19b: Flash chromatography on silica gel (5% ethyl acetate in hexanes) provided the product **19b** as a pale-yellow oil. **IR**: 3394, 3000, 2925, 1231 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) 7.16 – 6.98 (m, 4H), 6.79 (d, *J* = 8.9 Hz, 2H), 6.60 (app s, 2H), 5.91 –5.72 (m, 1H), 5.19 – 4.98 (m, 2H), 3.77 (s, 3H), 3.42 – 3.36 (m, 1H), 2.76 –2.25 (m, 2H), 2.34 (app t, 4H), 1.84 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) 152.4, 139.0,135.4, 134.7, 129.2, 128.4, 117.9, 115.5, 115.1, 55.9, 53.4, 38.4, 36.1, 32.0, 21.1.; HRMS (ESI): Exact mass calcd for $C_{20}H_{26}NO$ [M+H+], 296.2014. Found 296.2056.

19c: Flash chromatography on silica gel (10% ethyl acetate in hexanes) provided theproduct **19c** as a pale yellow oil. **IR**:3389, 3002, 2929, 1250 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) 7.09 (d, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 6.76 (d, *J* = 8.9 Hz, 2H),

6.52 (d, *J* = 8.9 Hz, 2H), 5.80 (ddt, *J* = 16.7, 10.5, 7.2 Hz, 1H), 5.12 – 4.98 (m, 2H), 3.79 (s, 3H), 3.75 (s, 3H), 3.38 – 3.32 (m, 1H), 2.74 – 2.58 (m, 2H), 2.33 – 2.28 (m, 2H), 1.92 – 1.66 (m, 2H), 1.26 (s, 1H). **^{13}C NMR** (126 MHz, CDCl3) 157.9, 152.1, 134.9, 134.2, 129.5, 117.8, 115.1, 115.0, 113.9, 56.0, 55.4, 52.9, 38.6, 36.4, 31.6.; HRMS (ESI): Exact mass calcd for $C_{20}H_{26}NO_2$ [M+H$^+$], 312.1964. Found 312.1960.

19d: Flash chromatography on silica gel (10% ethyl acetate in hexanes) provided the product **19d** as a brown oil. **IR**: 3394, 3035, 2997, 1213 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) 7.16 – 7.08 (m, 2H), 7.02 – 6.91 (m, 2H), 6.76 (d, *J* = 8.9 Hz, 2H), 6.53 (d, *J* = 8.9 Hz, 2H), 5.79 (ddt, *J* = 17.4, 10.4, 7.2 Hz, 1H), 5.17–5.01 (m, 2H), 3.75 (s, 3H), 3.37 – 3.31 (m, 1H), 2.79 – 2.62 (m, 2H), 2.31 (app t, 2H), 1.96–1.63 (m, 2H).**^{13}C NMR** (126 MHz, $CDCl_3$) 161.3 (d, *J* = 243.4 Hz), 152.0, 141.7, 137.6 (d, *J* = 3.5 Hz), 134.6, 129.8 (d, *J* = 8.2 Hz), 117.8, 115.1 (d, *J* = 20.9 Hz), 114.99, 114.92, 55.8, 52.7, 38.5, 36.2, 31.5. HRMS (ESI): Exact mass calcd for $C_{19}H_{23}FNO$ [M+H$^+$], 300.1767. Found 300.1800.

19e: Flash chromatography on silica gel (10% ethyl acetate in hexanes) provided the product **19e** as a dark yellow oil. **IR**: 3404, 3005, 2927, 1209 cm-1. **^{1}H NMR** (400 MHz, $CDCl_3$): 6.78 (d, *J* = 8.8 Hz, 2H), 6.59 (d, *J* = 8.9 Hz, 2H), 5.94 (ddt, *J* = 17.3, 10.3, 7.2 Hz, 1H), 5.22 – 4.96 (m, 2H), 3.77 (s, 3H), 3.40 (br s, 1H), 2.84 (m, 1H), 2.51 – 2.31 (m, 2H), 0.92 (m, 1H), 0.61 – 0.42 (m, 2H), 0.30 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) 152.2, 142.4, 135.3, 117.4, 115.3, 114.9, 58.0, 55.9, 39.8, 16.2, 3.4, 3.0.; HRMS (ESI): Exact mass calcd for $C_{14}H_{20}NO$ [M+H$^+$], 218.1545. Found 218.1585.

19f: Flash chromatography on silica gel (5% ethyl acetate in hexanes) provided the product **19f** as an orange oil. **IR** (film) 3395, 3073, 2929, 1209 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) 6.76 (d, *J*=8.9 Hz, 2H), 6.58 (d, *J* = 8.9 Hz, 2H), 5.78 (ddt, *J* = 17.3, 10.3, 7.2Hz, 1H), 5.13–4.80 (m, 2H), 3.75 (s, 3H), 3.30 (dt, *J* = 8.4, 5.3 Hz, 1H), 2.50–2.35 (m, 1H), 2.32–2.26 (m, 1H), 2.18– 2.13 (m, 1H), 2.02–1.97 (m, 2H), 1.93 – 1.71 (m, 4H). **^{13}C NMR** (126 MHz, $CDCl_3$) 151.9, 142.6, 135.0, 117.4, 115.1, 115.0, 58.7, 55.9, 40.3, 36.2, 26.04, 25.97, 18.1.; HRMS (ESI): Exact mass calcd for $C_{15}H_{22}NO$ [M+H$^+$], 232.1701. Found 232.1689.

19g: Flash chromatography on silica gel (5% ethyl acetate in hexanes) provided the product **19g** as a yellow oil. **IR**: 3395, 3028, 2952, 1206 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) 6.75 (d, *J* = 8.9 Hz, 2H), 6.56 (d, *J* = 8.9 Hz, 2H), 5.83 (ddt, J = 16.5, 10.8, 7.3 Hz, 1H), 5.12–4.87 (m, 2H), 3.74 (s, 3H), 3.23 (dt, *J* = 7.8, 5.3 Hz, 1H), 2.48–2.31 (m, 1H), 2.29–2.16 (m, 1H), 2.05 –1.91 (m, 1H), 1.86 – 1.71 (m, 2H), 1.68 – 1.58 (m, 2H), 1.57–1.50 (m, 2H), 1.36 – 1.23 (m, 2H).**^{13}C NMR** (126 MHz, $CDCl_3$) 151.8, 142.7, 135.3, 117.4, 115.1, 114.8, 58.2, 56.0, 44.5, 37.5, 29.9, 29.7, 25.8, 25.5.; HRMS (ESI): Exact mass calcd for $C_{16}H_{24}NO$ [M+H$^+$], 246.1858. Found 246.1904.

19h: Flash chromatography on silica gel (5% ethyl acetate in hexanes) provided the product 19h as a yellow oil. **IR**: 3406, 3090, 2925, 1220 cm-1. **^{1}H NMR** (400 MHz, $CDCl_3$) 6.75 (d, J = 8.9 Hz, 2H), 6.53 (d, J = 8.9 Hz, 2H), 5.80 (ddt, J = 17.3, 10.3, 7.0 Hz, 1H), 5.20 – 4.88 (m, 2H), 3.25 (s, 3H), 3.15 (m, J = 7.2, 5.2 Hz, 1H), 2.32 (m, 1H), 2.19 (m, 1H), 1.89 – 1.62 (m, 5H), 1.49 (m, 1H), 1.27 – 1.01 (m, 5H). **^{13}C NMR** (126 MHz, $CDCl_3$) 151.7, 142.9, 136.0, 117.1, 115.1, 114.6, 58.7, 56.0, 41.4, 36.0, 29.6, 29.3, 26.8, 26.62, 26.58.; HRMS (ESI): Exact mass calcd for C17H26NO [M+H$^+$], 260.2014. Found 260.2021.

19i: Flash chromatography on silica gel (5% ethyl acetate in hexanes) provided the product **19i** as a yellow oil. IR: 3407, 3005, 2923, 1212 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) 6.76 (d, J = 8.9 Hz, 2H), 6.53 (d, J = 8.9 Hz, 2H), 5.80 (ddt, J = 17.1, 10.2,7.1 Hz, 1H), 5.11 – 4.92 (m, 2H), 3.74 (s, 3H), 3.20 (dt, J = 8.6, 4.6 Hz, 1H), 2.33 – 2.26 (m, 1H), 2.20 – 2.12 (m, 1H), 1.81 – 1.64 (m, 4H), 1.59 – 1.33 (m, 4H), 1.32 – 1.20 (m,5H). **^{13}C NMR** (126 MHz, $CDCl_3$) 151.6, 142.5, 136.3, 116.8, 114.9, 114.5, 59.3, 55.9,41.8, 35.6, 30.3, 29.5, 28.4, 28.1, 27.3, 27.2.; HRMS (ESI): Exact mass calcd for $C_{18}H_{28}NO$[M+H$^+$], 274.2171. Found 274.2189.

19j: Flash chromatography on silica gel (5% ethyl acetate in hexanes) provided the product **19j** as a yellow oil. **IR**: 3395, 3073, 2994, 1228 cm-1. **^{1}H NMR** (400 MHz, $CDCl_3$) 6.77 (d, J = 9.0 Hz, 2H), 6.56 (d, J = 8.8 Hz, 2H), 5.80 (ddt, J = 16.8, 10.4,7.2 Hz, 1H), 5.15 – 4.98 (m, 2H), 3.75 (s, 3H), 3.47 – 3.41 (m, 1H), 2.33 – 2.18 (m, 2H), 1.78 – 1.52 (m, 6H), 1.48 – 1.38 (m, 1H), 1.38 – 1.27 (m, 3H), 1.27 – 1.14 (m, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) 151.9, 142.1, 135.1, 117.6, 115.1, 114.8, 55.9, 50.7, 42.7, 38.8, 34.5, 33.9, 33.5, 29.6, 26.7, 26.5.; HRMS (ESI): Exact mass calcd for $C_{18}H_{28}NO$ [M+H$^+$], 274.2171. Found 274.2150.

19k: Flash chromatography on silica gel (5% ethyl acetate in hexanes) provided the product **19k** as a brown oil. **IR**: 3417, 3010, 2926, 1216 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) 6.77 (d, *J* = 8.9 Hz, 2H), 6.55 (d, *J* =9.0 Hz, 2H), 5.81 (ddt, *J* = 16.0, 11.3, 7.2 Hz, 1H), 5.27 – 5.00 (m, 2H), 3.74 (s, 3H), 3.32(app t, *J* = 6.0 Hz, 1H), 2.35 – 2.18 (m, 2H), 1.39 – 1.13 (m, 12H), 0.98 – 0.69 (m, 3H).**^{13}C NMR** (126 MHz, $CDCl_3$) 151.9, 142.2, 135.2, 117.6, 115.1, 114.9, 56.0, 53.6, 38.6, 34.5, 32.0, 29.9, 29.4, 26.2, 22.8,

14.2. ; HRMS (ESI): Exact mass calcd for $C_{18}H_{30}NO$ [M+H^+], 276.2327. Found 276.2320.

4. Conclusions

Through systematic screening we developed a straight forward method for the synthesis of alpha-C-H or alphaα-C-C functionalized amines applying sequential amine oxidation and nucleophilic addition process promoted by a commercially available quinone which is mainly used as organo-catalyst. This new synthetic protocol is generic in nature and it offer α -branched amines in good to excellent yields.

Acknowledgments

The author acknowledges his indebtedness to Malda College, Malda, West Bengal for the cooperation and encouragement he has received thereof for this research work.

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