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Indium chloride/silica gel supported synthesis of pyrano/thiopyranoquinolines through intramolecular imino Diels–Alder reaction using microwave irradiation

Ekambaram Ramesh, Tarakkad Krishnaji Sree Vidhya, Raghavachary Raghunathan *

Department of Organic Chemistry, University of Madras, Guindy Campus, Chennai 600 025, India

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Abstract

A facile synthesis of pyrano/thiopyranoquinolines is accomplished in excellent yields through imino Diels–Alder reaction using silica gel impregnated with indium trichloride as catalyst.

Keywords: Imino Diels–Alder; Silica gel; Indium trichloride; Intramolecular

The importance of pyranoquinoline derivatives is well recognized by synthetic and biological chemists. Compounds possessing these types of ring systems have wide application as drugs and pharmaceuticals. Pyranoquinolines are an important class of compounds that constitute the basic framework of a number of alkaloids of biological significance, such as geibalasine, ribalinine, flindersine,[1–3] simulenoline, huajiaosimuline, demethoxyzanthodioline, khaplofoline, lunacrine and demethoxylunacrine.[4,5] In addition, thiopyranoquinolines are reported as interleukin-1 inhibitors.[6]

It is therefore not surprising that many synthetic methods have been developed for these compounds.[7–16] Among them, the aza-Diels–Alder reaction between *N*-arylimines with electron rich internal dienophiles is a powerful method for the construction of polycyclic heterocyclic ring systems. Since the pioneering work of Povarov,[17] $BF_3{\cdot}OEt_2$ has been the most commonly used catalyst for this reaction. Transition metal and transition metal complexes such as $Co_2(CO)_8$ and $Ni(CO)_4$ are also effective. However, many of these catalysts are not fully satisfactory with regard to operational simplicity and isolated yield. Hence, there is a quest to find a better and improved methodology for the synthesis of such molecules.

Recently, microwave irradiation (MWI) has become an established tool in organic synthesis,[18–23] because of the rate enhancements, higher yields and often, improved selectivity, with respect to conventional reaction conditions. In addition, solvent-free MW processes are also clean and efficient and moreover, using either organic or inorganic solid supports, have received increased attention.[24] There are several advantages of performing syntheses in solvent-free media: (i) short reaction times, (ii) increased safety, (iii) economic advantages due to the absence of solvent. Silica gel is effective solid support because the end products can easily be separated. Moreover, silica gel can function as a mild acidic catalyst (Table 1).

In continuation of our interest in cycloaddition chemistry,[25–27] we herein describe the excellent catalytic activity of $InCl_3$ in acetonitrile/silica gel impregnated $InCl_3$[28] for the synthesis of tetrahydropyrano/thioquinoline derivatives through intramolecular imino Diels–Alder reaction.

Thus, 2-chloro-3-formylquinoline[29] **1** (prepared from acetanilide, Scheme 1) on treatment with prenyl thiolate, generated by the decomposition of *S*-prenyl isothiourea salt with NaOH, furnished *S*-alkenyl aldehyde **3**[30] in a good 84% yield (Scheme 2).

* Corresponding author. Fax: +91 44 22300488, 22342494.
E-mail address: ragharaghunathan@yahoo.com (R. Raghunathan).

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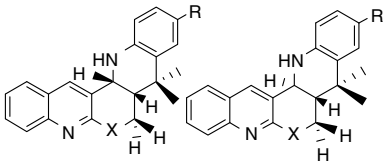
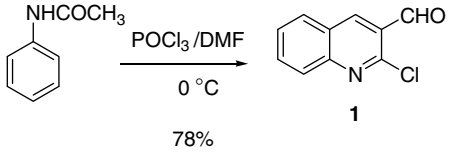
Table 1
Synthesis of tetrahydroquinoline[4,3:2,3]pyrano/thiopyrano[2,3-*b*]quinoline derivatives

Entry	R	X			Method A			Method B		
					Ratio of products cis:trans	Time (h)	Yield (%)	Ratio of products cis:trans	Time (min)	Yield (%)
1	H	S	**5a**	**6a**	65:35	2	73	69:31	1	92
2	CH_3	S	**5b**	**6b**	70:30	1.5	77	74:26	1.2	95
3	OCH_3	S	**5c**	**6c**	76:24	1	87	75:25	1	97
4	Cl	S	**5d**	**6d**	77:23	1.5	79	78:22	1.4	90
5	Br	S	**5e**	**6e**	81:19	2.0	80	78:22	1.4	80
6	NO_2	S	**5f**	**6f**	82:28	3.5	58	80:20	2.5	75
7	H	O	**9a**	**10a**	67:33	2	71	68:22	1	89
8	CH_3	O	**9b**	**10b**	70:30	1.5	73	73:27	1.2	93
9	OCH_3	O	**9c**	**10c**	77:23	1	82	77:23	1	90
10	Cl	O	**9d**	**10d**	79:21	1.5	75	81:19	1.4	89
11	Br	O	**9e**	**10e**	80:20	2.0	79	82:18	1.4	87
12	NO_2	O	**9e**	**10f**	83:27	3.5	55	84:26	3	89

Method A: $InCl_3$ in CH_3CN.
Method B: Silica gel impregnated $InCl_3$ under microwave irradiation.



Scheme 1.

S-Alkenyl aldehyde **3** thus prepared is well poised to undergo imino Diels–Alder reactions with a variety of anilines. Thus, the reaction of aniline **4a** with 2-*S*-prenyl-3-formylquinoline **3** in the presence of $InCl_3$ in acetonitrile resulted in the formation of a mixture of cis and trans products **5a** and **6a** in the ratio 65:35 by intramolecular cycloaddition reaction of the imine generated in situ in the one pot– reaction (Scheme 3).

The ratio of the products was determined by isolating the two diastereoisomers in pure form by flash column chromatography and the stereochemistry of the products was based on coupling constants in their ^1H NMR spectra and NOE experiments.

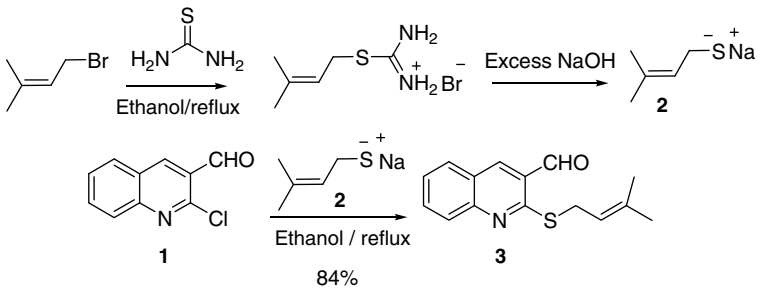
The structural assignments of the products were based on the analysis of NMR spectra. Compound **5a** exhibited a doublet of triplets at δ 2.11 ($J = 3.3$, 10.2 Hz) due to H_b, a doublet of doublets at δ 4.77 ($J = 3.5$, 11.2 Hz) for H_c and a triplet at δ 3.88 ($J = 11.2$ Hz) due to proton H_d. The H_a proton appeared as a doublet at δ 4.45 ($J = 3.3$ Hz). The coupling of H_d with H_b resulted in a doublet with a large J value ($J = 8.3$ Hz) and this was further split into a triplet with a small J value ($J = 3.0$ Hz) by coupling of the H_a and H_c protons. The aromatic protons exhibited multiplets in the region δ 6.61–7.83.

The trans isomer **6a**, exhibited a triplet of doublets at δ 2.06 ($J = 11.2$, 3.3 Hz) for the H_b proton, a triplet at δ 3.98 ($J = 11.2$ Hz) due to proton H_d, a doublet of doublets at δ 4.89 ($J = 3.3$, 10.89 Hz) due to proton H_c, a doublet at δ 4.45 ($J = 11.4$ Hz) due to proton H_a and multiplets in the range δ 6.68 and 7.89 due to the aromatic protons.

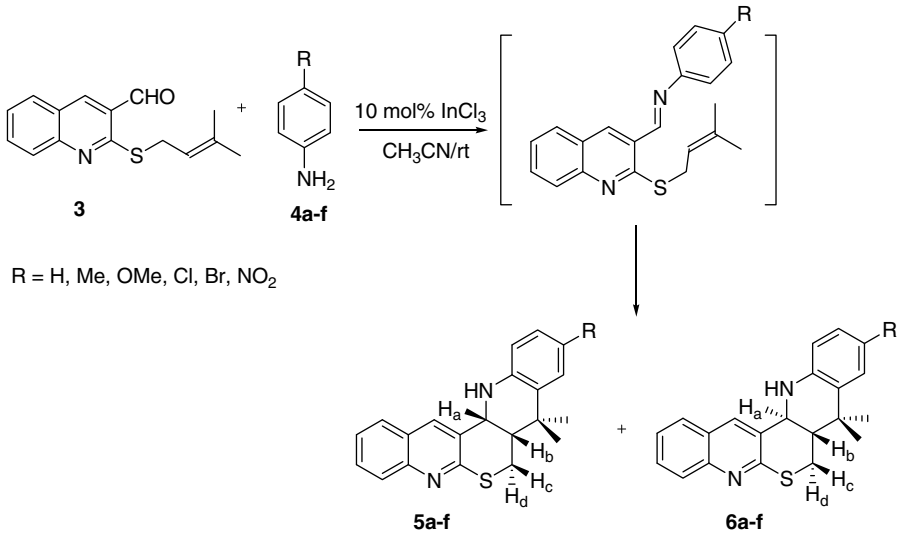
As a further extension of this work, reaction of **1** with prenyl alcohol **7** at 0 °C in the presence of potassium *tert*-butoxide yielded *O*-prenyl-3-formylquinoline[31] (**8**) in a good 72% yield (Scheme 4).

Under similar conditions,[32] *O*-prenyl-3-formylquinoline (**8**) reacted with various substituted anilines in the presence of $InCl_3$ in acetonitrile resulting in the formation of cis and trans **9a–f** and **10a–f** in 55–71% yields (Scheme 5).

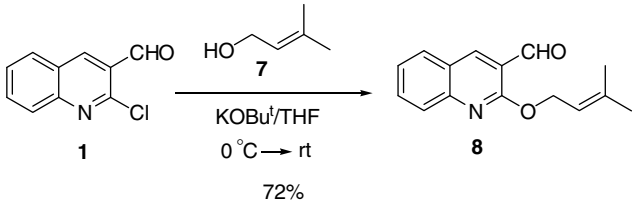
The stereochemistry of each isomer was assigned by ^1H NMR and NOE studies.[33] In **9a**, the coupling constant



Scheme 2.



Scheme 3.



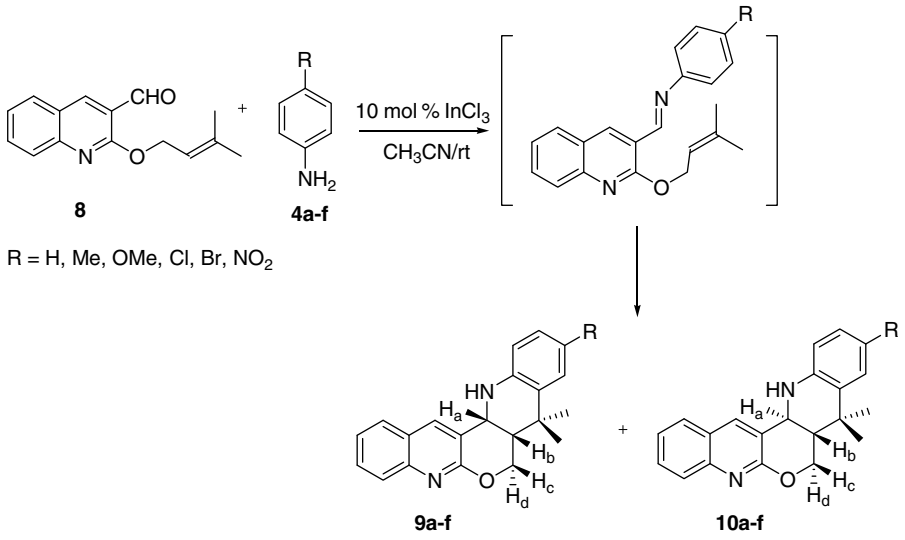
Scheme 4.

between H_a and H_b had a small J value ($J = 3.2$ Hz). This indicates cis-fusion at the ring junction, which was further confirmed by a strong NOE between H_a and H_b. For the trans isomer, the coupling constant between H_a and H_b had a large J value (J H_a–$H_b = 9.0$ Hz), the trans arrangement was further confirmed by the absence of an NOE.

Further, we examined the effect of various solvents on the above reaction and found acetonitrile to be the best solvent for obtaining good yields of the products.

To improve the yield, we carried out the same reaction using $InCl_3$ impregnated silica gel as catalyst under microwave irradiation and we found that there was a dramatic increase in the overall yield of the products, but the ratio of the cis and trans adducts remained almost the same in all cases. The method avoids the use of a solvent and the reaction was complete within 1–3 min.

Our attempts to accelerate the imino Diels–Alder cycloaddition by solid supported microwave irradiation were successful. For example, the reaction of **3** with *p*-substituted nitroanilines took 3.5 h for completion when performed using $InCl_3$ in acetonitrile, whereas the same cycloaddition using $InCl_3$/silica gel under microwave irradiation was complete in 2.5 min (entry 6).



Scheme 5.

In conclusion, the present procedure using indium trichloride on silica gel provides an efficient one-pot synthesis of novel pyranoquinoline derivatives. The notable advantages of this procedure are: (a) ecofriendly process (b) operational simplicity, (c) high reaction rate, (d) good yields and (f) general applicability, We believe that this process will provide a more practical alternative to the existing methods for the synthesis of pyranoquinolines.

Acknowledgement

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28. Prepared by adding silica gel to a stirred solution of $InCl_3$ (20 mol %) in dry $CHCl_3$ (5 mL) followed by complete evaporation of the solvent under reduced pressure.
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30. *2-(3-Methylbut-2-enylthio)quinoline-3-carbaldehyde* **3**: A solution of prenyl bromide (25 mmol) and thiourea (25 mmol) in ethanol (30 mL) was refluxed for 1 h, and then continued for another 1 h after the addition of ethanolic NaOH. The chloroaldehyde **1** was then added to the mixture, which was refluxed for 30 min. The mixture was extracted with dichloromethane, then the solvent was dried and evaporated to give **3** as a viscous liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.74 (s, 3H), 1.81 (s, 3H), 4.06 (d, $J = 7.0$ Hz, 2H, SCH_2), 5.46 (t, $J = 7.0$ Hz, 1H, vinylic proton), 7.26–8.46 (m, 5H), 10.28 (s, 1H, CHO). ^{13}C NMR (125 MHz, $CDCl_3$): δ 18.08, 25.78, 28.11, 118.87, 124.57, 126.09, 127.28, 128.08, 129.26, 132.92, 136.84, 141.97, 149.61, 159.53, 184.90. Anal. Calcd for $C_{15}H_{15}NOS$: C, 70.03; H, 5.83; N, 5.44. Found: C, 69.82; H, 5.90; N, 5.53.
31. *2-(3-Methylbut-2-enyloxy)quinoline-3-carbaldehyde* **8**: To a stirred ice-cooled solution of aldehyde **1** (5.52 g, 25 mmol) and prenyl alcohol **7** (2.9 g, 50 mmol) in tetrahydrofuran (50 mL) was added potassium *tert*-butoxide (3.08 g, 27 mmol). The reaction mixture was brought to room temperature and stirred for 1 h. After the addition of diethyl ether (200 mL), the mixture was filtered, and the filtrate was evaporated to give a low melting solid **8**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.79 (s, 3H), 1.81 (s, 3H), 5.04 (d, $J = 7.0$ Hz, 2H, OCH_2), 5.55 (t, $J = 7.0$ Hz, 1H, vinylic proton), 7.26–7.94 (m, 5H), 10.32 (s, 1H, CHO). ^{13}C NMR (125 MHz, $CDCl_3$): δ 18.28, 25.86, 62.97, 19.68, 124.12, 125.03, 125.22, 126.91, 127.39, 129.15, 135.48, 138.37, 145.91, 159.86, 189.99. Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.59; H, 6.21; N, 5.80. Found: C, 74.37; H, 6.32; N, 5.94.
32. *Method A*: $InCl_3$ (20 mol %) was added to a mixture of aniline and *O*/*S*-prenyl-3-formylquinoline **3/8** in acetonitrile (5 mL). The reaction mixture was stirred at room temperature until completion of the reaction as indicated by TLC. The mixture was then quenched with water and extracted with ethyl acetate. The organic layer was evaporated in vacuo and the crude product was purified by column chromatography on silica gel (ethyl acetate–hexane) to afford cis- and trans-isomers **5a–f**, **6a–f**, **9a–f** and **10a–f** in good yields.
Method B: A mixture of *O*/*S*-prenyl-3-formylquinoline **3/8** (1 mmol) and substituted anilines (1 mmol) was added to silica gel impregnated with indium(III) chloride (20 mol %). The whole mixture was stirred for 5 min for uniform mixing and was then irradiated with microwaves for 1–3 min as required to complete the reaction (TLC). The reaction mixture was extracted with ethyl acetate (20 mL) and the extract was washed with brine, dried over $CHCl_3$ and evaporated to leave the crude product which was purified by column chromatography over silica gel (EtOAc–hexane 98:2) to afford cis- and trans-products **5a–f**, **6a–f**, **9a–f** and **10a–f** in good yields.
33. *8a,14b-cis-9,9-Dimethylquinolino[2,3-b]thiopyrano[4′,3′:2,3]8a,9,14,14b-tetrahydroquinoline* **5a**: mp 152–154 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 1.73 (s, 3H, CH_3), 1.76 (s, 3H, CH_3), 2.11 (dt, 1H, H_b, $J = 3.5$, 10.2 Hz), 3.88 (t, 1H, H_d, $J = 10.2$ Hz), 4.45 (d, 1H, H_a, 3.3 Hz), 4.77 (dd, 1H, H_c, $J = 3.3$, 10.2 Hz), 6.61–7.83 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): 27.02, 27.51, 43.36, 47.25, 60.15, 65.40, 112.12, 116.23, 121.42, 121.53, 123.9, 123.39, 124.34, 124.75, 127.14, 128.71, 129.50, 132.02, 143.61, 146.82, 161.55; MS (EI) $m/z = 332.13$. Anal. Calcd for $C_{21}H_{20}N_2S$: C, 75.87; H, 6.02; N, 8.43. Found: C, 75.63; H, 6.17; N, 8.54.
8a,14b-trans-Dimethylquinolino[2,3-b]thiopyrano[4′,3′:2,3]-8a,9,14,14b-tetrahydroquinoline **6a**: mp 147–149 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 1.71 (s, 3H, CH_3), 1.74 (s, 3H, CH_3), 2.06 (td, 1H, H_b, $J = 11.2$, 3.3 Hz), 3.98 (t, 1H, H_d, $J = 10.8$ Hz), 4.45 (d, 1H, H_a, $J = 11.4$ Hz), 4.89 (dd, 1H, H_c, $J = 3.3$, 10.8 Hz), 6.68–7.89 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): 29.35, 29.57, 40.02, 46.02, 61.13, 65.92, 114.10, 116.21, 120.45,122.50,123.19, 123.3, 124.12, 124.45, 127.17, 128.32, 129.39, 32.16, 143.53, 146.42, 161.73; MS (EI) $m/z = 332.13$. Anal. Calcd for $C_{21}H_{20}N_2S$: C, 75.87; H, 6.02; N, 8.43. Found: C, 75.66; H,

6.20; N, 8.58. *8a,14b-cis-9,9-Dimethylquinolino[2,3-b]pyrano[4′,3′:2,3]-8a,9,14,14b-tetrahydroquinoline* **10a**: mp 126–128 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.73 (s, 3H), 1.44 (s, 3H), 1.81 (dt, $J = 3.0$, 8.3 Hz, $1H_b$), 3.85 (t, $J = 11.2$ Hz, $1H_d$), 4.26 (dd, $J = 3.5$, 11.2 Hz, $1H_c$), 4.56 (d, $J = 3.2$ Hz, $1H_a$), 6.36–7.24 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.29, 27.95, 34.51, 43.95, 47.68, 65.61, 116.18, 117.11, 118.84, 120.86, 123.77, 125.62, 126.92, 127.03, 127.52, 128.53, 129.03, 131.50, 131.56, 143.05, 158.18; MS (EI) $m/z = 316.16$. Anal. Calcd for $C_{21}H_{20}N_2O$: C, 79.64; H, 6.32; N, 8.84. Found: C, 79.40; H, 6.47; N, 8.98.

8a,14b-trans-9,9-Dimethylquinolino[2,3-b]pyrano[4′,3′:2,3]-8a,9,14,14b-tetrahydroquinoline **11a**: mp 119–121 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.73 (s, 3H), 1.79 (s, 3H), 2.08 (td, $J = 3.0$, 8.1 Hz, $1H_b$), 3.93 (t, $J = 11.1$ Hz,$1H_d$), 4.48 (dd, $J = 3.0$, 7.8 Hz, $1H_c$), 4.42 (d, $J = 9.0$ Hz, $1H_a$), 6.66–7.32 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.26, 27.85, 34.32, 43.51, 47.70, 65.73, 116.23, 117.16, 118.65, 120.74, 123.72, 125.68, 126.89, 127.11, 127.33, 128.43, 129.13, 131.52, 131.53, 143.25, 158.23; MS (EI) $m/z = 316.16$. Anal. Calcd for $C_{21}H_{20}N_2O$: C, 79.64; H, 6.32; N, 8.84. Found: C, 79.45; H, 6.47; N, 8.95.