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Tetrahedron Letters 46 (2005) 1751–1753

Tetrahedron Letters

Preparation of bisindolylalkanes from *N*-*tert*-butanesulfinyl aldimines

Bowen Ke, Yong Qin,* Qinfei He, Zhiyan Huang and Fengpeng Wang*

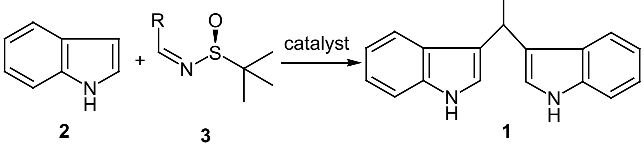
Department of Chemistry of Medicinal Natural Products, West China School of Pharmacy, Sichuan University, Chengdu 610041, PR China

Received 2 November 2004; revised 31 December 2004; accepted 4 January 2005
Available online 29 January 2005

Abstract—A series of bisindolylalkanes were synthesized by nucleophilic addition reactions of indole with *N*-*tert*-butanesulfinyl aldimines in good to excellent yields catalyzed by either iodine, potassium hydrogen sulfate and amberlyst.

Bisindolylalkane **1** is an important class of bioactive metabolite.[1] With the continuing isolation of structurally more diverted bisindolylalkanes,[2] the efficient syntheses of bisindolylalkanes become an increasing interest in organic synthesis.[3] Although bisindolylalkanes were usually prepared by the protic or Lewis acid-catalyzed addition reactions of indole with aldehydes, the electron nucleophilic additions of indole to Schiff bases are scarcely studied probably due to the low reactivity of Schiff bases compared with aldehydes. Banerji et al. reported that indole can react with aromatic aldimines[4] and nitrones[5] to afford bisindolylalkanes in low to moderate yields in the presence of BF_3 etherate or Me_3SiCl. $InCl_3$ was reported to be a catalyst for the addition reaction of indole with aromatic aldimines.[6a] the addition reaction of indole with aromatic aldimine was extremely difficult.[6b]

N-*tert*-Butanesulfinyl aldimine **3**[7] is a new type of Schiff base and has been found to have tremendous applications in the addition reactions of organometallic reagents in recent years,[8] but its electrophilic reactivity toward the weak nucleophilic indole remains unexplored. In this letter, we report that three agents, iodine, potassium hydrogen sulfate and amberlyst, can serve as mild and efficient catalysts for the addition reactions of indole with aldimines **3** to give bisindolylalkanes in moderate to excellent yields (Scheme 1).



Scheme 1. The addition reaction of indole with aldimine **3**.

Since the carbon-3 of indole possesses certain nucleophilic characteristics, we were wondering whether the addition reaction of indole with aldimine **3** could be accomplished without any additives. As shown in Table 1, when *N*-*tert*-butanesulfinyl *p*-methoxybenzal aldimine **3a** was used as a model compound, the reaction was not successful without additive at room temperature in dry CH_3CN, MeOH, CH_2Cl_2, THF, DMSO, toluene, and xylene. The reaction was very sluggish at an elevated temperature in toluene and xylene. Decomposition of aldimine **3a** occurred, and the desired bisindolylalkane **1a** was obtained in low yield (Table 1, entries 1 and 2).

Then we screened the effect of a variety of protic and Lewis acids on the addition reaction. The reaction catalyzed by 1 equiv of ammonium ceric nitrate proceeded slowly to give **1a** in 81% yield in MeOH and in 39% yield in toluene (Table 1, entries 3 and 4). NBS promoted the reaction in moderate yield in MeOH (entry 5). BF_3 etherate catalyzed the reaction in good yield in CH_2Cl_2, but a lower temperature was necessary (Table 1, entry 6). At room temperature, the reaction with aldimine **1a** gave a complicate mixture when BF_3 etherate was used. Protic acid H_2SO_4 catalyzed the addition reaction in MeOH at

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* Corresponding authors. Tel./fax: +86 28 85503842; e-mail: yanshuqin@yahoo.com

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doi:10.1016/j.tetlet.2004.12.140

Table 1. Catalyst screening for the addition of indole to aldimine **3**[a]

Entry	**1** R = 4-MeOPh	Catalyst	Solvent	Time (h)	Yield[b]
1[c]	**1a**	None	Toluene	48	36
2[d]	**1a**	None	Xylene	48	34
3	**1a**	Can	Toluene	48	39
4	**1a**	Can	MeOH	48	81
5	**1a**	NBS	MeOH	10	54
6[e]	**1a**	BF_3	CH_2Cl_2	16	71
7	**1a**	H_2SO_4	MeOH	6	61
8	**1a**	TFA	MeOH	24	0
9[f]	**1a**	TFA	MeOH	24	43
10[f]	**1a**	TsOH	MeOH	12	53
11	**1a**	Amberlyst	MeOH	24	89
12	**1a**	Amberlyst	CH_3CN	24	91
13	**1a**	$KHSO_4$	MeOH	20	93
14	**1a**	I_2	CH_3CN	5	94

[a] The reaction was conducted at room temperature except the one indicated in the table with 1 equiv additive.

[b] Isolated yield.

[c] At 110 °C.

[d] At 140 °C.

[e] At −20 °C.

[f] At 60 °C.

Table 2. Addition reaction of indole with aldimine **3**[9]

1,R	Entry	Reagent	Solvent	Time (h)	Yield[a]
1b	1	Amberlyst	MeCN	30	91
Ph	2	$KHSO_4$	MeOH	16	95
	3	I_2	MeCN	6	97
1c	4	Amberlyst	MeCN	24	94
4-MePh	5	$KHSO_4$	MeOH	24	95
	6	I_2	MeCN	5	95
1d	7	Amberlyst	MeCN	24	93
4-NO_2Ph	8	$KHSO_4$	MeOH	15	94
	9	I_2	MeCN	5	97
1e	10	Amberlyst	MeCN[b]	12	91
4-ClPh	11	$KHSO_4$	MeOH[b]	12	81
	12	I_2	MeCN	5	87
1f	13	Amberlyst	MeCN[b]	24	73
3,4-(MeO)$_2$Ph	14	$KHSO_4$	MeOH[b]	15	94
	15	I_2	MeCN	5	72
1g	16	Amberlyst	MeCN	12	81
2-Furyl	17	$KHSO_4$	MeOH	30	44
	18	I_2	MeCN	5	51
1h	19	Amberlyst	MeCN	10	81
Ph–(CH_2)$_2$–	20	$KHSO_4$	MeOH	30	69
	21	I_2	MeCN	4	90
1i	22	Amberlyst	MeCN	12	81
n-Butyl	23	$KHSO_4$	EtOH	30	76
	24	I_2	MeCN	5	95
1j	25	Amberlyst	MeCN	12	81
Isopropyl	26	$KHSO_4$	MeOH	20	0
	27	I_2	MeCN	5	90

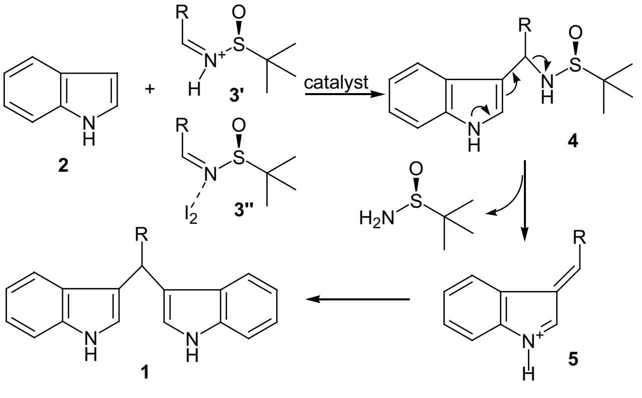
[a] Isolated yields.

[b] At 60 °C.

room temperature to afford **1a** in moderate yield, while TFA and TsOH required a higher temperature (entries 7–10). The observation that a simple protic acid can effectively promote the addition reaction encouraged us to test different acidic additives such as amberlyst (strong sulfonic acid form) and $KHSO_4$. Direct treatment of indole and aldimine **3a** with amberlyst or $KHSO_4$ at room temperature in MeOH or CH_3CN afforded the desired **1a** in 89–93% yields (entries 11–13). Further examination of additives led us to find that iodine promoted the addition reaction more effectively in short time (94% yield, entry 14).

Having found that amberlyst, $KHSO_4$, and I_2 are effective catalysts in the addition reaction of indole with aldimine **3a**, we then tested the applicable scope of current method in the addition reaction of indole with different aldimines in MeOH and CH_3CN. As shown in Table 2, the addition reactions of indole with aldimines **3** catalyzed by iodine were unexceptionably faster than the reactions catalyzed by amberlyst and $KHSO_4$. Three of these catalysts were able to catalyze the reactions of aromatic aldimines **3** bearing both electron-donating and electron-withdrawing groups smoothly in over 80% yields (entries 1–9 and 12) at room temperature. The exception was that the addition reactions of aldimine **3e** and aldimine **3f** catalyzed by amberlyst and $KHSO_4$ were very slow at room temperature, a higher temperature was required to promote the reaction (Table 2, entries 10–11 and 13–14). In the case of aldimine **3f**, the addition reaction with $KHSO_4$ was better than that with amberlyst (Table 2, entries 13 and 14). In contrast, amberlyst was superior to $KHSO_4$ in the addition reaction of aldimine **3g** (Table 2, entries 16 and 17). For the addition reaction with aliphatic aldimines **3**, iodine was the best choice of catalyst, which was still capable to catalyze the reactions in over 90% yields, while amberlyst and $KHSO_4$ promoted the reactions in good yields (Table 2, entries 19–27). $KHSO_4$ failed to catalyze the addition reaction of indole with more hindered isopropylal aldimine **3k** (Table 2, entry 26).

From the mechanistic point of view, the first step for the formation of bisindolylalkane **1** involves a nucleophilic attack of indole to aldimine activated by a catalyst. Both coordination of aldimine with iodine (intermediate **3′**[10]) and acidification of aldimine by amberlyst and $KHSO_4$ (intermediate **3″**) make the aldimine more electrophilic and more eligible to the attack of indole to give intermediate **4**. Consequent loss of *tert*-butanesulfinamide moiety provides the azafulvenium salts **5**. The azafulvenium



Scheme 2. A plausible mechanism for the addition reaction.

salts **5** can undergo further addition with second indole to afford **1** (Scheme 2).

In summary, we have described a new procedure for the preparation of bisindolylalkanes through a nucleophilic attack of indole to *N*-*tert*-butanesulfinyl aldimine catalyzed by amberlyst, iodine and $KHSO_4$.

Acknowledgements

Supports from Ministry of Education (NCET, RFDP, EYTP, SRF for ROCS), the Excellent Youth Foundation of Sichuan Province (No. 04ZQ026-011), and the National Natural Science Foundation of China (No. 20372048) are gratefully acknowledged.

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9. General procedure: Indole (1 mmoL)and *N*-*tert*-butanesulfinyl aldimine **3** (0.5 mmol) were mixed with 0.5 mmol of I_2 or $KHSO_4$, or 450 mg of amberlyst (strong sulfonic acid form) in 10 mL of dry solvent (as indicated in Table 2). The reaction mixture was stirred for 4–30 h at room temperature until **3** was completely consumed checked by TLC. For the I_2 catalyzed reaction, a saturated solution of $Na_2S_2O_4$ was added to the reaction mixture to destroy the excess I_2. For the $KHSO_4$ catalyzed reaction, the $KHSO_4$ was removed by a simple filtration. For the amberlyst catalyzed reaction, the amberlyst was recycled by a simple filtration. After removing the solvent, the mixture was subjected to chromatography to afford the corresponding bisindolylalkane **1**.
10. Aldehyde can be activated by the coordination of iodine with oxygen atom of aldehyde, see Refs. 3c and g.