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Synthesis of indene derivatives via reactions of vinylidenecyclopropanes with the *N*-acyliminium cations generated from hydroxylactams

Alexander V. Stepakov [a,*], Anna G. Larina [a], Vitaly M. Boitsov [b], Vladislav V. Gurzhiy [a], Alexander P. Molchanov [a], Rafael R. Kostikov [a]

[a] *Chemistry Department, Saint-Petersburg State University, Universitetsky prosp. 26, St-Petersburg 198504, Russian Federation*
[b] *Saint-Petersburg Academic University—Nanotechnology Research and Education Centre RAS, Khlopin Str. 8/3, St-Petersburg 194021, Russian Federation*

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ABSTRACT

A novel route for the synthesis of 1*H*-indene derivatives via the reactions of vinylidenecyclopropanes (VCPs) with the *N*-acyliminium cations generated from hydroxylactams is described.

The 1*H*-indene subunit appears in compounds displaying a considerable range of biological activity: cyclooxygenase-2 (COX-2) inhibitors,[1] oxytocin antagonists,[2] estrogen receptor modulators,[3] an 5-HT6 serotonin receptor[4] and in compounds with antiproliferative activity.[5] Indene derivatives are also used as precursors of metallocene complexes for catalytic polymerization processes and as functional materials.[6] Consequently, a number of approaches to the synthesis of the indene ring system have been developed, including new methods such as intramolecular cyclization of tetraaryl substituted 1,3-butadienes,[7] cycloaddition of methylenecyclopropanes with acetals,[8] cycloisomerizations of alkynes,[9] annulation of benzylic alcohols with alkynes,[10] rearrangement of *ortho*-(alkynyl)styrenes,[11] and cycloisomerization of arylvinylcyclopropenes.[12] Tsuji and co-workers have reported a novel synthetic method for the preparation of indenes by the reaction of aliphatic ketones with aryl-substituted alkynes in the presence of $NbCl_3$(DME)[13]

The chemistry of vinylidenecyclopropanes has been explored extensively. Novel intramolecular rearrangements and cycloaddition reactions have been studied.[14,15] However, reactions of vinylidenecyclopropanes with *N*-acyliminium cations have not been previously studied. *N*-Acyliminium ions are known as important reactive species in organic synthesis for the construction of carbon–carbon bonds.[16] Numerous examples of *N*-acyliminium ion based intramolecular cyclizations can be found in the synthesis of alkaloid derivatives.[17] Recently, Wang and Zhang reported the first examples of the Lewis acid catalyzed [4+2] cycloaddition reactions of *N*-acyliminium ions with alkenes.[18] In continuation of our earlier work,[19] we have studied the reactions of non-activated vinylidenecyclopropanes (VCPs) with *N*-acyliminium cations. In the present work we show for the first time that 1-(2-methylpropenylidene)-2,2-diarylcyclopropanes react with the *N*-acyliminium cations generated from hydroxylactams to give the corresponding 5-[2-methyl-1-(3-Ar^1-1*H*-inden-2-yl)prop-1-enyl]-1-Ar^2-1*H*-pyrrol-2(5*H*)-ones and 3-[2-methyl-1-(3-Ar^1-1*H*-inden-2-yl)prop-1-enyl]-2-Ar^2-isoindolin-1-ones in moderate yields. Of the Lewis acids and solvents screened, the combination of $BF_3·OEt_2$ and dichloromethane produced the best results in these reactions.

In our initial studies, the reaction of **1a** with VCP **2a** was investigated. Under a nitrogen atmosphere, compound **1a** was reacted with an equimolar amount of **2a** in the presence of $BF_3·OEt_2$ (1.0 equiv) in CH_2Cl_2 at ambient temperature for one hour, to give 3-{2-methyl-1-[6-methyl-3-(4-methylphenyl)-1*H*-inden-2-yl]prop-1-en-1-yl}-2-phenylisoindolin-1-one (**3a**) in 41%

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* Corresponding author. Fax: +7 812 4286939.
E-mail address: alstepakov@yandex.ru (A.V. Stepakov).

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isolated yield (Table 1, entry 1). Although several other products could be seen in the TLC analysis of the reaction mixture, no other potential products were successfully isolated. When the reaction of **1a** with VCP **2a** was carried out at low temperature (−20 °C), the corresponding indene **3a** was produced in 36% yield. Under refluxing conditions, product **3a** was isolated in only 14% yield. The reactions of hydroxylactams **1** with VCPs **2** were carried out in dichloromethane under similar conditions to those described previously (Table 1). The reactions proceeded smoothly to give the corresponding indene derivatives **3** in moderate yields at room temperature. The presence of either electron-donating or electron-withdrawing substituents on the benzene ring of the VCPs **2** had only a slight effect upon the yields of the produced indenes **3**. For example, decreased yields of the indenes **3** were obtained by using VCPs **2** with electron-donating groups (MeO) on the benzene ring (Table 1, entries 2 and 4). The presence of electron-donating or electron-withdrawing groups on the phenyl ring of the hydroxylactams **1** also had a minor effect upon the yields of the produced indenes **3**. 2-[Bis(4-methoxyphenyl)methylene]-5,5-dimethyldihydrofuran-3(2*H*)-one (**4**) was isolated in 7–9% yields as the side product in all the cases of the reactions with bis(4-methoxyphenyl)vinylidenecyclopropane (**2d**). In cases where R^1 was a phenyl group, or R^2 a methyl group (VCPs **2e–g**), complicated reaction mixtures were formed under the standard conditions (Table 1, entries 10–12). Dihydrofuranone **4** is the oxidation product of VCP **2d**; its formation might occur either due to aerial oxygen or during chromatographic separation. The exact reaction mechanism for the formation of **4** is still not clear. Using degassed solvent resulted in only a slight decrease of the amount of **4** in the reaction mixture. The reaction of **2d** with $BF_3{\cdot}OEt_2$ in CH_2Cl_2 resulted in the formation of dihydrofuranone **4** in 23% yield. Formation of analogous products **4** was not observed from VCPs **2a–c**. The compositions and structures of the products **3** and **4** were established by elemental and spectral analyses. The structures of compounds **3c** and **4** were confirmed by X-ray diffraction analysis (Figs. 1 and 2).[20,21] The single crystal of **3c** clearly showed that the aryl group on the indene segment and the aryl ring of the phthal-

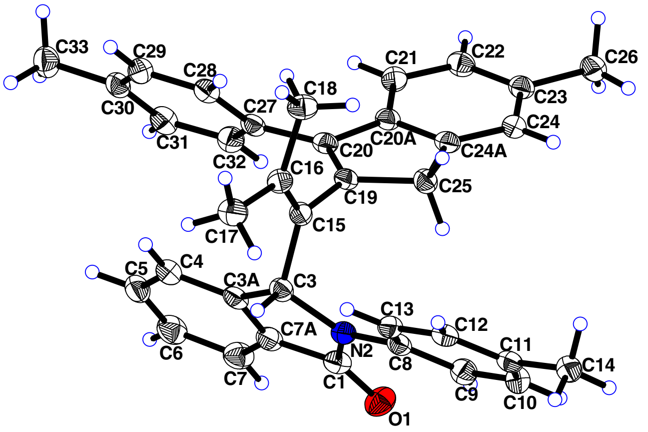


Figure 1. ORTEP representation of **3c**.

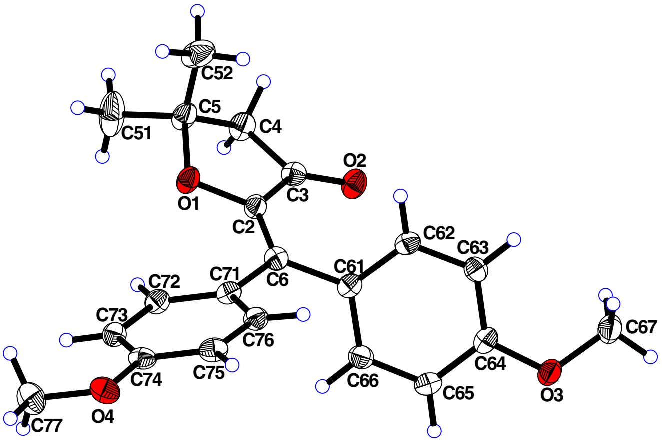
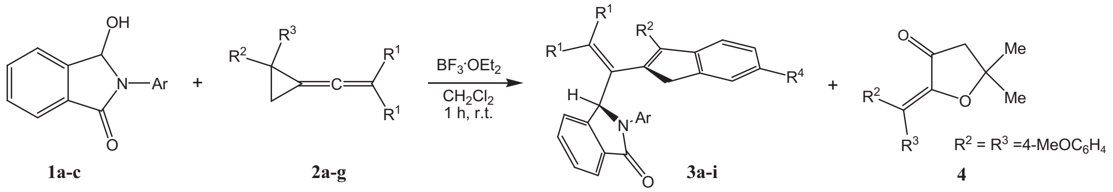


Figure 2. ORTEP representation of **4**.

Table 1
Reactions of hydroxylactams **1a–c** with vinylidenecyclopropanes **2a–d**



Entry	Ar	R^1	R^2	R^3	R^4	Yield of **3**[a] (%)
1	Ph (**1a**)	Me	4-MeC_6H_4	4-MeC_6H_4 (**2b**)	Me	41 (**3a**)
2	Ph (**1a**)	Me	4-$MeOC_6H_4$	4-$MeOC_6H_4$ (**2d**)	MeO	32 (**3b**)[b]
3	4-MeC_6H_4 (**1b**)	Me	4-MeC_6H_4	4-MeC_6H_4 (**2b**)	Me	39 (**3c**)
4	4-MeC_6H_4 (**1b**)	Me	4-$MeOC_6H_4$	4-$MeOC_6H_4$ (**2d**)	MeO	29 (**3d**)[c]
5	4-MeC_6H_4 (**1b**)	Me	Ph	Ph (**2a**)	H	40 (**3e**)
6	4-ClC_6H_4 (**1c**)	Me	4-ClC_6H_4	4-ClC_6H_4 (**2c**)	Cl	66 (**3f**)
7	4-ClC_6H_4 (**1c**)	Me	Ph	Ph (**2a**)	H	43 (**3g**)
8	Ph (**1a**)	Me	4-ClC_6H_4	4-ClC_6H_4 (**2c**)	Cl	58 (**3h**)
9	4-MeC_6H_4 (**1b**)	Me	4-ClC_6H_4	4-ClC_6H_4 (**2c**)	Cl	44 (**3i**)
10	Ph (**1a**)	Me	Me	Ph (**2e**)	H	—[d]
11	Ph (**1a**)	Ph	Me	Ph (**2f**)	H	—[d]
12	Ph (**1a**)	Ph	Ph	Ph (**2g**)	H	—[d]

[a] Isolated yield.
[b] 7% of **4** was also formed.
[c] 9% of **4** was also formed.
[d] A complicated reaction mixture was observed.