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Addition-elimination of nitroalkanes to 3-phenacylideneoxindoles—direct method for the synthesis of 3-alkenylphenacylidene-oxindoles

Yu-Xuan Fu, Shan-Shan Hu, Shao-Yi Li, and Xiao-Juan Li

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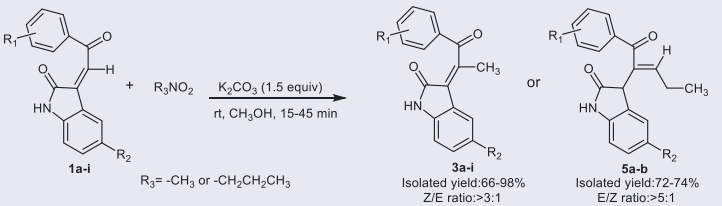
ABSTRACT

The first addition-elimination of nitroalkanes to 3-phenacylideneoxindoles was developed, affording the corresponding 3-alkenylphenacylidene-oxindoles with high yields.The addition-elimination mechanism of 3-phenacylideneoxindoles with nitroalkanes and removable NO_2 group in concert guarantees the high regioselectivity.

GRAPHICAL ABSTRACT



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KEYWORDS
Addition-elimination; nitroalkanes; 3-phenacylideneoxindoles

Introduction

3-phenacylideneoxindoles which can be easily derived from condensation of isatins with acetophenones,[1–3] have received wide concerns along with developments of isatin chemistry.[4–7] 3-phenacylideneoxindoles play an important role in rapid construction of molecule diversity indole derivatives[8–10] such as spiro oxindoles,[11] 3,3-substituted indoles.[12–16] But the synthesis of 3-alkenylphenacylideneoxindoles might be still in its beginning stage. Chao-Guo Yan reported the first example of synthesizing 3-alkenylphenacylideneoxindoles by substitution of 3-phenacylideneoxindoles with N-ethoxycarbonylmethylpyridinium bromide,[17,18] later they revealed the preparation of dispirocyclopentyl-3,3'-bisoxindoles by cyclization of 3-phenacylideneoxindoles with nitromethane in the presence of DBU.[19] It is well known that nitroalkanes undergo base-catalyzed 1,4-addition to various α,β-unsaturated carbonyl compounds.[20] However, if the nitro group is present in a suitable position on the substrate, it could act as a leaving group and subsequent elimination of nitrous acid from the Michael

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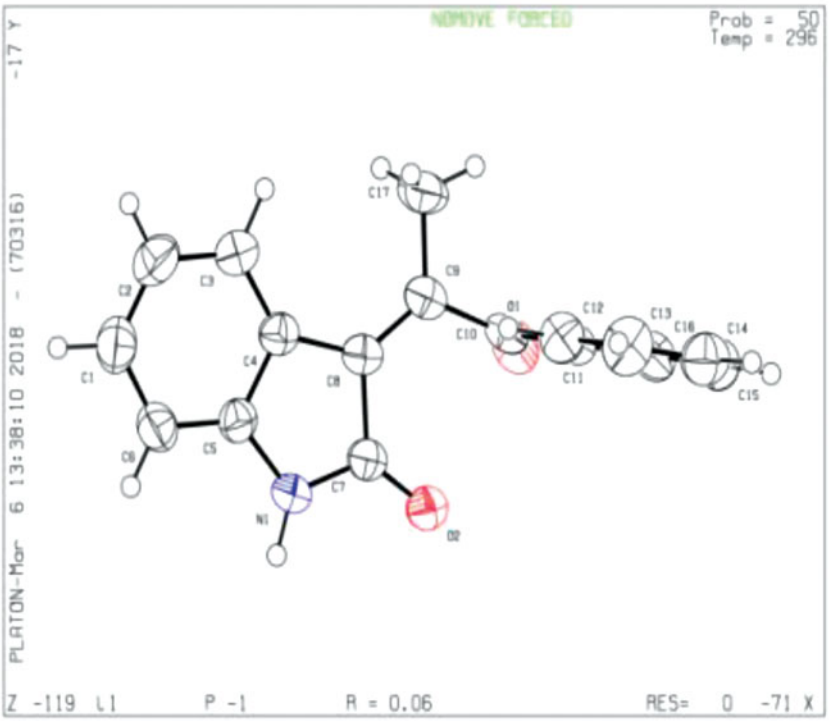


Figure 1. Crystal X-ray diffraction of compound **3a**.

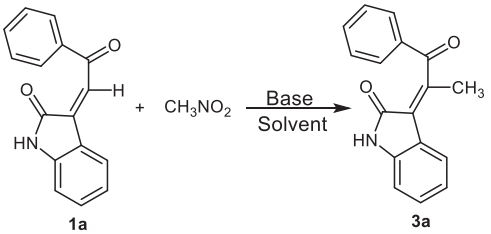
adduct.[21–25] Herein, we report 1,4-conjugate addition of 3-phenacylideneoxindoles with nitroalkanes followed by elimination of nitrous acid, affording 3-alkenylphenacylidene-oxindoles conveniently with 66-98% yields under mild conditions in the presence of a weak base.

Results and discussion

The reactions of 3-phenacylideneoxindoles with nitromethane in presence of weak bases were examined, affording 3-alkenylphenacylidene-oxindoles with good yields under room temperature. The structures of the prepared 3-alkenylphenacylidene-oxindoles **3a**–**i**, **5a**–**b** were characterized with spectroscopic methods (^{1}H and ^{13}C NMR, IR, HRMS) and confirmed by the X-ray diffraction of single crystal **3a** (Figure 1).

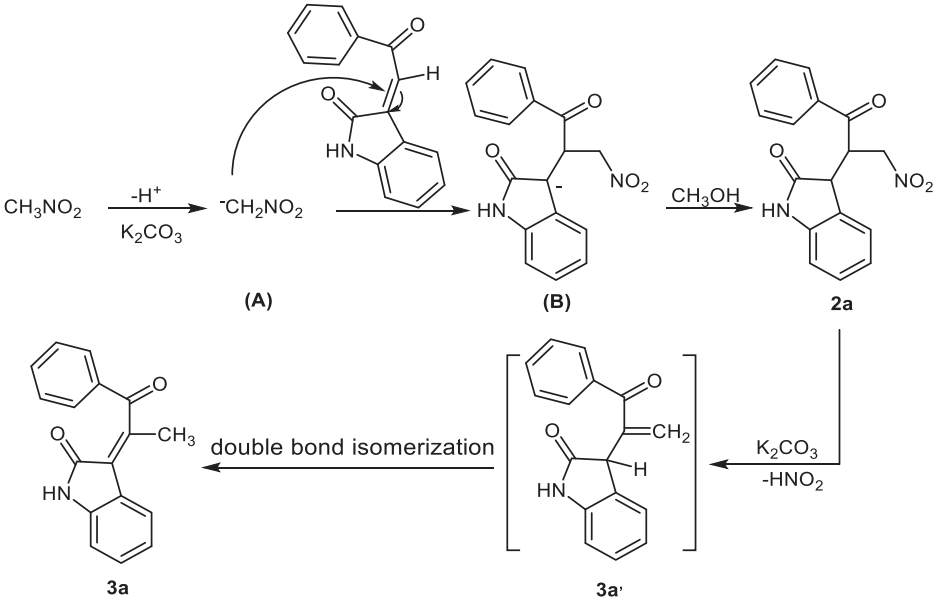
Initially, 3-phenacylideneoxindole **1a** and nitromethane were selected as the model substrates (Table 1). Although the reaction proceed slowly in the presence of 1.5 equiv. of $NaHCO_3$ in methanol (Table 1, entry 1), the expected 3-alkenylphenacylidene-oxindoles **3a** was isolated in 65% yield. To our delight, after checking the effects of different bases such as K_2CO_3, Na_2CO_3 for this reaction, we found that 1.5 equiv. of K_2CO_3 were sufficient to promote this reaction, and the yield of the desired product increased to 83% (Table 1, entry 3). We further explored the reaction in various solvents, and methanol was demonstrated as the best choice. The reaction was sensitive to temperature, lower temperature prolonged reaction time (Table 1, entry 6).

Table1. Optimization of reaction conditions.



Entry	Base	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	$NaHCO_3$, 1.5 equiv.	Methanol	Rt	16	65
2	Na_2CO_3, 1.5 equiv.	Methanol	Rt	8	79
3	K_2CO_3, 1.5 equiv.	Methanol	Rt	0.75	83
4	K_2CO_3, 1.0 equiv.	Methanol	Rt	2	78
5	K_2CO_3, 2.0 equiv.	Methanol	Rt	0.75	71
6	K_2CO_3, 1.5 equiv.	Methanol	0	16	46
7	K_2CO_3, 1.5 equiv.	CH_2Cl_2	Rt	8	64
8	K_2CO_3, 1.5 equiv.	Ethanol	Rt	0.75	72
9	K_2CO_3, 1.5 equiv.	CH_3CN	Rt	16	75

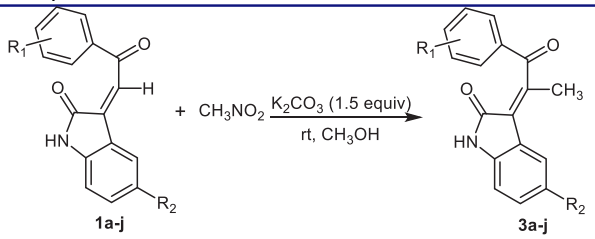
[a]The reactions were performed with **1a** (0.20 mmol, 1.0 equiv.) and nitromethane (0.20 mmol, 1.0 equiv.) in the presence of base in 4 mL methanol, under room temperature.
[b]Isolated yield.



Scheme 1. Possible mechanism for the formation of compound **3a**.

The preliminary investigation revealed that an alkane intermediate **2a** (separated and characterized by ^1H and ^{13}C NMR, HRMS, IR) formed in 5 min, then converted into the stable compound **3a** completely within 0.5 h (Scheme 1). To our surprise, dispirocyclopentyl-3,3'-bisoxindole did not appear in this reaction system. It should be pointed out that the intermediate **2a**, which performed relatively stable in dilute hydrochloric

Table 2. Synthesis of compounds **3a–i**.



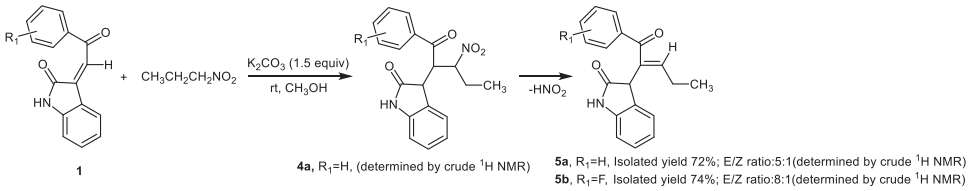
Entry	Product[a]	R_1	R_2	Yield[b] (%, Z/E ratio[c])
1	**3a**	H	H	83(8:1)
2	**3b**	*P*-CH_3	H	78(7:1)
3	**3c**	*P*-OCH_3	H	83(3:1)
4	**3d**	*p*-Cl	H	83(3:1)
5	**3e**	*p*-F	H	83(4:1)
6	**3f**	*o*-CH_3	H	98(7:1)
7	**3g**	*o*-F	H	66(4:1)
8	**3h**	*m*-Cl	H	97(4:1)
9	**3i**	H	F	71(4:1)
10	**3j**	H	OCH_3	Trace

[a]Reaction condition: 3-phenacylideneoxindoles (0.20 mmol), CH_3NO_2 (0.20 mmol), K_2CO_3 (0.30 mmol) in CH_3OH (4.0 mL), room temperature, within 45 min.
[b]Yield of pure, isolated product. [c]The Z/E ratio was determined by crude ^1H NMR.

acid under room temperature, transformed into product **3a** completely in presence of equal molar K_2CO_3 within 45 min. When a catalytic amount (30–50%) base was used, the transformation of **2a** to **3a** took longer time.

Based on the conjugate addition of nitroalkanes to electron-poor alkenes[21–23] a plausible mechanism for the formation of compound **3a–i** is proposed, shown as Scheme 1. Firstly, deprotonation of nitromethane with K_2CO_3 afforded the desired carbanion **(A)**. Secondly, Michael addition of carbanion **(A)** to the exocyclic double bond of 3-phenacylideneoxindole **1a** gives additional intermediate **(B)**. The proton transfer gave an alkane intermediate 2a, which can be separated and characterized by spectroscopic methods (^1H and ^{13}C NMR, IR, HRMS). The elimination of nitrous acid affording unsaturated derivative **3á**, followed by the double bond isomerization (through proton migration) gave compound **3a** as the final product. The reactions afforded a mixture of Z/E isomers, while thermodynamically stable Z isomer would be preferentially formed in this sequential reaction (Table 2, entries 1–8: Z/E isomers > 3:1).

After carefully testing various factors such as base, solvent, temperature, and molar ratio of substrates and base, we were pleased to find that the best reaction conditions is the 4 mL methanol solution of 3-phenacylidneoxindole (0.20 mmol) and nitromethane (0.20 mmol) in the presence of K_2CO_3 (0.30 mmol) at room temperature. Under the optimized conditions, the substrate scope was evaluated. All tested 3-phenacyclideneoxindoles underwent the addition-elimination reaction with nitromethane smoothly, affording the corresponding 3-alkenylphenacylidene-oxindoles **3a–h** with good to excellent yield. The electronic nature and the position of the substituents on oxindole backbones or benzoyl groups had little influence on both the yields and the stereoselectivities (Table 2, entries 1–8: yield > 66%, Z/E isomers > 3:1). Unfortunately, the substituents on oxindole backbone had a detrimental effect on the reaction (Table 2, entry 9 and 10). When the substituent on oxindole backbone (R_2) is an electron



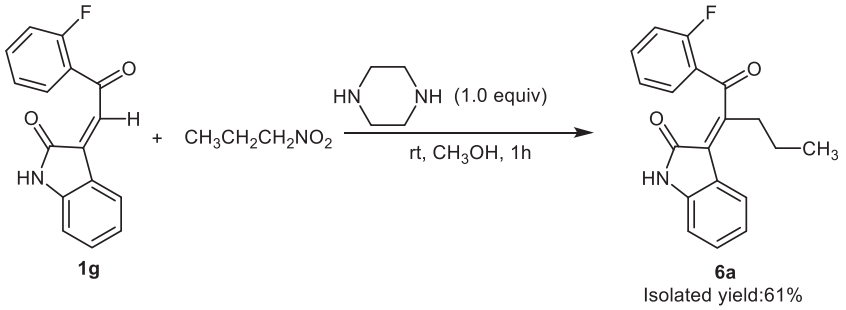
Scheme 2. Reactions of 3-phenacylideneoxindoles and 1-nitropropanes.

withdrawing group, the product **3i** (Table 2, entry 9) is directly obtained in profitable yields (71%), whereas, the product **3j** (Table 2, entry 10) expressed only trace amounts when R_2 is an electron-donating group. It seemed that the electron-donating group on oxindole backbone, such as $-OCH_3$, decreased the reactivity of double bond as Michael acceptors and prevented the addition-elimination reaction.

With methyl substituents on exocyclic C = C double bond, products **3a–i** seemed to be the next higher homologs of starting material 3-phenacylideneoxindoles. ^{1}H NMR spectra of crude compounds indicated that a mixture of major isomer and minor isomer existed in the most samples. For examples, the Z/E isomers with about 8:1 molecular ratio existed in crude product **3a** (Table 2, entry 1). The structure of representative compound **3a** was further confirmed by single crystal X-ray diffraction. It can be seen that the carbonyl group of ketone and carbonyl group of oxindole moiety existed in cis-configuration (Figure 1), which also suggested that the Z isomer of compounds **3a** was the major isomer. ^{1}H NMR spectrum of compound **3a–i** indicated that CH_3 unit of Z isomers showed single peaks between 2.45–2.51 ppm, while the CH_3 unit of E isomers displayed a singlet between 2.61–2.67 ppm. For example, in the ^{1}H NMR spectrums of single Z/E configuration of compound **3c**, the CH_3 units in Z isomer and E isomer display one singlet at 2.45 and 2.75 ppm respectively. Purification by flash column chromatography and recrystallization in methanol, single Z isomers of compound **3a–i** were obtained as final products.

In order to further develop the applicability of this reaction, 1-nitropropane was used to react with 3-phenacylideneoxindoles. To our surprise, compounds **5a–b** (separated and characterized by ^{1}H and ^{13}C NMR, IR, HRMS) were obtained under similar reaction conditions[a] in good yields (Scheme 2). The electron withdrawing group on the 3-phenacylideneoxindoles seemed to be necessary for the reaction. In the ^{1}H NMR spectrum of compound **5b**, the C = C–H units in E isomer and Z isomer display one triplet at 6.66–6.69 and 5.38–5.42 ppm, respectively. ^{1}H NMR spectrum of compound **5a** indicated that C = C–H unit of E isomers showed triple peaks between 6.65–6.69 ppm, while the C = C–H unit of Z isomers displayed triple peaks between 6.33–6.37 ppm. ^{1}H NMR spectra of crude product indicated that E isomer predominately existed in the prepared samples (E/Z ratio > 5:1). Single E isomer was obtained as final product after purification by flash column chromatography and recrystallization in methanol.

Structure of the compounds **5a–b**, in which the C = C double bond exists in 3,4-positions of α,β-unsaturated ketone system,[26] are different with **3a–i**. For example, 3-phenacylideneoxindole reacts with 1-nitropropane in the presence of K_2CO_3 to give Michael adduct **4a** that suffer elimination of nitrous acid affording unsaturated derivatives **5a** in good yield.



Scheme 3. Reactions of 3-phenacylideneoxindoles and 1-nitropropane in the presence of piperazine.

Weak base plays a crucial role in the addition-elimination of 3-phenacylideneoxindoles with 1-nitropropane. Notably, the unexpected unsaturated derivatives **6a** with exocyclic C = C double bond was obtained in moderate yield (Scheme 3) in the presence of piperazine. Electron-withdrawing substituent on benzoyl group seemed to be necessary for the reaction.

Experimental

General procedure for preparing 3-alkenylphenacylidene-oxindoles 2a, 3a–i, 4a, and 5a–b

K_2CO_3 (0.30 mmol) was added to a solution of 3-phenacylideneoxindole **1a–i** (0.20 mmol) and nitroalkane (0.20 mmol) in methanol (4 mL) at room temperature. When the reaction was complete (TLC), 10 mL sat. aq. NH_4Cl was added and the mixture was extracted with EtOAc (3 × 10 mL). The organic layer was combined, washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by column chromatography (silica gel) and recrystallization in methanol.

(Z)-3-(1-oxo-1-phenylpropan-2-ylidene)indolin-2-one 3a

Yellow solid. m.p: 198-199 °C. **IR** (KBr): 3137, 3026, 1706, 1469, 1344, 1235, 1104, 961, 773, 695 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 8.79(s, 1H), 7.94-7.92(d, 2 H, J = 8.0Hz), 7.58-7.54(t, 2 H, J_1=8.0Hz, J_2=16.0Hz), 7.46-7.43(t, 2 H, J_1=8.0Hz, J_2=12.0Hz), 7.23-7.19(t, 1 H, J_1=8.0Hz, J_2=16.0Hz), 7.06-7.02(t, 1 H, J_1=8.0Hz, J_2=16.0Hz), 6.65-6.63(d, 1 H, J = 8.0Hz), 2.46(s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 198.9, 167.8, 147.6, 142.2, 134.7, 133.5, 129.6, 128.8, 128.7, 126.4, 124.0, 122.1, 122.0, 110.6, 18.7. HRMS (ESI) calcd. for $C_{17}H_{12}O_2N$ ([M-H])$^+$ requires m/z 262.0868. Found m/z 262.0866.

(E)-3-(1-oxo-1-phenylpent-2-en-2-yl)indolin-2-one 5a

White solid. m.p: 157-158 °C. **IR** (KBr): 3191, 3082, 1717, 1651, 1472, 1316, 1218, 975, 751, 646, 579 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 8.15(s, 1H), 7.68-7.66(d, 2 H, J = 8.0Hz), 7.53-7.49(t, 1 H, J_1=8.0Hz, J_2=16.0Hz), 7.43-7.40(m, 2H), 7.21-7.17(t, 1 H, J_1=8.0Hz, J_2=16.0Hz), 7.06-7.04(d, 1 H, J = 8.0Hz), 6.98-6.94(t, 1 H, J_1=8.0Hz, J_2=16.0Hz), 6.90-6.88(d, 1 H, J = 8.0Hz), 6.71-6.67(t, 1 H, J_1=8.0Hz, J_2=16.0Hz),

4.71(s, 1H), 2.41(s, 2H), 1.15-1.11(t, 3 H, J_1=8.0Hz, J_2=16.0Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.3, 177.9, 152.4, 141.8, 137.8, 136.3, 131.8, 129.5, 128.9, 128.2, 128.1, 123.1, 122.3, 109.8, 46.0, 23.0, 13.4. HRMS (ESI) calcd. for $C_{19}H_{16}O_2N$ $([M-H])^+$ requires m/z 290.1181. Found m/z 290.1178.

Procedure for the preparation of 6a

To a stirred mixture of 3-phenacylideneoxindoles **1g** (0.20 mmol) and 1-nitropropane (0.20 mmol) in methanol (4 mL), a catalytic amount of piperazine (0.20 mmol) was added. The reaction mixture was stirred at room temperature and monitored by TLC. After the reaction, the mixture was extracted with EtOAc (3 × 5 mL), washed with brine, dried with Mg_2SO_4 and then concentrated. The crude product was further purification by column chromatography with 1:5 ethyl acetate and recrystallization in methanol.

Conclusions

In summary, a special kind of 3-alkenylphenacylidene-oxindoles, in which alkyl exist at the newly formed C = C double bond positions, were conveniently prepared in 66-98% yields by addition-elimination of nitromethane with 3-phenacylideneoxindoles in the presence of a weak base. The reactions have advantages of readily available starting materials, good yields, and operational simplicity.

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