SYNTHESIS OF IMIDAZO[1,2-A]QUINOLINES USING FE2O3 NANOPARTICLE CATALYST

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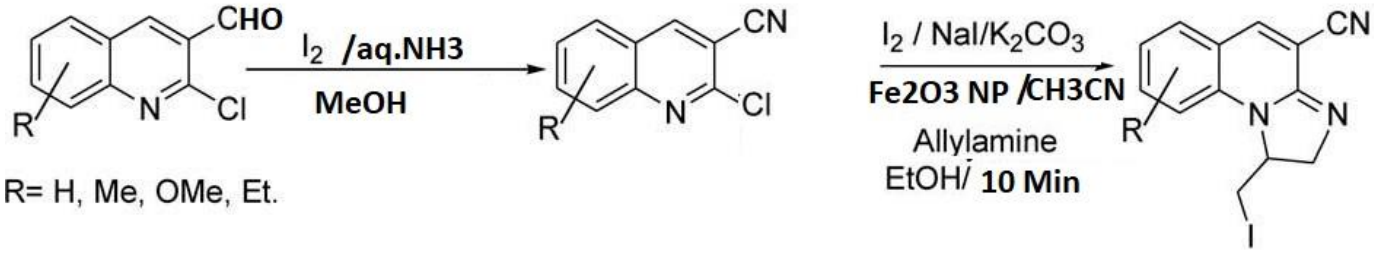
Abstract: A new and a facile route to the synthesis of imidazo[1,2-a]quinolines has been described via iodocyclization reaction of 2-allylaminoquinoline derivatives using Fe2O3 nanoparticle calatyst.

Key: **Nanoparticle, Imidazoquinoline, Fe_2O_3, Iodocyclization**

INTRODUCTION

Imidazo[1,2-a]quinoline is a bridgehead nitrogen hetero-cycle with one ring junction and one extra nitrogen atom. Its derivatives possess a significant range of biological activities such as contraceptive, hypertensive, antiallergic, and antiasthmatic anxiolytic agents [1]. On the other hand, its affinity to GABA receptor in the brain has been studied to reveal the action of the subunits [2]. Consequently, numerous syntheses of imidazo[1,2-a]quinolines have been reported, which mostly utilize various quinoline derivatives as starting materials. For example, reactions of 2-aminoqui-nolines with a-halo carbonyl compounds, related 1,2-bie-lectrophiles [3a] and from Strecker and Ugi reactions have lead to the synthesis of the imidazoquinolines [3b–d]. Simi-larly, other quinoline precursors such as 1-phenacylquino-lium salts and 2-chloro or 2-alkoxyquinolines are also used to the synthesis of target system [4]. However, 2-allylami-noquinoline derivatives have not been investigated to the synthesis of target system. Recently, Tu et al. [5] and Tver-dokhlebov and coworkers [6] have reported the domino approach to the synthesis of imidazo[1,2-a]quinolines

In recent years, iodocyclization of alkenes has emerged as one of the effective route to the synthesis of a variety of carbocyclic and heterocyclic ring systems[7]. Recently, we have reported an intramolecular iodo-cyclization of alkene moiety of 3-homoallyl-2-quino-lones to the synthesis of pyranoquinolines using I_2 rea-gent [8]. In continuation of our recent interest in the synthesis of annulated quinolines [9], this observation has prompted us to investigate the iodocyclization of alkene moiety of 2-allylaminoquinoline-3-carbonitriles 2. We were delighted to observe after a series of trials of iodine reagent with different bases and solvents that a combination of I_2 with NaI could be used for the facile synthesis of imidazo[1,2-a]quinolines. Herein, we report I_2-NaI reagent catalyzed iodocyclization of 2-allylamino quinoline-3-carbonitriles as an alternate route to the syn-thesis of 1-iodomethyl-1,2-dihydro imidazo[1,2-a]quino-lines 3, an alternate route under mild conditions.



RESULTS AND DISCUSSIONS

To initiate our studies, we treat 2-chloro-3-cyanoquino-lines [10] 2a–f (1 equiv) with allylamine (3 equiv) in ethanol (4 mL) followed by I_2 (1.2 equiv) NaI (1.2 equiv), Cat. Fe_2O_3 NP, and K_2CO_3 (3.0 equiv) in acetonitrile (3–4 mL) under a nitrogen atmosphere at room temperature. for 10 min. The structures of compounds 3a–f were ascer-tained from spectroscopic data. I_2 (1.2 equiv) and NaI (1.2 equiv), Cat. Fe_2O_3 NP, and K_2CO_3 (3.0 equiv) in acetonitrile (3–4 mL) under a nitrogen atmosphere at room temperature. The reaction mixture instantaneously changed color from yellow to green and then dark violet and thin layer chromatography (TLC) indicated the dis-appearance of starting compound in 10 min.

After work-up and chromato-graphic separation cyclized product was characterized as 1-iodomethyl-1,2-dihydroimidazo[1,2-a] quinoline-4-carbon-itrile 4a from its spectral and analytical data (90% yield). We optimize the reaction condition for iodocycliza-tion using different conc of Fe_2O_3 Nano particle. In same reaction condition for iodocycliza-tion using 1 eq.and 1.5 eq. of Fe_2O_3 Nano particle increases the time and reduces the yield of product.

(Table 1, entries 2-5)

Table 1

Optimization of the reaction conditions for the synthesis of 1-iodomethyl-1,2-dihydroimidazo[1,2-a] quinoline-4-carbon-itrile with different conc. Of Fe2O3 NP

Entry	Substrate	Nanoparticle	Amount (eq.)	Time (Min)	Yield of 4a (%)
1	3a	Fe2O3	0.5	10 min	90
2	3a	Fe2O3	1	20	75
3	3a	Fe2O3	1.5	25	65
4	3a	Fe2O3	1.5	25	30
5	3a	Fe2O3	1.5	25	65

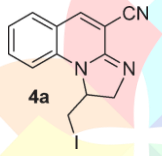
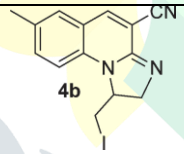
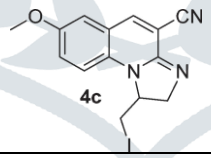
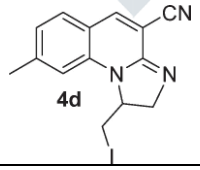
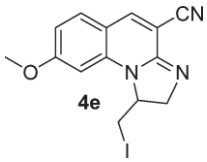
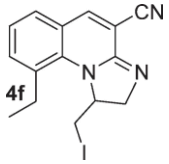
However, same reaction with-out K_2CO_3 is completed in 20 min with 85% yield. Reaction was also carried out with molecular iodine yield decreased to 75%. The reaction was also attempted by changing the base and sol-vent to optimize the reaction conditions. The use of tetra-hydro furan (THF) as solvent lowered the yield of 3a (Table 2, entry 4), while the use of Na_2CO_3 as base pro-vided the same yield of cyclized product (Table 2, entry 5).

Table 2

Optimization of the reaction conditions for the synthesis of 1-iodomethyl-1,2-dihydroimidazo[1,2-a] quinoline-4-carbon-itrile with different base and solvent

Entry	**Substrate**	**Reagent**	**Time (Min)**	**Yield of 4a (%)**
1	3a	Fe2O3NP/I_2/NaI/K_2CO_3/CH_3CN	10 min	90
2	3a	Fe2O3NP/I_2/NaI/CH_3CN	20	85
3	3a	Fe2O3NP/K_2CO_3/CH_3CN	25	75
4	3a	Fe2O3NP/I_2/K_2CO_3/THF	25	35
5	3a	Fe2O3NP/I_2/Na_2CO_3/CH_3CN	25	75

After all these we explore the scope of the reaction to other sub-strates 3b–f. The reactions proceeded smoothly to afford the desired products 4b–f in excellent yields (85–98%). The results are summarized in (Table 3).

Entry	**Substrate**	**Product**	**Time**	**Yield**
1	3a	 4a	10	90
2	3a	 4b	10	92
3	3a	 4c	5	85
4	3a	 4d	10	90
5	3a	 4e	5	80
6	3a	 4f	10	89

In summary, we have developed a new and an effi-cient route to the synthesis of biologically important imidazo[1,2-a]quinolines from 2-aminoquinoline-3-carbonitriles under very mild reaction conditions.

EXPERIMENTAL

To a solution of 2-chloro-3-cyanoquinoline (1 mmol) in ethanol (4 mL) was added allylamine (3 mmol) followed by CH3CN (5 mL) were added I2 (1.2 mmol), NaI (1.2 mmol) and K2CO3 (3 mmol) and 05 eq. Of Fe2O3 NP under N2 atmosphere the reaction mixture stirred at room temperature. After completion of the reaction, as indicated by TLC, a saturated aqueous solution of Na2SO3 (5 mL) was added, a dark violet color of resultent solution turns into yellow solution. Finally, the reaction mixture was extracted with EtOAc (3-4 mL), the organic layer was washed with brine (2 4 mL) and dried over anhydrous MgSO4 and evaporated under vaccum to yield a residue, which was purified via silica gel column chromatography employing Hexane-EtOAc (70:30, v/v) as eluent to afford product as a solid.

Yellow solid, Yield: 89%; mp: 105 C; ir (KBr): CN 2225; 1H-NMR (300 MHz, CDCl3): d 3.32 (t, 1H, J ¼ 9.2 Hz), 3.34–3.44 (m, 1H), 3.96 (dd, 1H, J ¼ 3.6, 15.9 Hz), 4.23 (dd, 1H, J ¼ 10.2, 15.7 Hz), 4.68–4.74 (m, 1H), 6.83 (d, 1H, J ¼ 8.1 Hz), 7.04 (t, 1H, J ¼ 7.5 Hz), 7.38 (d, 1H, J ¼ 7.5 Hz), 7.49 (t, 1H, J ¼ 7.8 Hz), 7.7 (s, 1H); 13C-NMR (75 MHz, CDCl3): d 6.33, 59.14, 60.46, 102.6, 111.4, 114.5, 119.2, 121.5, 129.1, 139.0, 146.0, 148.5, 152.6; Anal. Calcd. for C13H10N3I: C, 46.59; H, 3.01; N, 12.54; Found: C, 46.81; H, 2.95; N, 12.29

1-Iodomethyl-7-methyl-1,2-dihydro-imidazo[1,2-a]quinoline4-carbonitrile(4b). Yellow solid, Yield: 93%; mp: 107 C; ir (KBr): CN 2227; 1H-NMR (300 MHz, CDCl3): d 2.33 (s, 3H), 3.31 (t, 1H, J ¼ 9.9 Hz), 3.41–3.44 (m, 1H), 3.96 (dd, 1H, J ¼ 3.9, 15.6 Hz), 4.23 (dd, 1H, J ¼ 9.9, 15.6 Hz), 4.66–4.73 (m, 1H), 6.73 (d, 1H, J ¼ 8.4 Hz), 7.18 (s, 1H), 7.30 (d, 1H, J ¼ 8.4 Hz), 7.65 (s, 1H); 13C-NMR (75 MHz, CDCl3): d 6.3, 29.6, 59.1, 60.4, 102.6, 114.4, 114.5, 119.1, 122.5, 131.0, 134.1, 139.0, 146.0, 152.6; Anal. Calcd. for C14H12N3I: C, 48.16; H, 3.46; N, 12.03; Found: C, 48.41; H, 3.35; N, 11.91.

1-Iodomethyl-7-methoxy-1,2-dihydro-imidazo[1,2-a]quinoline-4-carbonitrile(4c). Yellow solid, Yield: 89%; mp: 105 C; ir (KBr): CN 2225; 1H-NMR (300 MHz, CDCl3): d 3.35 (t, 1H, J ¼ 9.9 Hz), 3.43–3.46 (m, 1H), 3.91 (s, 3H), 3.97 (d, 1H, J ¼ 4.5 Hz), 4.24 (dd, 1H, J ¼ 15.3, 10.2 Hz), 4.70– 4.77 (m, 1H), 6.30 (s, 1H), 6.63 (d, 1H, J ¼ 10.8 Hz), 7.3– 7.34 (m, 1H), 7.6 (s, 1H); 13C-NMR (75 MHz, CDCl3): d 6.0, 29.1, 55.7, 59.1, 96.4, 109.5, 111.4, 114.5, 122.2, 132.5, 141.1, 145.0, 153.0, 1 162.6; Anal. Calcd. for C14H12N3IO: C, 46.03; H, 3.31; N, 11.51; Found: C, 46.27; H, 3.28; N, 11.39.

1-Iodomethyl-8-methyl-1,2-dihydro-imidazo[1,2-a]quinoline4-carbonitrile(4d). Yellow solid, Yield: 92%; mp: 109 C; ir (KBr): CN 2226; 1H-NMR (300 MHz, CDCl3): d 2.4 (s, 3H), 3.31 (t, 1H, J ¼ 9.9 Hz), 3.42–3.46 (m, 2H), 3.97 (dd, 1H, J ¼ 3.6, 15.7 Hz), 4.22 (dd, 1H, J ¼ 10.2, 15.6 Hz), 4.65– 4.72 (m, 1H), 6.59 (s, 1H), 6.85 (d, 1H, J ¼ 7.8 Hz), 7.65 (s, 1H); 13C-NMR (75 MHz, CDCl3): d 6.4, 22.3, 59.0, 60.4, 101.2, 111.7, 114.7, 117.1, 122.8, 130.3, 139.1, 145.7, 145.8, 152.8; Anal. Calcd. for C14H12N3I: C, 48.16; H, 3.46; N, 12.03; Found: C, 47.78; H, 3.29; N, 12.35

1-Iodomethyl-8-methoxy-1,2-dihydro-imidazo[1,2-a]quinoline-4-carbonitrile(4e). Yellow solid, Yield: 84%; mp: 112 C; ir (KBr): CN 2225; 1H-NMR (300 MHz, CDCl3): d 3.32 (t, 1H, J ¼ 9.9 Hz), 3.42–3.45 (m, 1H), 3.90 (s, 3H), 3.97 (d, 1H, J ¼ 3.9 Hz), 4.23 (dd, 1H, J ¼ 10.5, 15.6 Hz), 4.63– 4.70 (m, 1H), 6.26 (s, 1H), 6.61 (d, 1H, J ¼ 7.5 Hz), 6.30 (d, 1H, J ¼ 8.7 Hz), 7.63 (s, 1H); 13C-NMR (75 MHz, CDCl3): d 6.3, 29.6, 56.2, 59.2, 97.1, 109.3, 113.6, 114.8, 121.4, 132.3, 140.4, 146.2, 153.1, 164.9; Anal. Calcd. for C 14H12N3IO: C, 46.03; H, 3.31; N, 11.51; Found: C, 46.16; H, 3.29; N, 11.42.

1-Iodomethyl-9-ethyl-1,2-dihydro-imidazo[1,2-a]quinoline4-carbonitrile(4f). Yellow solid, Yield: 89%; mp: 117 C; ir (KBr): CN 2224; 1H-NMR (300 MHz, CDCl3): d 1.24 (t, 3H, J ¼ 7.5 Hz), 2.76 (q, 2H, J ¼ 7.2 Hz), 3.05 (d, 1H, J ¼ 9.9 Hz), 3.14 (t, 1H, J ¼ 10.2 Hz), 4.01–4.04 (m, 2H), 4.91–4.97 (m, 1H), 7.03 (t, 1H, J ¼ 7.5Hz), 7. 26 (s, 1H), 7.34 (d, 1H, J ¼ 7.5 Hz), 7.67 (s, 1H); 13C-NMR (75 MHz, CDCl3): d 6.3, 14.7, 27.4, 58.0, 63.2, 102.5, 114.5, 121.5, 122.7, 128.2, 129.7, 136.7, 137.9, 147.1, 154.1; Anal. Calcd. for C15H14N3I: C, 49.60; H, 3.89; N, 11.57; Found: C, 49.74; H, 3.84; N, 11.62

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