SYNTHESIS OF DIINDOLYLMETHANES — MONTMORLLONITE CLAY K10 AND KSF CATALYZED CONDENSATION OF INDOLE WITH IMINES

Xin-Liang Feng, Ye Zhang, Zheng-Huan Lin and Cheng-Xue Zhao*
Department of Chemistry, Shanghai Jiaotong University, Shanghai 200240, China and
Tahsin Chow
Institute of Chemistry, Academia Sinica, Taipei 115

Abstract: Condensation of indole with imines was catalyzed by montmorllonite clay K10 and KSF under mild conditions to give diindolylmethanes (DIM) as the sole product.

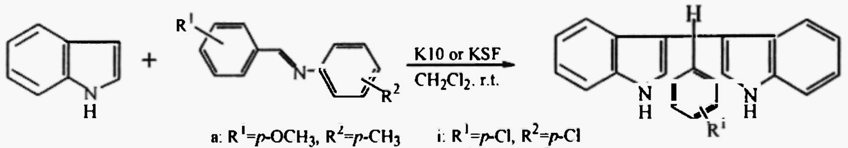
Key Words: Diindolylmethane; Indole; Imine; K10; KSF.

Introduction

The condensation of indoles with electrophiles allows the preparation of important intermediates related to some compounds of pharmaceutical interest.[1] Diindolylmethanes (DIM) are a group of plant compounds with health-promoting properties. DIM and other plant indoles are found in all cruciferous vegetables including cabbage, broccoli, Brussels sprouts and cauliflower.[2] Recent studies have proved that the health-promoting effects resulted by regular use of supplementary DIM arise from a beneficial shift in the balance of the sex hormones, estrogen and testosterone.[3] Traditionally among the various tested electrophiles, aldehydes are the most important reagents which react with indole to get the DIM. Protic acids[4] as well as Lewis acids[5] are known to promote these reactions. Irradiation[6] and molecular iodine[7] are recently reported to be efficient in activating these reactions. Vallee et al.[8] have reported a general synthesis of DIM by the reaction of indoles with nitrones in the presence of Me_3SiCl. Very recently, ion exchange resins[9] and inexpensive solid acids such as Montmorllonite clay K10[10] were also tested in the synthesis of DIM.

The use of environmentally friendly solid acid K10 and KSF may eliminate the corrosive or noxious volatile liquid acids.[11] After the reactions, the solid acid catalyst can be easily separated and regenerated.

Imines are also electrophilic and similar to aldehydes or ketones, their reactions with indole can be effectively activated by K10 and KSF (Scheme-1).



a: R^1=p-OCH_3, R^2=p-CH_3
b: R^1=p-OCH_3, R^2=H
c: R^1=p-OCH_3, R^2=p-Cl
d: R^1=H, R^2=H
e: R^1=H, R^2=p-Cl
f: R^1=H, R^2=m-NO_2
g: R^1=p-Cl, R^2=p-CH_3
h: R^1=p-Cl, R^2=H
i: R^1=p-Cl, R^2=p-Cl
j: R^1=p-CN, R^2=H
k: R^1=p-CN, R^2=p-Cl
l: R^1=o-NO_2, R^2=H
m: R^1=p-NO_2, R^2=p-CH_3
n: R^1=p-NO_2, R^2=H
o: R^1=p-NO_2, R^2=p-Cl

Scheme-1

Experimental

General Procedure:

To 100mg of clay K10 were added indole (1.0mmol), imine (1.0mmol) and 5ml of CH_2Cl_2 as solvent. Then the mixture was stirred at room temperature (and the reaction process was monitored by TLC). The solid catalyst was then filtered and washed with ethyl acetate three times. The combined solution was evaporated under reduced pressure. The residue was purified via column chromatography (silica gel) to give sole product Diindolylmethane (DIM) characterized as follows:

di(3-indolyl)phenylmethane: mp 89-91℃. ^{1}HNMR ($CDCl_3$, 400 MHz): 5.89 (s, 1H), 6.69 (d, 2H, J=3.2 Hz), 7.00 (t, 2H, J=8 Hz), 7.17 (t, 2H, J=8 Hz), 7.30 (m, 9H) and 7.93 (brs, 2H, NH); IR (KBr): 3412, 3046, 1637 and 746 cm^{-1}.

di(3-indolyl)-4-methoxyphenylmethane: mp 120℃; 1H NMR: δ3.79 (s, 3H), 5.84 (s, 1H), 6.64 (s, 2H), 6.82 (d, 2H, J=8Hz), 7.01 (t, 2H, J=8Hz), 7.17 (t, 2H, J=8Hz), 7.25 (d, 2H, J=8Hz), 7.34 (d, 2H, J=8Hz), 7.39 (d, 2H, J=8Hz), 7.88 (brs, 2H, NH); IR(KBr): 3412, 3050, 1260, 1170, 785 and 738 cm^{-1}.

di(3-indolyl)-4-nitrophenylmethane: mp 220~222℃; 1H NMR: δ5.99 (s, 1H), 6.68 (s, 2H), 7.01 (t, 2H, J=8Hz), 7.21 (t, 3H J=8Hz), 7.33~7.40 (m, 5H), 7.50 (d, 2H, J=2Hz), 8.01 (brs, 2H, NH); IR(KBr): 3478, 3046, 1637, 1513, 1341, 1217, 734 cm^{-1}.

di(3-indolyl)-2-nitrophenylmethane: mp 110~112℃; 1H NMR: δ6.65 (d, 2H, J=2.4Hz), 6.68 (s, 1H), 7.02 (t, 2H, J=8Hz), 7.18 (t, 2H, J=7.6Hz), 7.34 (m, 3H), 7.38 (s, 1H), 7.40 (m, 2H), 7.41 (m, 1H), 7.84 (d, 1H, J=7.2Hz), 7.94 (brs, 2H, NH); IR(KBr): 3471, 3054, 1641, 1520, 1357, 1213, 746 cm^{-1}.

di(3-indolyl)-4-chlorophenylmethane: mp 77~81℃; 1H NMR: δ5.86(s, 1H), 6.64(s, 2H), 7.02(t, 2H, J=8Hz), 7.18(t, 2H, J=8Hz), 7.25(m, 2H), 7.27(m, 2H), 7.36(d, 4H, J=8Hz), 7.93(brs, 2H, NH); IR(KBr): 3441,2929, 1635, 1088, 750cm^{-1}.

di(3-indolyl)-4-cyanophenylmethane: mp 220~222℃; 1H NMR: δ5.94 (s, 1H), 6.65 (s, 2H), 7.03 (t, 2H, J=7.2Hz), 7.20 (t, 2H, J=7.2Hz), 7.34~7.38(m, 4H), 7.44 (d, 2H, J=8.4Hz), 7.56 (d, 2H, J=8.4Hz), 8.00 (brs, 2H, NH).

Results and Discussions

We recently examined K10 and KSF catalyzed reactions of indole with a variety of imines. In the preliminary experiments, the reaction of indole with equimolar N-benzylidene aniline (d) was carried out in the presence of K10 (30 wt %) in the different solvents. The yields of DIM (R^1=H) are given in Table-1. Among the solvents examined, dichloromethane is proved to be the best. The reaction completed within 3 hrs, and afforded DIM as the sole product (isolated yield 93%). Whereas the reactions in polar solvents such as ethyl alcohol and acetonitrile, proceeded slowly with decreased yields down to 42% and 36%, respectively. Consequently, dichloromethane was used as the ideal solvent in K10 (30wt%) catalyzed condensation of all the N-benzylidenes (a~o) with indole under the same condition.

Table-1: Solvent effect to the yield of K10 (30 wt %) catalyzed condensation of N-benzylidene (d) with indole at r.t.

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* Correspondence: Cheng-Xue Zhao, Department of Chemistry, Shanghai Jioatong University, 800 Dongchuan Road, Shanghai 200240, China. Fax: 86-21-54741297; e-mail: cxzhao@sjtu.edu.cn

2	$CHCl_3$	3	85
3	benzene	3	87
4	EtOH	3.5	42
5	CH_3CN	3.5	36

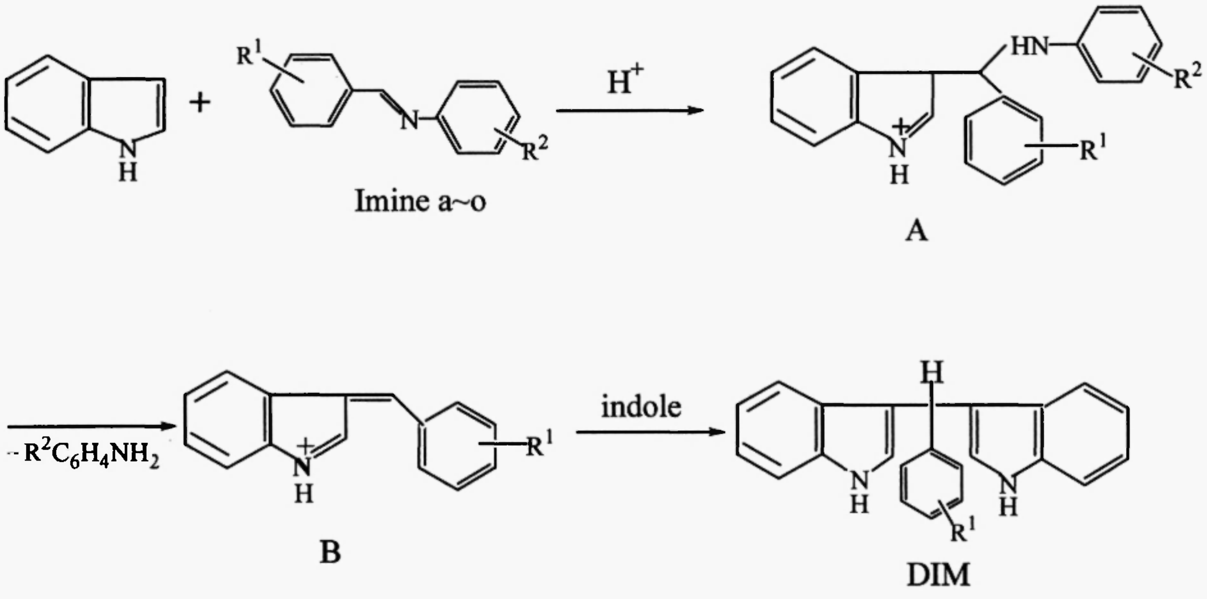
In the Wang's report,[12] the reactions of indole with imines catalyzed by Dy(OTf)3 in protic solvents, afforded the main product secondary indolylamines and by product DIM. At lower temperature (0^{0}C), the yields of the major products can be improved. However, in our experiments, only DIM was formed at both room temperature and 0^{0}C (Entry 4 and 11, Table-2). We run all the reactions in dry solvents in order to minimize the side reactions—hydrolysis of the imines to aldehydes and deterioration of the product DIM.

A plausible pathway of formation of DIM may be as follows: the first indole-imine adduct A eliminates a molecule of aniline with substituent R^2, then the intermediate B reacts with the second molecule of indole to give the final product DIM (Scheme-2). However, hydrolytic deterioration of both starting material imines and the products DIM (R^1) may not be avoided in the whole process, especially for more reactive imines and their derivatives in the presence of strong protic acids.[13]

Table-2: Reactions of indole with imines (a~o) in CH_2Cl_2 at r.t.

Entry	Imines	Reaction Time		Yield (%)[a] of DIM	
		K10	KSF	K10	KSF
1	a	13	13	13	6
2	b	12	12	69	50
3	c	12	12	72	60
4	d	3	12	93	86
5	d	12	--	92[b]	--
6	e	3	12	94	93
7	f	4	12	94	92
8	g	18	18	81	21
9	h	7.5	18	94	73
10	i	3.5	12	81	78
11	i	12	--	100[b]	--
12	j	11.5	11.5	96	87
13	k	11.5	11.5	99	89
14	l	3	12	93	82
15	m	3	12	70	53
16	n	3.5	3.5	85	58
17	o	3	6	88	61

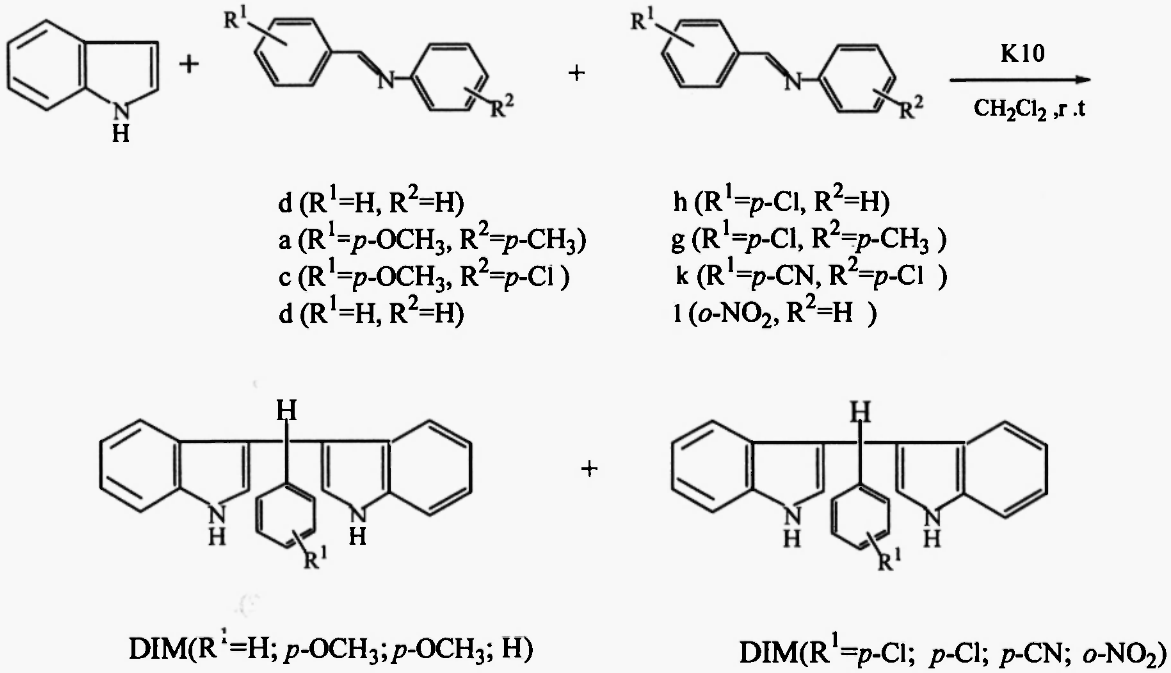
[a] Isolated yield. [b] At 0□



Scheme-2

As shown in Table-2, K10 behaves more effective than KSF in all the cases. It took shorter time for K10 catalyzed reactions for completion and got higher yields of DIM. Either electron-donating or electron-withdrawing substituents of imines can affect the reaction rate and yield. The imines bearing electron-withdrawing R^2 groups, such as Cl and NO_2, afforded much higher yields (Entry 3,11,13,17) than those with electron-donating group CH_3 (Entry1,8,15). A explanation for this trend is, once the intermediate A (shown in Scheme-2) formed, it decomposed rapidly to form a basic amine, which in turn trapped and thus deactivated the acidic catalyst in some extent. The amines with electron-donating groups are more basic and could deactivate the catalysts lively. Concern with the effects of substituents R^1, it is found that the nonsubstituted imine or those having electron-withdrawing R^1s reacted more quickly and with higher yields of DIM compared to those bearing electron-donating R^1s (Entry 1~3). And for some reactions tested, electron-withdrawing R groups have positive impacts (Entry 9, 10, 12~14) compare to R^1=H.

In order to study the chemoselectivity of the reactions, the competition experiments between two imines bearing different R^1 substituents with indole under the catalysis of K10 were studied (Scheme-3). As shown in Table-3, from the every competitive pair, the main product was predominantly derived from the imine bearing stronger electron-withdrawing R^1 group. These results are also coincided with the substituent effects depicted above (Table-2). The main reason for the chemoselectivity might be the intrinsic difference in the protonation ability of the imino-nitrogen atoms by the catalyst.



Scheme-3

Table-3: Competitive reactions between two imines with different R^1 toward indole under the catalysis of K10 at r.t.

Entry	Imine Pair (R^1,R^2)	(R^1,R^2)	Time (h)	Yield (%)[a] DIM(R^1)	DIM(R^1)
1	d (H,H)	h (p-Cl,H)	3.5	20 (H)	74 (p-Cl)
2	a (p-CH_3O,p-CH_3)	g (p-Cl, p-CH_3)	4.5	3 (p-OCH_3)	32 (p-Cl)
3	c (p-CH_3O,p-Cl)	k (p-CN, p-Cl)	4	16 (p-OCH_3)	81 (p-CN)
4	d (H,H)	l (o-NO_2,H)	4	21 (H)	64 (o-NO_2)

[a] Isolated yield.

Conclusions

The synthesis of diindolylmethanes DIM can be completed by chemoselective condensation of indole and imines using inexpensive montmorllonite clay K10 and KSF catalysts under mild conditions.

Acknowledgements

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References

1. a. Z. Iqbal, A.H. Jackson, K.R.N. Rao, *Tetrahedron Lett.* 29 (21), 2577(1988).
   b. P. Harrington and M.A. Kerr, *Synlett.* 1047(1996).
   c. M. Johannsen, *Chem. Commun.* 2233(1999).
   d. M. Bandini, P.G. Cozzi, P. Melchiorre and A. Umani-Ronchi, *J. Org. Chem.* 67 (15), 5386(2002).
   e. D.A. Evans, K.A. Scheidt, K.R. Fandrick, H.W. Lam and J.J. Wu, *J. Am. Chem. Soc.* **125** (36), 10780(2003).

2. I.C. Jacobs and M.A. Zaligs, *Proceedings of 27-th International Symposium on Controlled Release of Bioactive Materials*, pp.1324(2002).
3. J.J. Michnovicz and H.L. Bradlow, *Nutrition and Cancer*, **16**, 59(1991).
4. a. M. Roomi and S. MacDonald, *Can. J. Chem.* **48**, 139(1970).
   b. B. Gregorovich, K. Liang, D. Clugston and S. MacDonald, *Can. J. Chem.* **46**, 3291(1968).
5. a. A. Chatterjee, S. Manna, J. Benerji, C. Pascard, T. Prange and J. Shoolery, *J. Chem. Soc., Perkin Trans. 1*, 553(1980).
   b. D.P. Chen, L.B. Yu and P.G. Wang, *Tetrahedron Lett.* **37** (27), 4467(1996).
   c. G. Babu, N. Sridhar and P.T. Perumal, *Synth. Commun.* **30** (9), 1609(2000).
   d. R. Nagarajan and P.T. Perumal, *Synth. Commun.* **32** (1), 105(2002).
   e. J.S. Yadav, B.V.S. Reddy, C.V.S.R Murthy, G.M. Kumar and C. Madan, *Synthesis*, 783(2001).
6. M. D'Auria, *Tetrahedron*, 47 (44), 9225(1991).
7. B.P. Bandgar and K.A. Shaikh, *Tetrahedron Lett.* 44 (9), 1959(2003).
8. J.N. Denis, H. Mauger and Y. Vallee, *Tetrahedron Lett.* **38** (49), 8515(1997).
9. X.L Feng,. C.J. Guan and C.X. Zhao, *Synth. Commun.* **34** (3), 487(2004).
10. M. Chakrabarty, N. Ghosh, R. Basak and Y. Harigaya, *Tetrahedron Lett.* **43**, 4075(2002).
11. R.S. Varma, *Tetrahedron*, **58**, 1235(2002).
12. W.H. Xie, K.M. Bloomfield, Y.F. Jin, N.Y. Dolney and P.G. Wang, *Synlett.* 498(1998).
13. S. Kobayashi, M. Araki and M. Yasuda, *Tetrahedron Lett.* **36** (32), 5773(1995).

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