Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 61 (2005) 11751–11757

I_2-catalyzed Michael addition of indole and pyrrole to nitroolefins

Chunchi Lin, Jianming Hsu, M. N. V. Sastry, Hulin Fang, Zhijay Tu, Ju-Tsung Liu and Yao Ching-Fa*

Department of Chemistry, National Taiwan Normal University 88, Sec. 4, Tingchow Road, Taipei, 116 Taiwan, ROC

Received 15 August 2005; revised 8 September 2005; accepted 9 September 2005

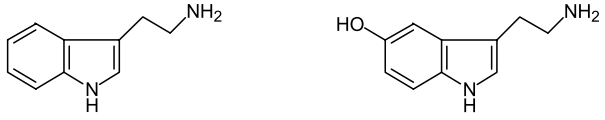
Available online 14 October 2005

Abstract—An easy and efficient method to generate indolyl nitroalkane **5** and pyrrolyl nitroalkane **7** in high yields using β-nitrostyrene and indole/pyrrole at room temperature in the presence of catalytic amount of iodine is reported. The short reaction times and high yields of product are noteworthy. Molecular iodine promoted Michael addition is operationally simple and efficient method compared to the known Lewis acids or rare earth metal catalysts to generate different indolyl/pyrrolyl nitroalkanes in high yield.

1. Introduction

Indole and many of its derivatives are most important units in many naturally occurring compounds, because of a wide variety of their pharmacological and biological properties.[1] The hapalindole alkaloids, which exhibit significant antibacterial and antimycotic activity, and several indole alkaloids such as uleine, aspidospermidine, ibophyllidine alkaloids, and numerous tryptamine derivatives are also associated with important biological activity.[2] Likewise, important pyrrole derivatives also present in compounds such as bile pigments, vitamin B_{12}, haemin, chlorophyll, and related natural products.[3] In addition, several pyrrole derivatives are important intermediates not only for the synthesis of drugs, pigments and pharmaceuticals but also for the development of organic functional groups.[4] Therefore, development of new synthetic methods of indole and pyrrole derivatives have been widely studied using various Lewis acids as well as Bronsted acids.[5] Since the 3-position of the indole is the ideal site for electrophilic attack, 3-substituted indoles are versatile intermediates for the synthesis of a wide variety of indole derivatives. Conversely, C-2 position of pyrrole is indeed the electron-rich site for Michael addition. Michael addition of indoles and pyrroles to various nucleophiles has been well documented in the literature using either protic or Lewis acids.[6–9] However, Lewis acid-catalyzed Michael addition of indole and pyrrole necessitate careful control over the acidity to avoid the undesirable side reactions such as dimerization and polymerization.[10] Incidentally, the polymerized products of indole and pyrrole derivatives involves troublesome isolation procedures to obtain the desired product with some of the Lewis acids. Furthermore, many procedures require longer reaction times, expensive and toxic reagents in stoichiometric amounts, air sensitive conditions, difficult workup procedures.

The use of molecular iodine in organic synthesis has been known for a long time. In recent years molecular iodine has received considerable attention as an inexpensive, nontoxic, readily available catalyst for various organic transformations under mild and convenient conditions to afford the corresponding products in excellent yields with high selectivity.[11] Another advantage in using iodine as catalyst, will not influence the nitro group, which is very significant for β-nitrostyrene **3**. Herein, some important pharmaceutical compounds, tryptamine **1** and serotonin **2**, which can be obtained as a result of Michael addition between indole and nitroalkene (Fig. 1). Especially serotonin, a simple derivative of indole is a major neurotransmitter and many indole derivatives also mimic the binding of neurotransmitter to its receptors also have been synthesized.[12] In continuation of our work in exploring the methods using β-nitrostyrene, we had the opportunity to focus on the iodine catalyzed Michael addition of



1 (tryptamine) 2 (serotonin)

Figure 1.

Keywords: β-Nitrostyrene; Indole; Pyrrole; Iodine; Michael addition.
* Corresponding author. Tel.: +886 2 29309092; fax: +886 2 29324249; e-mail: cheyaocf@scc.ntnu.edu.tw

0040–4020/$ - see front matter © 2005 Published by Elsevier Ltd.
doi:10.1016/j.tet.2005.09.038

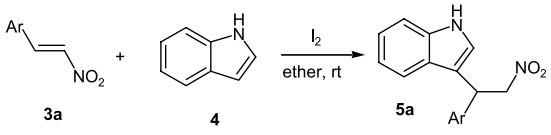
β-nitrostyrene **3** with indole, because the resultant products are analogs of **1** and **2** after reducing the nitro group (Fig. 1).

In this paper, we wish to report that elemental iodine can be used as a mild and efficient catalyst for the Michael addition of β-nitrostyrene **3** with indole **4** and pyrrole **6** at room temperature to afford products 2-indolyl-2-phenyl-1-nitroalkane **5** and 2-pyrrolyl-2-phenyl-1-nitroalkane **7** in high to excellent yields.

2. Results and discussion

In the beginning, Michael reaction between indole and β-nitrostyrene **3** was carried out using iodine (30 mol%) in chloroform (0.5 mL) led to the formation of 2-indolyl-2-phenyl-1-nitroalkane **5** in 95% yield. With this encouraging result, next we investigated the fate of reaction in different solvents. Conducting the reaction in DMSO did not proceed and DMF as a solvent afforded only 10% of the product with several unwanted side products. After substantial experimentation with different solvents (CH_2Cl_2, 82% yield; $CHCl_3$, 95% yield; EtOAc, 91% yield), diethylether came out as a solvent of choice. The iodine catalyzed reaction in ether not only improved the product yields, but also reduced the reaction times. We next, investigated the amount of iodine required to catalyze the transformation. As less as 10 mol% of iodine afforded the products in 43% yield, after 18 h. By means of 20 mol% of iodine though product yields were improved to 72%, but the reaction time is almost same as that of 10 mol%. On the other hand, using 30 mol% of iodine as a catalyst afforded the products in 99% yield in 2 h (Scheme 1).

To check the versatility of iodine catalyzed Michael reaction, various substituted β-nitrostyrenes (**3a**–**c**) were reacted with indole **4** using iodine (30 mol%) in ether (0.5 mL) solution and the results were summarized



a: Ar = C_6H_5

Serial no.	amount of I_2(mol%)	solvent	5a[a]
1	30	$CHCl_3$ (0.5ml)	95%
2	30	DMSO (0.5ml)	10%
3	30	DMF (0.5ml)	10%
4	30	CH_2Cl_2 (0.5ml)	82%
5	30	EtOAc (0.5ml)	91%
6	30	ethyl ether (0.5ml)	99%[b]
7	10	ethyl ether (0.5ml)	43%[b]
8	20	ethyl ether (0.5ml)	72%[b]

a) NMR yields of the crude products
b) The reaction of serial no. 6 was 2h but were over 18h in serial no. 7 and 8

Scheme 1.

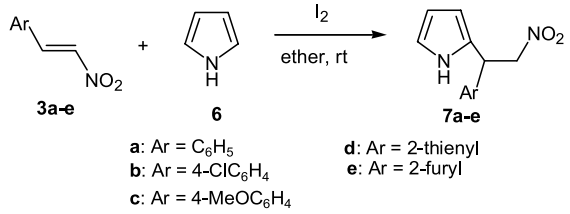
Table 1. Iodine catalyzed Michael addition between nitroolefins and indole

Serial no.	Entry[a]	Time (h)	Product[b]	Yield (%)[c]
1	**3a**	2	**5a**	99
2	**3b**	2.5	**5b**	99
3	**3c**	18	**5c**	99
4	**3d**	2	**5d**	89
5	**3e**	6	**5e**	94

[a] All reactions were performed at 1 mmol scale using 30 mol% of iodine in 0.5 mL of ether.
[b] All products were well characterized by ^1H NMR, ^{13}C NMR, and mass spectroscopy.
[c] NMR yields of the crude products.

(Table 1). Although all Michael adducts were obtained in excellent yields, but the reaction times varied according to the nature of the substitution pattern on the phenyl ring. The electron donating groups substituted in the phenyl ring of the nitrostyrene led to the formation of products with longer reaction times. The heterocyclic nitroolefins (**3d**–**3e**) also afforded the adducts in high yield. The lower yield of **5d** over **5e** can be explained on the basis of the product stability.

In order to extend the scope of this methodology, pyrrole **6** was subjected as a nucleophile in Michael addition with differnet β-nitrostyrenes, to generate 2-pyrrolyl-2-phenyl-1-nitroalkanes **7a**–**e** in good yields (Scheme 2).



Scheme 2.

The reasons for the lower product yields in case of pyrrole, when compared to indole may be ascribed due to polymerization of products in some cases. This is due to high nucleophilicity of pyrroles, which facilitates to react rapidly than indole. Using molecular iodine in catalytic amount to generate 2-alkyl pyrroles in excellent yields is noteworthy (Table 2).

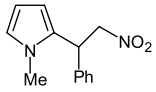
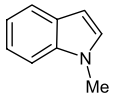
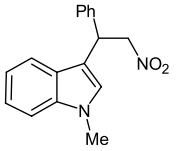
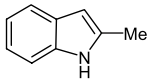
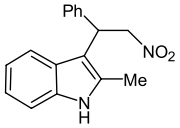
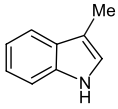
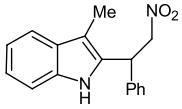
Table 2. Iodine catalyzed Michael addition between nitroolefins and pyrrole

Serial no.	Entry[a]	Time (h)	Product[b]	Yield (%)[c]
1	**3a**	1	**7a**	86
2	**3b**	1	**7b**	76
3	**3c**	1.5	**7c**	79
4	**3d**	1.3	**7d**	85
5	**3e**	1.2	**7e**	81

[a] All reactions were performed at 1 mmol scale using 30 mol% of iodine in 0.5 mL of ether.
[b] All products were well characterized by ^1H NMR, ^{13}C NMR, and mass spectroscopy.
[c] NMR yields of the crude products.

So as to utilize this extensively effective protocol, we examined by taking various other indole and pyrrole derivatives with β-nitrostyrene **3**. *N*-methylpyrrole **8**

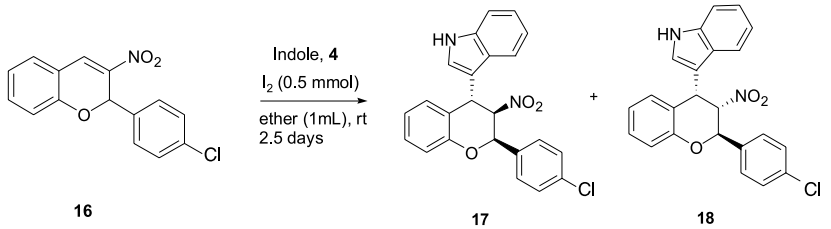
Table 3. Iodine catalyzed Michael addition of β-nitrostyrene with methyl substituted indole or pyrrole

Serial no.	Entry (indole/pyrrole)[a]	Time	Product[b]	Yield (%)[c]
1	 **8**	45 min	 **9**	99
2	 **10**	20 min	 **11**	99
3	 **12**	20 min	 **13**	99
4	 **14**	2 days	 **15**	70

[a] All reactions were performed at 1 mmol scale using 30 mol% of iodine in 0.5 mL of ether.
[b] All products were well characterized by ^{1}H NMR, ^{13}C NMR, and mass spectroscopy.
[c] NMR yields of the crude products.

and methyl substituted indoles such as *N*-methylindole **10**, 2-methylindole **12**, and 3-methylindole **14** afforded the products in good to excellent yields under similar reaction conditions (Table 3). Besides, we have not observed any byproducts, which are iodated either on indole or pyrrole nucleus. The substituted derivatives of both indole and pyrrole gave the products in excellent yield during less time, when compared to their unsubstituted counterparts. A possible explanation may be due to the presence of the methyl group, which not only increases the electron density of the aromatic ring to accelerate the reaction, but also prevents the unwanted side reactions such as polymerization. In case of 3-methylindole **14**, which undergoes conjugate addition at the 2-position may involve more complicated mechanism. It has been reported in the literature, that the mechanism involving addition at 2-position proceeds through the initial attack of the electrophile at C-3, followed by a 1,2-shift in the intermediate cation leads to the formation of final product.[3] The longer reaction times and lower product yields in the addition of β-nitrostyrene to 3-methylindole clearly supports the above proposed mechanism.

In addition to this, we have also examined the fate of a different nitroolefin like 2-(4-chlorophenyl)-3-nitro-2*H*-chromene **16**, since the resultant 2*H*-benzopyran derivatives such as flavonols[13] and amines[14] belongs to medicinally important compounds. In our previous report, we have provided an easy and efficient method to prepare **16** using DABCO in catalytic amount.[15] Using 50 mol% of iodine, 2-(4-chlorophenyl)-3-nitro-2*H*-chromene in a reaction with indole gave 73% of **17** and 26% of **18** in ether solution at room temperature after 2.5 days (Scheme 3). The two stereoisomers were separated through column chromatography and the ratio was determined by the crude NMR analysis. In addition to this, the two stereoisomers were also characterized by the single X-ray crystallography (Figs. 2 and 3) and suggested a trans configuration between the aryl substituent at 2-position and the indolyl group at 4-position for the compound **17**. The formation of major product as



Scheme 3.

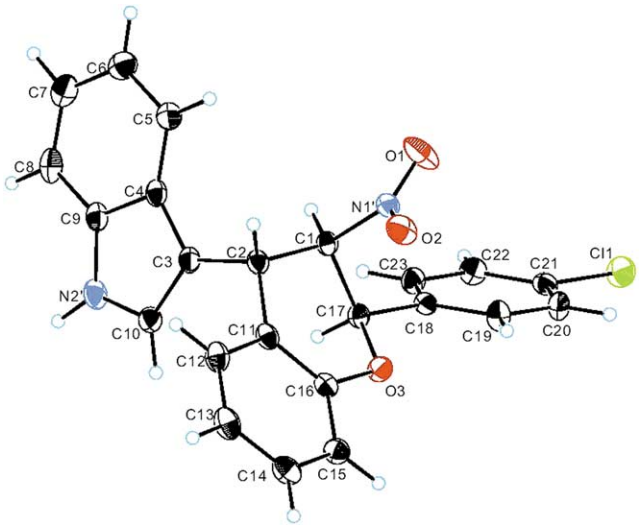


Figure 2. X-ray crystal structure of **17**.

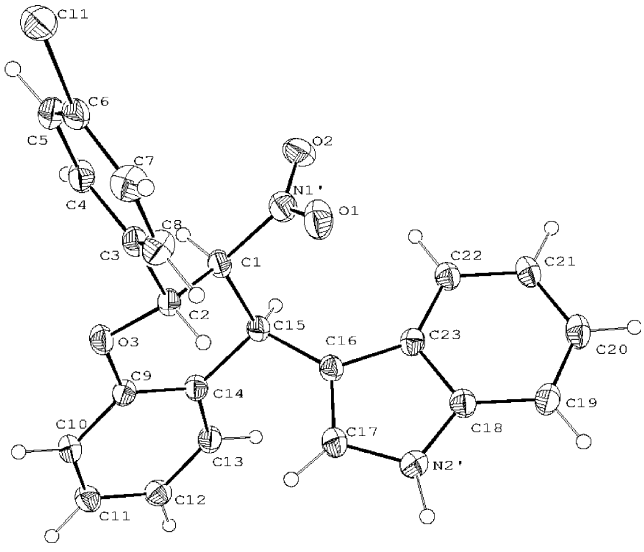
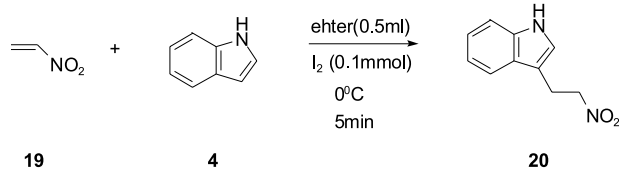


Figure 3. X-ray crystal structure of **18**.

trans isomer can be explained on the basis of steric hindrance in which the two bulky groups are trans to each other separated by a nitro group.

In order to apply the remarkable catalytic activity of iodine, for the synthesis of biologically important compound, a less hindered nitroolefin like nitroethylene **19**[16] was used as Michael acceptor. Using 10 mol% of iodine, nitroethylene **19** reacts readily with indole at 0 °C, to afford the product **20**[17] in 98% yield (Scheme 4). The formation of 2-indolyl-1-nitroethane **20** in less than 5 min, and the formation of 2-(4-chlorophenyl)-4-indolyl-3-nitrochroman **17** in 2.5 days,



Scheme 4.

clearly indicates the steric hindrance of the nitroolefin plays a significant role in determining the reaction time. Moreover, the product **20** is an important intermediate and can be reduced to tryptamine **1**, a neurotransmitter.[17a–b]

3. Conclusions

In summary, we have achieved a simple, efficient, and practical Michael addition process for the synthesis of various 2-indolyl-2-aryl-1-nitroalkanes **5** and 2-pyrrolyl-2-aryl-1-nitroalkanes **7** from β-nitrostyrene using catalytic amount of iodine. The significant advantage of this catalytic reaction lies in its usage under mild and ambient conditions. The yields are generally excellent (up to 98%) without any byproducts and the reaction times are also short. Further investigations are in progress on the application of this methodology to the synthesis of natural product molecules with indole or pyrrole moiety and other heterocyclic ring systems.

4. Experimental

4.1. General

All reactions were performed in room temperature and all chemicals including solvent used for reactions without drying. Analytical thin-layer chromatography was performed with E. Merck silica gel 60F glass plates and flash chromatography by use of E. Merck silica gel 60 (230–400 mesh). MS or HRMS were measured by JEOL JMS-D300 or JEOL JMS-HX110 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded with Bruker Aavance EX 400.

4.2. Material

β-Nitrostyrene **1**, indole, pyrrole, and iodine were purchased from Aldrich Chemical Co. and other commercially available reagents were used without further purification. 2-(4-Chlorophenyl)-3-nitro-2*H*-chromene **16**, nitroethylene **19** were prepared according to the literature procedures and spectral data was consistent with the literature report.

4.3. Typical experimental procedure for the synthesis of adducts 5 or 7 (a: Ar=Ph, b: Ar=4-ClC$_6$H$_4$, c: Ar=4-MeOC$_6$H$_4$, d: Ar=thienyl, e: Ar=furyl)

Indole **4** (4.0 mmol) or pyrrole **6** (4.0 mmol) was added to a suspension of β-nitrostyrene **3** (1.0 mmol) in diethyl ether (0.5 mL) along with iodine (0.3 mmol) at room temperature for several minutes to hours. After completion the reaction (monitored by TLC), it was quenched with water and washed with (2×10 mL) aq $Na_2S_2O_3$ and extracted into CH_2Cl_2 (3×20 mL). The combined organic phases were washed sequentially with brine and water and dried over anhyd Na_2SO_4. Evaporation of the organic solvent afforded the crude products **5a–e** or **7a–e**.

4.3.1. 2-Phenyl-2-indolyl-1-nitroethane (5a). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.40 (d, J=8.00 Hz, 1H), 7.27–7.10 (m, 8H), 6.82 (d, J=2.36 Hz, 1H), 5.12 (dd, J=8.36, 7.68 Hz, 1H), 4.95 (dd, J=12.52, 7.68 Hz, 1H), 4.84

(dd, J=12.52, 8.36 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.13, 136.26, 128.72, 127.58, 127.36, 125.88, 122.38, 121.56, 119.67, 118.66, 113.86, 111.37, 79.33, 41.35. MS *m/z* (relative intensity) 266 (M^+, 8), 219 (100), 204 (44), 178 (19), 115 (11), 108 (17). HRMS calcd for $C_{16}H_{14}N_2O_2$ (M^+) 266.1055, found 266.1051.

4.3.2. 2-(4-Chlorophenyl)-2-indolyl-1-nitroethane (5b). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.39 (d, J= 7.96 Hz, 1H), 7.33 (d, J=8.20 Hz, 1H), 7.29–7.07 (m, 6H), 6.98 (s, 1H), 5.14 (dd, J=8.56, 7.40 Hz, 1H), 5.02 (dd, J= 12.52, 7.40 Hz, 1H), 4.88 (dd, J=12.52, 8.56 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.64, 136.25, 133.04, 128.96, 128.83, 125.67, 122.55, 121.46, 119.80, 118.55, 113.38, 111.43, 79.03, 40.70. MS *m/z* (relative intensity) 300 (M^+, 33), 254 (41), 253 (100), 240 (64), 218 (37), 115 (14), 108 (25). HRMS calcd for $C_{16}H_{13}ClN_2O_2$ (M^+) 300.0666, found 300.0671.

4.3.3. 2-(4-Methoxylphenyl)-2-indolyl-1-nitroethane (5c). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.43 (d, J=7.92 Hz, 1H), 7.36–7.16 (m, 4H), 7.09–7.00 (m, 2H), 6.87–6.23 (m, 2H), 5.13 (dd, J=8.44, 7.48 Hz, 1H), 5.03 (dd, J=12.24, 7.48 Hz, 1H), 4.89 (dd, J=12.24, 8.44 Hz, 1H), 3.77 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.95, 136.57, 131.24, 128.84, 126.15, 122.72, 121.47, 119.97, 119.03, 114.86, 114.33, 111.38, 79.79, 55.28, 40.90. MS *m/z* (relative intensity) 296 (M^+, 38), 250 (32), 249 (88), 236 (100), 218 (20), 115 (12). HRMS calcd for $C_{17}H_{16}N_2O_3$ (M^+) 296.1161, found 296.1161.

4.3.4. 2-Thienyl-2-indolyl-1-nitroethane (5d). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.52–7.50 (m, 1H), 7.38–7.36 (m, 1H), 7.24–7.09 (m, 4H), 6.99–6.93 (m, 2H), 5.44 (dd, J=8.16, 7.56 Hz, 1H), 5.05 (dd, J=12.48, 7.56 Hz, 1H), 4.98 (dd, J=12.48, 8.16 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.85, 136.16, 126.81, 125.48, 125.08, 124.73, 122.45, 121.94, 119.79, 118.57, 113.49, 111.49, 79.78, 36.70. MS *m/z* (relative intensity) 272 (M^+, 33), 226 (26), 225 (100), 212 (74), 210 (20), 167 (9), 115 (15). HRMS calcd for $C_{14}H_{12}N_2O_2S$ (M^+) 272.0619, found 272.0620.

4.3.5. 2-Furyl-2-indolyl-1-nitroethane (5e). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.44 (d, J=7.92 Hz, 1H), 7.21–7.00 (m, 4H), 6.73–6.71 (m, 1H), 6.15–6.13 (m, 1H), 6.01–5.99 (m, 1H), 5.12 (dd, J=8.20, 7.40 Hz, 1H), 4.85 (dd, J=12.56, 8.20 Hz, 1H), 4.69 (dd, J=12.56, 7.40 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.03, 141.96, 135.98, 125.37, 122.68, 122.20, 119.66, 118.34, 111.48, 110.80, 110.25, 107.03, 77.57, 35.39. MS *m/z* (relative intensity) 256 (M^+, 32), 210 (22), 209 (100), 196 (84), 167 (23), 117 (16), 115 (12). HRMS calcd for $C_{14}H_{12}N_2O_3$ (M^+) 256.0848, found 256.0846.

4.3.6. 2-Phenyl-2-pyrrolyl-1-nitroethane (7a). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.35–7.19 (m, 5H), 6.40 (dd, J=4.04, 2.60 Hz, 1H), 6.14 (dd, J=6.04, 2.84 Hz, 1H), 6.05–6.07 (m, 1H), 4.94 (dd, J=11.88, 7.28 Hz, 1H), 4.86 (dd, J=7.52, 7.28 Hz, 1H), 4.76 (dd, J=11.88, 7.52 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.95, 129.13, 128.85, 128.04, 127.83, 118.14, 108.57, 105.73, 79.12, 42.84. MS *m/z* (relative intensity) 216 (M^+, 10), 170 (22), 169 (100), 156 (40), 154 (39), 77 (12). HRMS calcd for $C_{12}H_{12}N_2O_2$ (M^+) 216.0899, found 216.0900.

4.3.7. 2-(4-Chlorophenyl)-2-pyrrolyl-1-nitroethane (7b). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.30 (d, J= 8.40 Hz, 2H), 7.15 (d, J=8.40 Hz, 2H), 6.69–6.67 (m, 1H), 6.16 (dd, J=5.76, 2.76 Hz, 1H), 6.07–6.05 (m, 1H), 4.94 (dd, J=12.12, 7.12 Hz, 1H), 4.84 (dd, J=7.88, 7.12 Hz, 1H), 4.75 (dd, J=12.12, 7.88 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.53, 133.99, 129.32, 129.22, 128.28, 118.43, 108.72, 105.95, 78.94, 42.27.

4.3.8. 2-(4-Methoxylphenyl)-2-pyrrolyl-1-nitroethane (7c). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.14–7.11 (m, 2H), 6.88–6.84 (m, 2H), 6.67–6.65 (dd, J=5.96, 2.76 Hz, 1H), 6.16–6.14 (m, 1H), 6.06–6.04 (m, 1H), 4.94 (dd, J=11.92, 6.96 Hz, 1H), 4.82 (dd, J=8.04, 6.96 Hz, 1H), 4.74 (dd, J=11.92, 8.04 Hz, 1H), 3.78 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.30, 129.84, 129.24, 128.98, 118.03, 114.53, 108.58, 105.54, 79.37, 55.26, 42.18. MS *m/z* (relative intensity) 246 (M^+, 13), 199 (100), 186 (66), 171 (14), 168 (20), 77 (9). HRMS calcd for $C_{13}H_{14}N_2O_3$ (M^+) 246.1004, found 246.1006.

4.3.9. 2-Thienyl-2-pyrrolyl-1-nitroethane (7d). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.25–7.23 (m, 1H), 6.93–6.92 (m, 2H), 6.68–6.70 (m, 1H), 6.18–6.15 (m, 1H), 6.11–6.09 (m, 1H), 5.19 (dd, J=7.96, 7.52 Hz, 1H), 4.92 (dd, J= 12.88, 7.52 Hz, 1H), 4.82 (dd, J=12.88, 7.96 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.99, 128.29, 127.17, 125.86, 125.55, 118.25, 108.81, 105.92, 79.66, 38.19. MS *m/z* (relative intensity) 222 (M^+, 1), 206 (2), 168 (11), 88 (37), 73 (40), 79 (78), 61 (100). HRMS calcd for $C_{10}H_{10}N_2OS$ (M^+-16) 206.0463, found 206.0540.

4.3.10. 2-Furyl-2-pyrrolyl-1-nitroethane(7e). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.39–7.38 (m, 1H), 6.72–6.60 (m, 1H), 6.33–6.31 (m, 1H), 6.18–6.13 (m, 2H), 6.09–6.07 (m, 1H), 5.00 (dd, J=7.76, 7.56 Hz, 1H), 4.88 (dd, J=12.76, 7.76 Hz, 1H), 4.79 (dd, J=12.64, 7.56 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.71, 142.70, 126.19, 118.27, 110.56, 108.79, 107.76, 106.65, 77.74, 36.94. MS *m/z* (relative intensity) 206 (M^+, 10), 159 (100), 158 (9), 146 (52), 80 (6). HRMS calcd for $C_{10}H_{10}N_2O_3$ (M^+) 206.0691, found 206.0687.

4.4. Typical experimental procedure for the synthesis of adducts 9, 11, 13 and 15

Methyl substituted indole **10**, **12**, **14** (4.0 mmol) or methyl substituted pyrrole **8** (4.0 mmol) was added to a suspension of β-nitrostyrene **3** (1.0 mmol) in diethyl ether (0.5 mL) along with iodine (0.3 mmol) at room temperature for several minutes to hours. After completion the reaction (monitored by TLC), it was quenched with water and washed with (2×10 mL) aq $Na_2S_2O_3$ and extracted into CH_2Cl_2 (3×20 mL). The combined organic phases were washed sequentially with brine and water and dried over anhyd Na_2SO_4. Evaporation of the organic solvent afforded the crude products **9**, **11**, **13**, **15**.

4.4.1. 2-(*N*-methylpyrroyl)-2-phenyl-1-nitroethane (9). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20–7.07 (m, 5H), 6.43

(s, 1H), 6.04–6.01 (m, 2H), 4.80–4.72 (m, 2H), 4.60–4.52 (m, 1H), 3.05 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.82, 129.00, 128.59, 127.53, 127.30, 122.47, 106.45, 105.42, 78.79, 41.18, 33.06. MS *m/z* (relative intensity) 230 (M^+, 41), 184 (40), 183 (66), 170 (100), 128 (17), 96 (35), 77 (13). HRMS calcd for $C_{12}H_{12}N_2O_2$ (M^+) 230.1055, found 230.1053.

4.4.2. 2-(*N*-methylindolyl)-2-phenyl-1-nitroethane (11). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–6.93 (m, 9H), 6.67 (s, 1H), 5.06 (dd, J=8.72, 7.92 Hz, 1H), 4.83 (dd, J=12.32, 7.92 Hz, 1H), 4.76 (dd, J=12.32, 8.72 Hz, 1H), 3.14 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.31, 136.99, 128.59, 127.49, 127.19, 126.32, 126.07, 121.89, 119.15, 118.71, 112.43, 109.33, 79.19, 41.23, 32.24. MS *m/z* (relative intensity) 280 (M^+, 44), 234 (50), 233 (74), 220 (100), 217 (17), 146 (17), 115 (13). HRMS calcd for $C_{17}H_{16}N_2O_2$ (M^+) 280.1212, found 280.1213.

4.4.3. 2-(2-Methylindolyl)-2-phenyl-1-nitroethane (13). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.62 (d, J=7.8 Hz, 1H), 7.50–7.25 (m, 8H), 5.40–5.28 (m, 2H), 5.23 (dd, J=11.76, 8.84 Hz, 1H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.30, 135.11, 132.85, 128.46, 127.00, 126.76, 126.51, 120.87, 119.33, 118.21, 110.65, 108.22, 78.24, 40.21, 11.28. MS *m/z* (relative intensity) 280 (M^+, 62), 234 (49), 220 (100), 146 (49), 115 (8), 77 (8). HRMS calcd for $C_{17}H_{16}N_2O_2$ (M^+) 280.1212, found 280.1218.

4.4.4. 2-(3-Methylpyrroyl)-2-phenyl-1-nitroethane (15). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.52 (d, J=7.68 Hz, 1H), 7.41–7.08 (m, 8H), 5.25 (dd, J=8.28, 7.64 Hz, 1H), 5.08 (dd, J=12.88, 8.28 Hz, 1H), 4.95 (dd, J=12.88, 7.64 Hz, 1H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.00, 135.66, 130.55, 129.23, 128.98, 127.88, 127.16, 122.16, 119.49, 118.56, 110.75, 109.25, 77.41, 40.96, 8.51. MS *m/z* (relative intensity) 280 (M^+, 45), 234 (72), 233 (69), 218 (100), 217 (80), 204 (42), 146 (52), 128 (40), 105 (45), 77 (68). HRMS calcd for $C_{17}H_{16}N_2O_2$ (M^+) 280.1212, found 280.1212.

4.5. Typical experimental procedure for the synthesis of adducts 17 and 18

Indole **4** (4.0 mmol) was added to a suspension of 2-(4-chlorophenyl)-3-nitro-2*H*-chromene **16** (1.0 mmol) in diethyl ether (1.0 mL) along with iodine (0.5 mmol) at room temperature for several minutes to hours. The reaction was monitored by TLC. After completion the reaction mixture was quenched and washed with (2×10 mL) aqueous $Na_2S_2O_3$ solution and extracted with CH_2Cl_2 (3×20 mL). The combined organic phases were washed sequentially with brine and water and dried (Na_2SO_4). The solvent was removed to obtain the crude product **17** and **18**.

4.5.1. (2*R*,3*R*,4*S*)-2-(4-chlorophenyl)-4-indolyl-3-nitrochroman (17). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.64 (d, J=7.80 Hz, 1H), 7.45 (d, J=8.12 Hz, 1H), 7.32–7.00 (m, 10H), 6.71 (d, J=2.28, 1H), 5.34 (d, J=2.20 Hz, 1H), 5.29 (dd, J=2.28, 2.24 Hz, 1H), 5.03 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.76, 136.66, 134.58, 134.28, 130.47, 128.82, 128.55, 127.21, 125.16, 125.13, 123.21, 122.03, 120.66, 119.85, 118.04, 117.66, 117.02, 111.84, 87.20, 72.01, 37.05. MS *m/z* (relative intensity) 406 (M^++2, 8), 404 (M^+, 23), 359 (18), 358 (22), 357 (53), 243 (100), 241 (30), 220 (44), 130 (18). HRMS calcd for $C_{23}H_{17}ClN_2O_3$ (M^+) 404.0928, found 404.0928. Anal. Calcd for $C_{23}H_{17}ClN_2O_3$: C, 68.23; H, 4.23; N, 6.92. Found: C, 68.99; H, 5.02; N, 6.97.

4.5.2. (2*R*,3*S*,4*S*)-2-(4-chlorophenyl)-4-indolyl-3-nitrochroman (18). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.39–6.93 (m, 12H), 6.88 (d, J=2.56 Hz, 1H), 5.54 (d, J=9.32 Hz, 1H), 5.37 (dd, J=9.32, 5.56 Hz, 1H), 5.16 (d, J=5.56 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.06, 136.07, 135.22, 135.03, 130.26, 129.24, 128.96, 126.93, 124.79, 122.67, 121.96, 121.64, 120.37, 118.20, 116.70, 113.43, 111.48, 87.20, 73.51, 37.90. MS *m/z* (relative intensity) 406 (M^++2, 14), 404 (M^+, 45), 359 (13), 358 (17), 357 (36), 243 (27), 241 (89), 220 (100), 132 (37). HRMS calcd for $C_{23}H_{17}ClN_2O_3$ (M^+) 404.0928, found 404.0932. Anal. Calcd for $C_{23}H_{17}ClN_2O_3$: C, 68.23; H, 4.23; N, 6.92. Found: C, 68.54; H, 3.98; N, 6.80.

4.6. Typical experimental procedure for the synthesis of adduct 20

Indole **4** (2.0 mmol) was added to a suspension of nitroethylene **19** (1.0 mmol) in diethyl ether (0.5 mL) along with iodine (0.1 mmol) at 0 °C less than 5 min. The reaction was monitored by TLC. After completion the reaction mixture was quenched and washed with (2× 10 mL) aqueous $Na_2S_2O_3$ solution and extracted with CH_2Cl_2 (3×20 mL). The combined organic phases were washed sequentially with brine and water and dried (Na_2SO_4). The solvent was removed to obtain the crude product **20**.

4.6.1. 2-Indolyl-1-nitroethane 20. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 1H), 7.47–6.75 (m, 4H), 6.75 (s, 1H), 4.47 (t, J=7.12 Hz, 2H), 3.31 (t, J=7.08 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.92, 126.36, 122.57, 122.08, 119.47, 117.86, 111.34, 109.40, 75.50, 23.22.

Acknowledgements

Financial support by the National Science Council of the Republic of China and National Taiwan Normal University (ORD93-C) is gratefully acknowledged.

References and notes

1. (a) Sundberg, R. J. The Chemistry of Indoles; Academic: New York, 1996; p 113. (b) Livingstone, R. In Ansell, M. F., Ed.; Rodd's Chemistry of Carbon Compounds; Elsevier: Oxford, 1984; Vol. 4.
2. (a) Moore, R. E.; Cheuk, C.; Yang, X.-Q.; Patterson, G. M. L.; Bonjouklian, R.; Smitka, T. A.; Mynderse, J.; Foster, R. S.; Jones, N. D.; Swartzendruber, J. K.; Deeter, J. B. *J. Org. Chem.* **1987**, *52*, 1036. (b) Moore, R. E.; Cheuk, C.; Patterson, G. M. L. *J. Am. Chem. Soc.* **1984**, *106*, 6456. (c) Sakagami, M.;

Muratake, H.; Natsume, M. *Chem. Pharm. Bull.* **1994**, *42*, 1393. (d) Fukuyama, T.; Chen, X. *J. Am. Chem. Soc.* **1994**, *116*, 3125.
3. Thomas, L. G., 3rd ed. In *Heterocyclic Chemistry*, *Vol. 11*; Longman: England, 1997; Part 1, 2 and 5.
4. (a) Jones, R. A.; Bean, G. P. *The Chemistry of Pyrroles*; Academic: London, 1977. (b) Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795.
5. (a) Malcolm, M. C.; Nicholas, C.; Li, Z.; Malcolm, S. *Tetrahedron* **1987**, *43*, 1117. (b) Iwata, S.; Ishiguro, Y.; Utsugi, M.; Mitsuhashi, K.; Tanaka, K. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2432. (c) Lounasmaa, M.; Tolvanen, A. *Nat. Prod. Rep.* **2000**, *17*, 75. (d) Joule, J. A. In Thomas, E. J., Ed.; Science of synthesis; Thieme: Stuttgart, 2000; Vol. 10, p 361. (e) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045. (f) Patterson, J. M.; Soedigdo, S. *J. Org. Chem.* **1968**, *33*, 2057. (g) Reinecke, M. G.; Johnson, H. M.; Sebastian, J. F. *J. Am. Chem. Soc.* **1963**, *85*, 2859. (h) Yadav, J. S.; Abraham, S.; Reddy, B. V. S.; Sabitha, G. *Tetrahedron Lett.* **2001**, *42*, 8063. (i) Yadav, J. S.; Reddy, B. V. S.; Parimala, G. *Synlett* **2002**, 1143.
6. (a) Wang, S.-Y.; Ji, S.-J.; Loh, T.-P. *Synlett* **2003**, 2377. (b) Leonid, I.; Belen, K. *Heterocycles* **1994**, *37*, 2029.
7. Arcadi, A.; Bianchi, G.; Chiarini, M.; Anniballe, G. D.; Marinelli, F. *Synlett* **2004**, 944.
8. (a) Yadav, J. S.; Reddy, B. V. S.; Satheesh, G. *Tetrahedron Lett.* **2003**, *44*, 8331. (b) Yadav, J. S.; Reddy, B. V. S.; Abraham, S.; Sabitha, G. *Synlett* **2002**, 1550. (c) Harrington, P. E.; Kerr, M. A. *Synlett* **1996**, *11*, 1047. (d) Agnusdei, M.; Bandini, M.; Melloni, A.; Umani-Ronchi, A. *J. Org. Chem.* **2003**, *68*, 7126. (e) Evans, D. A.; Scheidt, K. A.; Fandrik, K. R.; Wai Lam, H.; Wu, J. *J. Am. Chem. Soc.* **2003**, *125*, 10780. (f) Jørgensen, K. A. *Synthesis* **2003**, 1117. (g) Bandini, M.; Cozzi, P. G.; Giacobini, M.; Melchiorre, P.; Selva, S.; Umani-Ronchi, A. *J. Org. Chem.* **2002**, *67*, 3700. (h) Bandini, M.; Fagioli, M.; Melchiorre, P.; Melloni, A.; Umani-Ronchi, A. *Tetrahedron Lett.* **2003**, *44*, 5843. (i) Bandini, M.; Fagioli, M.; Melloni, A.; Umani-Ronchi, A. *Synthesis* **2003**, 397.
9. (a) Firouzabadi, H.; Iranpoor, N.; Nowrouzi, F. *Chem. Commun.* **2005**, 789. (b) Loh, T. P.; Pei, J.; Lin, M. *Chem. Commun.* **1996**, *20*, 2315. (c) Babu, G.; Perumal, P. T. *Aldrichim. Acta* **2000**, *33*, 16. (d) Loh, T. P.; Wei, L. L. *Synlett* **1998**, 975.
10. (a) Chakrabarty, M.; Basak, R.; Ghosh, N. *Tetrahedron Lett.* **2001**, *41*, 8331. (b) Komoto, I.; Kobayashi, S. *Org. Lett.* **2002**, *4*, 1115.
11. (a) Kim, K. M.; Ryu, E. K. *Tetrahedron Lett.* **1996**, *37*, 1441. (b) Firouzabadi, H.; Iranpoor, N.; Hazarkhani, H. *J. Org. Chem.* **2001**, *66*, 7527. (c) Firouzabadi, H.; Iranpoor, N.; Sobhani, S. *Tetrahedron Lett.* **2002**, *43*, 3653. (d) Yadav, J. S.; Reddy, B. V. S.; Reddy, M. S.; Prasad, A. R. *Tetrahedron Lett.* **2002**, *43*, 9703. (e) Bandgar, B. P.; Shaikh, K. A. *Tetrahedron Lett.* **2003**, *44*, 1959. (f) Saeeng, R.; Sirion, U.; Sahakitpichan, P.; Isobe, M. *Tetrahedron Lett.* **2003**, *44*, 6211. (g) Ji, S. J.; Wang, S. Y.; Zhang, Y.; Loh, T. P. *Tetrahedron* **2004**, *60*, 2051. (h) Yadav, J. S.; Reddy, B. V. S.; Shubashree, S.; Sadashiv, K. *Tetrahedron Lett.* **2004**, *45*, 2951. (i) Phukan, P. *J. Org. Chem.* **2004**, *69*, 4005. (j) Phukan, P. *Tetrahedron Lett.* **2004**, *45*, 4785. (k) Sun, J.; Dong, Y.; Wang, X.; Wang, S.; Hu, Y. *J. Org. Chem.* **2004**, *69*, 8932. (l) Bhosale, R. S.; Bhosale, S. V.; Wang, T.; Zubaidha, P. K. *Tetrahedron Lett.* **2004**, *45*, 9111. (m) Ke, B.; Qin, Y.; He, Q.; Huang, Z.; Wang, F. *Tetrahedron Lett.* **2005**, *46*, 1751. (n) Banik, B. K.; Fernandez, M.; Alvarez, C. *Tetrahedron Lett.* **2005**, *45*, 2479.
12. David, T. D. In *Aromatic heterocyclic chemistry*, *Vol. 12*; Oxford University Press: New York, 1992; Part 1, p 53.
13. (a) Rao, T. S.; Singth, A. K.; Trievdi, G. K. *Heterycycles* **1984**, *22*, 1377. (b) Deshpande, S.; Mathur, H. H.; Trivedi, G. K. *Synthesis* **1983**, 835.
14. Booth, H.; Huckle, D.; Lockhart, I. M. *J. Chem. Soc., Perkin Trans. 2* **1973**, 227.
15. Yao, C. F.; Yan, M. C.; Jang, Y. J. *Tetrahedron Lett.* **2001**, *42*, 2717.
16. (a) Noland, W. E. *Org. Synth.* **1964**, *41*, 67. (b) Ranganathan, D.; Rao, C. B.; Ranganathan, S.; Mehrotra, A. K.; Iyengar, R. *J. Org. Chem.* **1980**, *45*, 1185. (c) Zimmerman, H. E.; Wang, P. *J. Org. Chem.* **2002**, *67*, 9216. (d) Flintoft, R. J.; Buzby, J. C.; Tucker, J. A. *Tetrahedron Lett.* **1999**, *40*, 4485. (e) Ranganathan, S.; Ranganathan, D.; Mehrotra, A. K. *J. Am. Chem. Soc.* **1974**, *96*, 5261. (f) Ranganathan, S.; Ranganathan, D.; Iyengar, R. *Tetrahedron* **1976**, *32*, 961. (g) Ranganathan, S.; Ranganathan, D.; Mehrotra, A. K. *Synthesis* **1977**, 289.
17. (a) Noland, H. *J. Am. Chem. Soc.* **1954**, *76*, 3227. (b) Henry, L. *J. Am. Chem. Soc.* **1957**, *79*, 5254. (c) Lyttle, W. *J. Am. Chem. Soc.* **1955**, *77*, 5747. (d) Hino, T.; Hasegawa, A.; Liu, J. J.; Nakagawa, M. *Chem. Pharm. Bull.* **1990**, *38*, 59–64. (e) Takeshita, M.; Yoshida, S.; Kohno, Y. *Heterocycles* **1994**, *37*, 553. (f) Kruse, L. I.; Hilbert, E. L. *Heterocycles* **1983**, *37*, 1373. (g) Hermkens, P. H. H.; Maarseveen, J. H. V.; Ottenheijm, H. C. J.; Kruse, C. G.; Scheeren, H. W. *J. Org. Chem.* **1990**, *55*, 3998. (h) Hermkens, P. H. H.; Maarseveen, J. H. V.; Ottenheijm, H. C. J.; Kruse, C. G.; Scheeren, H. W. *Tetrahedron* **1990**, *46*, 833. (i) Somei, M.; Karasawa, Y.; Kaneko, C. *Heterocycles* **1981**, *16*, 941. (j) Chikashita, H.; Morita, Y.; Itoh, K. *Synth. Commun.* **1985**, *15*, 527. (k) Liu, J.; Nakagawa, M.; Hino, T. *Tetrahedron* **1989**, *45*, 7729. (l) Viaud, M. C.; Rollin, P. *Tetrahedron Lett.* **1990**, *30*, 1417. (m) Iwao, M.; Motol, O. *Tetrahedron Lett.* **1995**, *36*, 5929.