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Stereoselective cycloaddition of *N*-acyliminium cations with α,β-unsaturated ketones and esters

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Abstract

The cycloaddition of *N*-acyliminium cations with some deactivated alkenes such as α,β-unsaturate ketones and esters has been investigated. In most cases, the *N*-acyliminium cations produced from 3-hydroxy-2-arylisoindol-1-ones in the presence of $BF_3{\cdot}OEt_2$ could be reacted with α,β-unsaturated ketones and esters to afford stereoselectively the cycloaddition products 6-acylisoindolo[2,1-a]quinolin-11-ones in moderate to high yields.

Keywords: Cycloaddition; *N*-acyliminium cation; 3-Hydroxy-2-arylisoindol-1-one; α,β-Unsaturated ketones; 6-Acylisoindolo[2,1-a]quinolin-11-ones

N-acyliminium ions are known as important, reactive species in organic synthesis for the construction of carbon–carbon and carbon–heteroatom bonds [1]. Numerous examples of *N*-acyliminium cation cycloaddition and intramolecular cyclization can be found in the synthesis of alkaloid natural products [2]. It is noticed that the alkenes and arenes which could couple with *N*-acyliminium ions are often activated by electron-donating groups. Alkenes that are deactivated by carbonyl group and cyano group, even by virtue of one halogen substituent, usually do not participate with facility in *N*-acyliminium reactions [3]. Although the intramolecular reactions of *N*-acyliminium ions with unsaturated ester catalyzed by proton acid or Lewis acid could provide cyclization product in low yield [4a], but the intermediate was proposed to be enolate anion produced after the nucleophilic addition of iodide anion to α,β-unsaturated ester [4b]. No report has been found in literatures for the intermoleculer cycloadition of *N*-acyliminium ions with deactivated alkenes such as α,β-unsaturated ketones and esters.

As a part of our research program directed towards the synthesis of polycyclic heterocycles, we recently reported the synthesis of 5-aryl-5,6,6a,12-tetrahydro-isoindolo[2,1-a]quinlin-11-ones and 5-aryl-3a,9a-dihydro-pyrrolo[2,1-a]quinolin-1-ones by the [4+2] reactions of *N*-acyliminium ions with electron-rich alkenes [5]. It was found that the cycloaddition reactions of the *N*-acyliminium ions produced from 3-hydroxy-2-arylisoindol-1-ones and 5-hydroxy-1-arylpyrrol-2-ones in the presence of $BF_3{\cdot}OEt_2$ with electron-rich alkenes were generally finished in a few minutes to produce the mixtures of two or three stereoisomers. In our further study, we tried the reaction of *N*-acyliminium ions with somedeactivated alkenes such as α,β-unsaturated ketones or esters. We found that the *N*-acyliminium ions,

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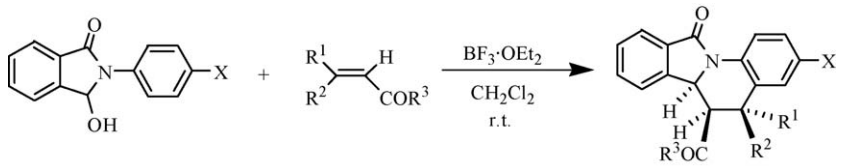


1a-e 2a-g 3a-l

Scheme 1. Reactions of 3-hydroxy-2-arylisoindol-1-ones with α,β-unsaturated ketones or esters.

produced from 2,3-dihydro-3-hydroxy-2-arylisoindol-1-one (**1a–e**) in the presence of $BF_3{\cdot}OEt_2$, could also react with some deactivated alkenes such as mesityloxide (**2a**), 4-aryl-3-buten-2-ones (**2b–d**) and methyl cinnamate (**2e**) to give the cycloaddition products isoindolo[2,1-a]quinolinones as shown in Scheme 1, but the cycloaddition reaction rate was much slow in comparison with that of *N*-acyliminium ions with electron-rich alkenes [5].

1. Experimental

To a solution of the 3-hydroxy-2-phenylisoindol-1-one (**1a–e**) (2.0 mmol) and α,β-unsaturated ketones or esters (**2a–g**) (2.5 mmol) in 50 mL anhydrous methylene dichloride was added at room temperature $BF_3{\cdot}OEt_2$ (2.5 mmol) at one portion under stirring. After continued stirring at room temperature or refluxing for certain time until the **1a–e** disappeared (monitored by TLC), the reaction was quenched with an aqueous solution of sodium carbonate. The organic phase was washed with water and dried over anhydrous sodium sulfate. After the solvent was removed under reduced pressure the residue was separated on silica gel column eluted with chloroform and hexane (1:6, v/v) to give products **3a–l**.

2. Results and discussion

It could be noticed from Table 1 that only **1a** and **1b** could be reacted with mesityloxide (**2a**) to afford **3a** and **3b** in high yields at room temperature, while **1d** and **1e** did not react with **2a** even under refluxing condition because the presence of electron-withdrawing group (–Cl and $–NO_2$) at *para* position of 2-phenyl group in **1d** and **1e**. When **2a** was

Table 1
Reactions of 3-hydroxy-2-arylisoindol-1-ones with α,β-unsaturated ketones and esters.

Entry	Reactants						*t* (h)	*T* (°C)	Product	Yield[a] (%)
		X		R^1	R^2	R^3				
1	**1a**	H	**2a**	Me	Me	Me	8	r.t.	**3a**	60
2	**1b**	Me	**2a**	Me	Me	Me	8	r.t.	**3b**	63
3	**1c**	OMe	**2a**	Me	Me	Me	12	Reflux	–[b]	–[b]
4	**1d**	Cl	**2a**	Me	Me	Me	12	Reflux	–[b]	–[b]
5	**1e**	NO_2	**2a**	Me	Me	Me	12	Reflux	–[b]	–[b]
6	**1a**	H	**2b**	Ph	H	Me	5	r.t.	**3c**	72
7	**1b**	Me	**2b**	Ph	H	Me	5	r.t.	**3d**	72
8	**1c**	OMe	**2b**	Ph	H	Me	12	Reflux	–[b]	–[b]
9	**1d**	Cl	**2b**	Ph	H	Me	5	r.t.	**3e**	76
10	**1e**	NO_2	**2b**	Ph	H	Me	5	Reflux	**3f**	70
11	**1f**	H	**2c**	4-$MeOC_6H_4$	H	Me	5	r.t.	**3g**	75
12	**1g**	H	**2d**	3,4-$(MeO)_2C_6H_3$	H	Me	3	r.t.	**3h**	85
13	**1a**	H	**2e**	Me	H	OMe	12	Reflux	–[b]	–[b]
14	**1a**	H	**2f**	Me	Me	OMe	12	Reflux	–[b]	–[b]
15	**1b**	H	**2g**	Ph	H	OMe	5	r.t.	**3i**	75
16	**1c**	Me	**2g**	Ph	H	OMe	5	r.t.	**3j**	73
17	**1d**	Cl	**2g**	Ph	H	OMe	5	r.t.	**3k**	71
18	**1e**	NO_2	**2g**	Ph	H	OMe	8	r.t.	**3l**	66

[a] Isolation yields based on **1a–e**.
[b] No reaction detected.

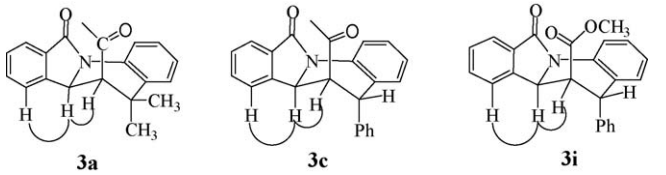
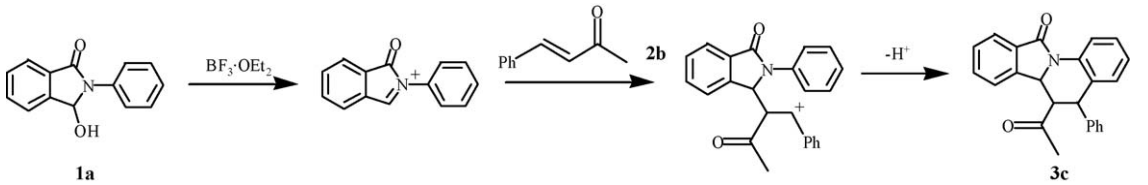


Fig. 1. NOE correlations of the **3a**, **3c** and **3i**.



Scheme 2. The proposed mechanism of cycloaddition reaction.

replaced by 4-phenyl-3-buten-2-ones (**2b**), it was found the reactions of **1a**, **1b**, **1d** and **1e** with **2b** could all give the normal products **3c–f** at room temperature or under refluxing in high yields except **1c**. Obviously, phenyl at β-position of α,β-unsaturated ketone in **2b** has greater stabilization effect to the carbocations produced after addition of *N*-acyliminium cation to double bond of **2b** than that of methyl in **2a**. The electron-donating groups on phenyl groups in **2c** and **2d** seemed more helpful to enhance both reaction rate and the yields of cycloaddition products. This effect could also be observed from the different results of reactions of **1a** with methyl crotonate (**2e**), methyl 3-methylcrotonate (**2f**) and methyl cinnamate (**2 g**). No reaction took place between **1a** and crotonate (**2e**) or methyl 3-methylcrotonate (**2f**) after prolonged heating in the presence of $BF_3{\cdot}OEt_2$, while the cycloaddition reaction between **1a** and methyl cinnamate (**2 g**) could proceed smoothly to afford **3i**. It has been also found that the cycloaddition reactions of **2 g** with **1d** and **1e** were not affected by Cl or NO_2 groups on *para* position of 2-phenyl group in **1d** and **1e**.

The cycloaddition reaction occurred with complete regio and stereoselectivity to give only one isomer in each reaction in moderate to high yields as listed in Table 1. The products were fully characterized by ^1H, ^{13}C NMR, MS and NOE correlation [6]. For example, the chemical shifts of H-1 in all products (**3a–l**) are 8.5–9.0 ppm which can be taken as a signal for cyclization because they are much higher than those in reactants **1a–e**; the chemical shifts and peak shapes of H-5, H-6 and H-6a in all products **3a–l** are similar to each other. The *cis* orientation of the H-6 and H-6a in **3a** was assigned by the significantly smaller vicinal coupling constants $J_{6-6a} = 4.0$ Hz typical for a gauche conformation of H-6 and H-6a and confirmed by NOE correlation (Fig. 1); the *anti* orientation of H-5 and H-6 in **3c–l** was assigned by NOE correlation because the peak of H-5 is singlet in ^1H NMR of products **3a–l** indicating no coupling effect can be observed between H-5 and H-6.

The plausible reaction mechanism can be visualized as initial dehydroxylation of 3-hydroxy-2-arylisoindol-1-one **1a–e** by $BF_3{\cdot}OEt_2$ to produced *N*-acyliminium cation followed by electrophilic attack of *N*-acyliminium cation to α,β-unsaturated ketones and ester, leading to new carbocations. Then, the intramolecular Friedel-Crafts reaction of carbocations affords 6-acylisoindolo[2,1-a]quinolin-11-one **3a–l** (Scheme 2).

Acknowledgment

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References

[1] (a) B.E. Maryanoff, Han-cheng Zhang, J.H. Cohen, I.J. Turchi, C.A. Maryanoff, Chem. Rev. 104 (2004) 1431;
(b) J. Royer, M. Bonin, L. Micouin, Chem. Rev. 104 (2004) 2311.
[2] (a) F. He, Y. Bo, J.D. Altom, E.J. Corey, J. Am. Chem. Soc. 121 (1999) 6771;
(b) H. Hiemstra, W.N. Speckamp, The Alkaloids, vol. 32, Academic Press, 1988, p. 271;
(c) L.R. Jin, J.L. Ye, Y. Xie, J.H. Shi, P.Q. Huang, Chin. Chem. Lett. 10 (1999) 543;
(d) P.Q. Huang, S.L.O.X.Z. Wang, J.L. Ye, L.R. Jin, Chin. Chem. Lett. 10 (1999) 735.

[3] (a) A. Padwa, A.G. Waterson, J. Org. Chem. 65 (2000) 235;
(b) H. Heaney, M.O. Taha, Tetrahedron Lett. 39 (1998) 3341;
(c) J.P. Gesson, J.C. Jacquesy, D. Rambaud, Tetrahedron 49 (1993) 2239;
(d) A.W. Lochead, G.R. Proctor, M.P.L. Caton, J. Chem. Soc., Perkin Trans. 1 (1984) 2477;
(e) B.P. Wijnberg, W.N. Speckamp, Tetrahedron Lett. 22 (1981) 5079;
(f) J.B.P.A. Wijnberg, W.N. Speckamp, Tetrahedron 34 (1978) 2579.
[4] (a) K.H. Meching, H. Hiemstra, W.J. Klaver, W.N. Spechamp, Tetrahedron Lett. 27 (1986) 4799;
(b) D.F. Taber, R.S. Hoerrner, M.D. Hagen, J. Org. Chem. 56 (1991) 1287.
[5] (a) W. Zhang, A. Zhen, A.Z. Liu, L. Yang, Z.L. Liu, Tetrahedron Lett. 46 (2005) 5691;
(b) W. Zhang, L. Huang, J. Wang, Synthesis (2006) 2053.
[6] Spectral data for products. **3a**: ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 1.44 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 1.63 (s, 3H, CH_3), 3.34 (d, 1H, J = 4.0 Hz), 5.13 (d, 1H, J = 4.0 Hz), 7.15–7.19 (m, 1H), 7.32 (dd, 1H, J = 8.0, 1.2 Hz), 7.35–7.43 (m, 1H), 7.54 (t, 2H, J = 8.0 Hz,), 7.60–7.64 (m, 1H), 7.93 (d, 1H, J = 7.6 Hz), 8.62 (dd, 1H, J = 8.4, 1.2 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 27.0 (CH_3), 32.4 (*C*H), 35.1 (CH_3), 35.7 (CH_3), 55.7 (C), 60.2 (*C*H), 120.2 (*C*H), 122.1 (*C*H), 122.2 (*C*H), 124.5 (*C*H), 126.2 (*C*H), 127.0 (*C*H), 129.1 (*C*H), 132.2 (*C*H), 132.8 (*C*), 133.1 (*C*), 134.9 (*C*), 141.5 (*C*), 166.2 (*C*═O), 206.2 (*C*═O). EIMS (*m*/*z* %): 305 (M^+, 7), 282 (6), 232 (19), 208 (100). **3e**: ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 1.75 (s, 3H, CH_3), 3.50–3.51 (m, 1H), 4.62 (s, 1H), 4.93 (d, 1H, J = 3.6 Hz), 7.08–7.11 (m, 3H), 7.29–7.40 (m, 5H), 7.48–7.60 (m, 2H), 7.92 (d, 1H, J = 7.2 Hz), 8.74 (d, 1H, J = 8.7 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 30.9 (CH_3), 44.8 (*C*H), 54.4 (*C*H), 55.4 (*C*H), 120.8 (*C*H), 121.9 (*C*H), 124.6 (*C*H), 126.8 (*C*H), 127.4 (*C*H), 128.1 (*C*H), 128.6 (2*C*H), 129.1 (2*C*H), 129.1 (*C*), 129.2 (*C*H), 130.2 (*C*H), 132.4 (*C*), 132.9 (*C*), 135.4 (*C*), 141.6 (*C*), 144.2 (*C*), 166.3 (*C*═O), 204.6 (*C*═O). EIMS (*m*/*z* %): 387 (M^+, 2), 344 (27), 266 (14), 43 (100).