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Rapid synthesis of tetrahydroquinolines by indium trichloride catalyzed mono- and bis-intramolecular imino Diels–Alder reactions

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Abstract—A rapid synthesis of mono- and bis-tetrahydropyrazolo[4′,3′:5,6]thiopyrano[4,3-*b*]quinolines has been achieved by the reaction of aldimines derived from aromatic amines and *S*-prenylated aldehydes in acetonitrile with $InCl_3$ as a catalyst, in excellent yields and short reaction times, under mild conditions.

Hetero Diels–Alder reactions are becoming a mainstay of heterocycle and natural product synthesis.[1] Heterocycles containing nitrogen or sulfur (or both) are incorporated in the structures of numerous natural products and pharmaceutical compounds and the development of simple and effective methods for their preparation is a major concern in medicinal chemistry. In this regard, the imino Diels–Alder reaction[2] represents one of the most attractive routes for preparing heterocycles with maximum atom economy and high selectivity. In addition, the intramolecular Diels–Alder reaction provides opportunities for the stereoselective construction of tetrahydroquinolines. Thiopyranoquinolines[3] are reported as interleukin-1 inhibitors additionally thiopyrazoles[4] are known as a series of cox-2-selective inhibitors which demonstrate an anti-inflammatory activity and are reported as functional inhibitors of interleukin-1.

It has previously been reported that $BiCl_3$[5] was used for the intramolecular imino Diels–Alder reaction of aldimines derived from aromatic amines and *S*-prenyl derivatives of pyrazole, as Lewis acid catalyst. However, this reaction required harsh reaction conditions and a long reaction time which may be attributed to the deactivation or decomposition due to the generation of water during imine formation. Indium trichloride ($InCl_3$) has emerged as a mild and water-tolerant Lewis acid imparting high regio- and chemoselectivity in various organic transformations.[6] It can be conveniently used in both aqueous and non-aqueous media and can also be recovered from the aqueous layer on work-up and recycled for use in subsequent reactions. Furthermore, $InCl_3$ is highly efficient in activating nitrogen-containing compounds such as imines and hydrazones, etc.[7]

In the imino Diels–Alder reaction, the imine double bond must be activated due to the low electrophilicity of imines as compared to the corresponding carbonyl compounds. The activation of imines can be efficiently achieved using indium trichloride as a catalyst. In continuation of our interest in cycloaddition chemistry,[8] we herein describe a remarkable catalytic activity of $InCl_3$ in the synthesis of tetrahydropyrazolo[4′,3′:5,6]-thiopyrano[4,3-*b*]quinoline derivatives.

The treatment of various substituted anilines with *S*-prenyl pyrazoles[9] in the presence of $MgSO_4$ in acetonitrile afforded the corresponding imines which were characterized by spectral analysis. The obtained imine, without further purification, underwent [4+2] cycloaddition in the presence of $InCl_3$ (5–20 mol %). The best results were obtained when $InCl_3$ was used in 20 mol % (Table 1).

From the synthetic point of view, the imines generated in situ from aldehydes **1a** or **1b** and amines **2a**–**e** should

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Table 1. Effect of the amount of $InCl_3$ on the reaction of **1a** and **2b**

Entry	$InCl_3$ (mol %)	Yield (%)
1	5	16
2	10	30
3	15	54
4	20	92

immediately be reacted with the dienophile in a one-pot reaction. It was found that the reaction of various anilines **2a**–**e** with **1a**, **1b** was effectively catalyzed by $InCl_3$ (20 mol %) under mild reaction conditions (Scheme 1)[10] to afford *cis*-tetra hydropyrazolo[4′,3′:5,6]thiopyrano-[4,3-*b*]quinolines **3a**–**j** as the major products with trans-isomers **4a**–**j** being formed in minor amounts in overall yields of 85–96%.

The influence of various solvents on the yield of the reaction of **1a** with **2b** was investigated (Table 3). The results indicated that acetonitrile was the best solvent for the cycloaddition reaction.

The increased yield in acetonitrile may be attributed to the higher polarity and miscibility with the water formed during imine formation. Several amines were examined and the results are listed in Table 2. In all cases, the reaction proceeded smoothly to give the corresponding cis and trans isomers which could be isolated by column chromatography. In some cases the product precipitated from the reaction mixture. The structures of the compounds were confirmed by spectral studies. The cis and trans-stereochemistries of the products was assigned

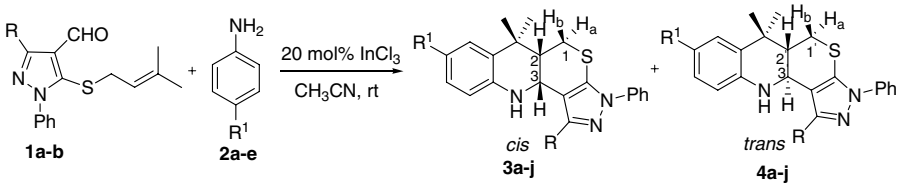
Table 3. Effect of the solvent on the yield of the reaction of **1a** and **2b** with 20 mol % of $InCl_3$

Entry	Solvent	Time (min)	Yield (%)
1	Toluene	40	81
2	CH_2Cl_2	35	76
3	$CHCl_3$	34	80
4	CH_3CN	20	92

on the basis of the coupling constants of the protons in the ^1H NMR spectra[11] and also by a direct comparison with the literature data wherever available.[5]

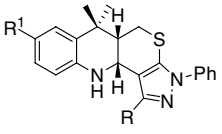
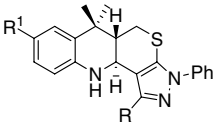
With these encouraging results, we next examined the reactivity of bis-anilines **5a** and **5b** with aldehyde **1a**. The imines derived in situ from **1** and 4,4′-methylene dianiline or 4,4′-oxo dianiline in acetonitrile in the presence of 40 mol % $InCl_3$ underwent intramolecular Diels–Alder reactions to give the corresponding bis-4,4′-methylene or 4,4′-oxo tetrahydropyrazolo[4′,3′:5,6]-thiopyrano[4,3-*b*]quinolines as a mixture of three isomers **6a**, **7a** and **8a** or **6b**, **7b** and **8b** (Scheme 2). These isomers were successfully isolated by column chromatography on silica gel. The product ratio was determined by the examination of the ^1H NMR spectrum of the crude product mixture. All the products are inseparable diastereoisomeric mixtures which could not be distinguished by ^1H NMR. Similarly, the *N*-arylimines from aldehyde **1b** were examined and the results are summarized in Table 4.

The stereochemistry of each isomer was assigned by ^1H NMR and NOE studies. In the cis–trans isomer **7a**, the

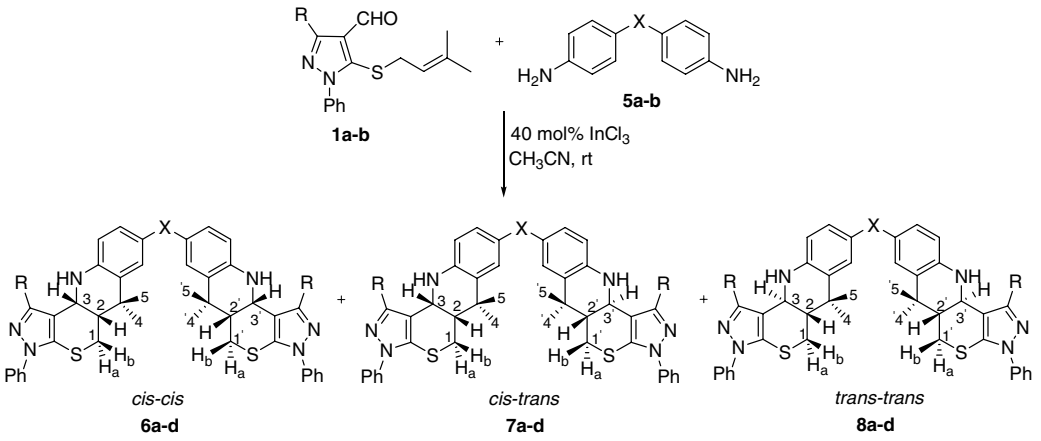


Scheme 1.

Table 2. $InCl_3$-catalyzed synthesis of tetrahydropyrazolo[4′,3′,5,6]thiopyrano[4,3-*b*]quinoline derivatives

Entry	R	R^1	Product[a]		Time (min)	Ratio	Yield (%)
							
1	CH_3	H (**2a**)	**3a**[a]	**4a**	15	86:14	88
2	CH_3	OCH_3 (**2b**)	**3b**	**4b**	20	90:10	92
3	CH_3	CH_3 (**2c**)	**3c**	**4c**	25	91:9	90
4	CH_3	Cl (**2d**)	**3d**[a]	**4d**	20	87:13	95
5	CH_3	NO_2 (**2e**)	**3e**	**4e**	20	93:7	85
6	PH	H (**2a**)	**3f**[a]	**4f**	25	94:6	96
7	PH	OCH_3 (**2b**)	**3g**	**4g**	30	88:12	87
8	PH	CH_3 (**2c**)	**3h**[a]	**4h**	20	90:10	90
9	PH	Cl (**2d**)	**3i**	**4i**	15	92:8	92
10	PH	NO_2 (**2e**)	**3j**	**4j**	25	94:6	94

[a] All the products were characterized by IR, ^1H, ^{13}C NMR and mass spectroscopy.



Scheme 2.

Table 4. $InCl_3$-catalyzed synthesis of bis-4,4′-methylene or bis-4,4′-oxatertrahydropyrazolo[4,3′:5,6]thiopyrano[4,3-*b*]quinolines

Entry	R	X	Products[a]			Time (min)	Ratio	Yield (%)
			cis–cis	cis–trans	trans–trans			
1	CH_3	CH_2	**6a**	**7a**	**8a**	35	85:10:5	92
2	CH_3	O	**6b**	**7b**	**8b**	20	83:13:4	86
3	Ph	CH_2	**6c**	**7c**	**8c**	25	84:10:6	90
4	Ph	O	**6d**	**7d**	**8d**	20	86:9:5	89

[a] All the products were characterized by IR, ^1H, ^{13}C NMR and mass spectroscopy.

coupling constant between H-3 and H-2 had a small *J* value ($J_{2-3} = 2.6$ Hz). This indicates cis-fusion at the ring junction, which was further confirmed by a strong NOE between H-3 and H-2. Also, the coupling constant between H-3′ and H-2′ had a large *J* value ($J_{2'-3'} = 11.0$ Hz) which indicates a trans fusion at the ring junction, which was further confirmed by the absence of an NOE.

In summary, indium trichloride was shown for the first time to be a very efficient catalyst for the synthesis of tetrahydropyrazolo[4′,3′:5,6]thiopyrano[4,3-*b*]quinolines. This method also provides excellent yields of products in short reaction times.

Acknowledgements

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10. Representative procedure for the cycloaddition: To a solution of aromatic amine (1 mmol) and *S*-prenylated aldehyde **2** (1 mmol) in acetonitrile (20 mL) over anhydrous $MgSO_4$ was added 20 mol % $InCl_3$. (For bis-amines, 2 equiv of *S*-prenylated aldehyde and 40 mol % $InCl_3$ were used.) The reaction mixture was stirred for 15–35 min. On completion of the reaction as indicated by TLC, the

mixture was extracted with chloroform. The organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was subjected to column chromatography (hexane–EtOAc mixture) to afford pure diastereoisomers in excellent yields.

11. Representative spectral data: Compound **3b**: Pale yellow solid, mp: 185 °C (uncorrected); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.44 (s, 3H), 1.51 (s, 3H), 1.87 (dt, $J = 12.0$, 2.1 Hz, 1H, H-2), 2.39 (s, 3H), 2.84 (dd, $J = 12.5$, 2.1 Hz, 1H, H-1b), 2.91 (t, $J = 12.0$ Hz, 1H, H-1a), 3.75 (s, 3H), 4.73 (d, $J = 2.5$ Hz, 1H, H-3), 6.41–7.60 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.7, 24.4, 26.7, 34.5, 36.1, 42.8, 43.5, 48.7, 55.9, 112.4, 112.9, 114.7, 115.9, 122.5, 126.9, 128.6, 129.2, 132.3, 134.9, 139.7, 148.3, 152.1 ppm; Mass *m*/*z*: 391 (M^+); Anal. Calcd for $C_{23}H_{25}N_3OS$: C, 70.58; H, 6.39; N, 10.74. Found: C, 70.85; H, 6.50; N, 10.61.

Compound **6a**: yellow solid, mp: 190 °C (uncorrected); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.42 (s, 6H), 1.48 (s, 6H), 1.86 (dt, $J = 12.0$, 2.0 Hz, 2H, H-2), 2.39 (s, 6H), 2.84 (dd, $J = 10.0$, 2.0 Hz, 2H, H-1b), 2.93 (t, $J = 10.0$ Hz, 2H, H-1a), 3.77 (s, 2H, –CH_2–), 4.74 (d, $J = 2.4$ Hz, 2H, H-3), 6.37–7.60 (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.2, 23.9, 26.2, 34.1, 35.3, 42.4, 42.9, 105.6, 113.3, 115.3, 121.9, 125.8, 126.5, 126.6, 127.2, 128.6, 130.2, 131.9, 138.2, 139.1, 147.7 ppm; Mass *m*/*z*: 734 (M^+); Anal. Calcd for $C_{45}H_{46}N_6S_2$: C, 73.56; H, 6.26; N, 11.44. Found: C, 73.74; H, 6.36; N, 11.32.

Compound **7a**: yellow solid, mp: 180 °C (uncorrected); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.42 (s, 3H), 1.45 (s, 3H), 1.47 (s, 3H), 1.50 (s, 3H), 1.87 (dt, $J = 9.0$, 2.4 Hz, 1H, H-2), 2.00 (td, $J = 12.0$, 3.0 Hz, 1H, H-2′), 2.34 (s, 6H), 3.70 (s, 2H, –CH_2–), 3.77 (t, $J = 10.6$ Hz, 1H, H-1a), 3.84 (t, $J = 10.4$ Hz, 1H, H-1′a), 3.91 (dd, $J = 10.6$, 2.4 Hz, 1H, H-1b), 4.21 (dd, $J = 10.4$, 3.0 Hz, 1H, H-1′b), 4.75 (d, $J = 11.0$ Hz, 1H, H-3′), 4.82 (d, $J = 2.6$ Hz, 1H, H-3), 6.43–7.71 (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.8, 24.7, 27.4, 35.1, 36.8, 43.8, 43.9, 106.7, 113.6, 115.1, 121.2, 126.1, 127.7, 127.8, 128.6, 129.7, 130.7, 131.1, 132.3, 133.0, 135.7, 135.9, 138.0, 139.5, 140.3, 148.7 ppm; Mass *m*/*z*: 734 (M^+); Anal. Calcd for $C_{45}H_{46}N_6S_2$: C, 73.56; H, 6.26; N, 11.44. Found: C, 73.75; H, 6.38; N, 11.30.

Compound **8a**: yellow solid, mp: 150 °C (uncorrected); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (s, 6H),1.35 (s, 6H), 1.91 (dt, $J = 11.0$, 2.4 Hz, 2H, H-2), 2.40 (s, 6H), 2.74 (t, $J = 9.8$ Hz, 2H, H-1a), 2.83 (dd, $J = 9.8$, 2.4 Hz, 2H, H-1b), 3.77 (s, 2H, –CH_2–), 4.81 (d, $J = 11.2$ Hz, 2H, H-3), 6.55–7.27 (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.5, 25.7, 27.4, 28.0, 33.5, 35.1, 47.8, 47.9, 112.5, 113.6, 117.4, 120.4, 120.8, 121.0, 122.6, 123.8, 125.7, 126.1, 127.4, 128.4, 129.6, 131.5, 133.9, 139.4, 140.1, 147.1, 147.4 ppm; Mass *m*/*z*: 734 (M^+); Anal. Calcd for $C_{45}H_{46}N_6S_2$: C, 73.56; H, 6.26; N, 11.44. Found: C, 73.70; H, 6.38; N, 11.35.