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SHORT COMMUNICATIONS

Noncatalytic destruction of 5-acylcomanic acid esters in the presence of 2-methylindoles as a new method for the synthesis of indolylchalcones

Dmitrii L. Obydennov[1]*, Ekaterina O. Pan'kina[1], Vyacheslav Ya. Sosnovskikh[1]

[1] *Institute of Natural Sciences and Mathematics,*
Ural Federal University named after the first President of Russia B. N. Yeltsin,
51 Lenina Ave., Yekaterinburg 620000, Russia; e-mail: dobydennov@mail.ru

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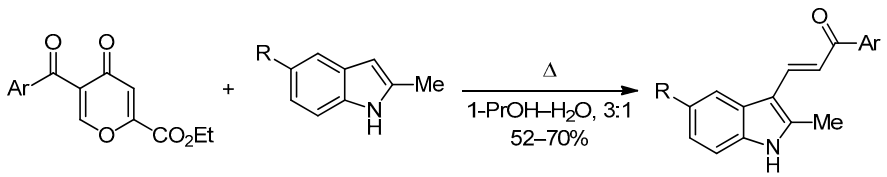


Ar = Ph, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-MeOC$_6$H$_4$, 2-Naphth, 2-thienyl; R = H, MeO

Ethyl esters of 5-acylcomanic acids reacted with 2-methylindoles in 3:1 propanol–water mixture in the absence of catalyst, resulting in pyrone ring opening and destruction of the molecular framework and leading to *trans*-indolylchalcones in 52–70% yields.

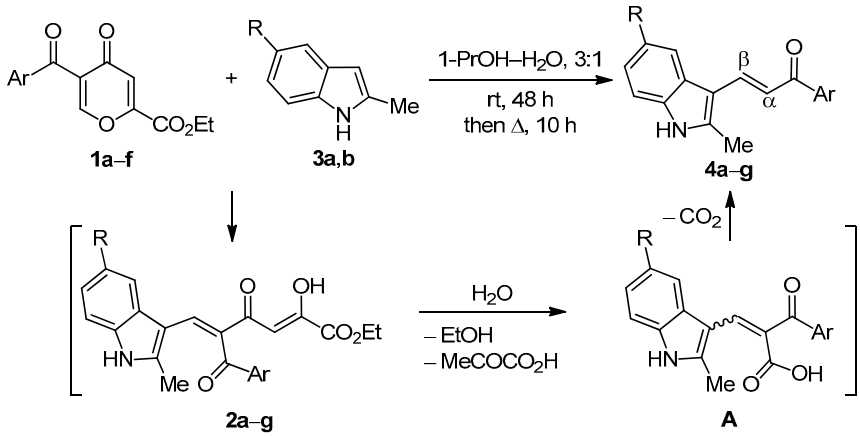
Keywords: chalcones, indoles, 4-pyrones, alkenylation, ring destruction.

Indolylchalcones (1-aryl-3-indolylprop-2-en-1-ones) are an important class of indole derivatives that attracts significant attention of researchers due to notable anticancer activity[1] and possibilities for use as synthetic intermediates.[2] The main method used for the preparation of these compounds is aldol condensation of indolecarbaldehydes with acetophenones.[1] New approaches have been actively explored over recent years, based on acid-catalyzed reactions of indoles with 1,3-diketones[3] or with enones containing a good leaving group at the β-position.[4] However, in contrast to indole alkylation and arylation reactions that have been relatively well developed,[5] there is very limited information available about direct alkenylation of indoles.[6]

We have recently demonstrated[7] that ethyl 5-acylcomanoates **1** react with indole, as well as with 1- and 2-methylindoles in ethanol in the presence of $MeSO_3H$, forming *Z*-indolyldiketohexenoates **2** over the temperature range from 0 to 60°C. During this study we found that performing the reaction of pyrones **1a**–**f** with 2-methylindole (**3a**) by prolonged heating in ethanol or hexafluoroisopropanol produced not only diketohexenoates **2a**–**f**, but also a small amount of *E*-indolylchalcones **4a**–**f** resulting from partial destruction of the molecular framework and isomerization relative to the C=C bond (Scheme 1). It should be noted that some 4-pyrone ring opening reactions are accompanied by cleavage of C–C bonds, but such processes usually occur in the presence of nucleophiles in either acidic[8a] or basic[8b] medium. For this reason, we were interested in a more detailed study of the conditions facilitating the tandem transformation of pyrones **1** by a reaction with 2-methylindole derivatives in the absence of any catalysts. This approach allowed us to develop an alternative method for the preparation of indolylchalcones **4** that are valuable compounds for medicinal chemistry efforts. Obviously, this reaction is not an example of atom-economical transformations, but it demonstrates a new type of reactivity for the highly active 5-acylcomanoates **1** and clearly deserves attention.

We established that the optimal procedure for the synthesis of chalcones **4a**–**g** starts with maintaining the appropriate 2-methylindoles **3a**,**b** and pyrones **1a**–**f** in a 3:1 propanol–H_2O mixture at room temperature for 2 days (pyrone ring opening occurs at this stage), followed by refluxing of the reaction mixture for 10 h (control by TLC method). The target indolylchalcones **4a**–**g**, including compounds **4e**–**g** that were synthesized for the first time, formed under these conditions in 52–70% yields without impurities of the intermediate compounds **2a**–**g** (Scheme 1, Table 1). When the reaction was performed without the

Scheme 1



initial maintaining of the starting material mixture at room temperature, the product yields were reduced by 5–20%. The most suitable solvent for this transformation was propanol, due to its relatively high boiling point, miscibility with water, and the ability to dissolve the starting materials. When propanol was replaced with ethanol or hexafluoroisopropanol, incomplete conversion of ester **2** to chalcone **4** was observed even after prolonged refluxing. The use of anhydrous propanol led to longer refluxing, apparently due to the fact that water is a nucleophile that participates in the destruction of the molecular framework. The aroyl substituent at the pyrone ring practically did not affect the course of the transformation, while the nature of substituent at position 2 of the indole ring was very important. Thus, the less nucleophilic starting materials 2-phenylindole and unsubstituted indole did not participate in this reaction, and were either recovered in unchanged form, as in the case of 2-phenylindole, or gave intractable products.

The obtained compounds **4a**–**g** had a *trans*-configuration of the double bond, as evidenced by the large value of their vicinal spin-spin coupling constants (J = 15.1–15.5 Hz) between the α-CH (δ 7.35–7.65 ppm) and β-CH (δ 7.99–8.10 ppm) protons, distinguishing these compounds from the diketohexenoates **2**, the molecules of which contained aroyl and indole moieties in a *cis* orientation relative to each other.[7]

The possible mechanism of the described transformation includes ketonic cleavage of the diketohexenoate ester **2** by a molecule of water, resulting in the formation of 2-acyl-3-indolylacrylic acid **A**, which underwent decarboxylation with the formation of *trans*-chalcone **4**. The inversion of double bond configuration when changing from esters **2** to chalcones **4** can be explained by the isomerization of either compound **2** or the intermediate **A**. The main factor facilitating the destruction of molecular framework is probably associated with the unfavorable interactions due to the presence of methyl group at position 2 of indole.

Thus, we have developed a new method for the preparation of *trans*-indolylchalcones on the basis of catalyst-free reaction between ethyl 5-acylcomanoates and 2-methylindoles, which is accompanied by pyrone ring opening and destruction of the molecular framework. The obtained products are of interest for further studies in the field of medicinal chemistry, as well as in the role of synthetic intermediates.

Table 1. Yields of chalcones **4a**–**g**

Chalcone	Ar	R	Yield, %
4a	Ph	H	59
4b	4-MeC_6H_4	H	64
4c	4-ClC_6H_4	H	65
4d	4-$MeOC_6H_4$	H	52
4e	2-naphthyl	H	70
4f	2-thienyl	H	61
4g	Ph	MeO	68

Experimental

IR spectra were recorded on a PerkinElmer Spectrum BX II instrument with an ATR accessory. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker Avance II spectrometer (400 and 100 MHz, respectively) in DMSO-d_6, with TMS as internal standard. The indole ring protons are denoted as H Ind, naphthalene ring protons – as H Naphth, thiophene ring protons – as H Th. Elemental analysis was performed on a PE 2400 automatic analyzer. Melting points were determined on an SMP30 apparatus.

The starting pyrones **1a**–**f** were obtained according to a published procedure.[9]

Preparation of compounds 4a–**g** (General method). A mixture of the appropriate pyrone **1a**–**f** (0.35 mmol) and 2-methylindole (**3a**) or 5-methoxy-2-methylindole (**3b**) (0.42 mmol) was maintained in a 3:1 mixture of 1-PrOH–H_2O (1 ml) for 2 days at room temperature. An additional amount (1 ml) of 3:1 mixture of 1-PrOH–H_2O was added to the obtained precipitate of diketohexenoate **2a**–**g**, and the obtained mixture was heated for 10 h at 100°C, maintained overnight at room temperature, the precipitate was then filtered off and washed with cold EtOH.

(*E*)-3-(2-Methyl-1*H*-indol-3-yl)-1-phenylprop-2-en-1-one (4a). Yield 54 mg (59%), yellow powder, mp 182–183°C (mp 183°C[4a]). ^{1}H NMR spectrum, δ, ppm (J, Hz): 2.59 (3H, s, CH_3); 7.16–7.24 (2H, m, H-5,6 Ind); 7.37–7.43 (1H, m, H-7 Ind); 7.54 (1H, d, J = 15.5, α-CH); 7.54–7.60 (2H, m, H-3,5 Ph); 7.60–7.66 (1H, m, H-4 Ph);

7.99–8.04 (1H, m, H-4 Ind); 8.06 (1H, d, *J* = 15.5, β-CH); 8.09–8.13 (2H, m, H-2,6 Ph); 11.86 (1H, s, NH).

(*E*)-3-(2-Methyl-1*H*-indol-3-yl)-1-(*p*-tolyl)prop-2-en-1-one (4b). Yield 62 mg (64%), orange powder, mp 233–234°C (mp 210°C[4a]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.44 (3H, s, C$\underline{H}_3$C$_6$H$_4$); 2.60 (3H, s, CH$_3$ Ind); 7.08–7.18 (2H, m, H-5,6 Ind); 7.30 (2H, d, *J* = 8.1, H-3,5 Ar); 7.34 (1H, dd, *J* = 7.0, *J* = 1.6, H-7 Ind); 7.44 (1H, d, *J* = 15.3, α-CH); 7.89 (1H, dd, *J* = 6.9, *J* = 1.2, H-4 Ind); 7.93 (2H, d, *J* = 8.1, H-2,6 Ar); 8.00 (1H, d, *J* = 15.3, β-CH); 11.61 (1H, s, NH).

(*E*)-1-(4-Chlorophenyl)-3-(2-methyl-1*H*-indol-3-yl)-prop-2-en-1-one (4c). Yield 67 mg (65%), yellow powder, mp 227–228°C (mp 215°C[4a]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.64 (3H, s, CH$_3$); 7.11–7.20 (2H, m, H-5,6 Ind); 7.37 (1H, dd, *J* = 6.8, *J* = 1.5, H-7 Ind); 7.44 (1H, d, *J* = 15.3, α-CH); 7.52 (2H, d, *J* = 8.5, H-3,5 Ar); 7.93 (1H, dd, *J* = 7.1, *J* = 1.3, H-4 Ind); 8.06 (1H, d, *J* = 15.3, β-CH); 8.07 (2H, d, *J* = 8.5, H-2,6 Ar); 11.70 (1H, s, NH).

(*E*)-1-(4-Methoxyphenyl)-3-(2-methyl-1*H*-indol-3-yl)-prop-2-en-1-one (4d). Yield 53 mg (52%), orange powder, mp 171–172°C (mp 170°C[4a]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.58 (3H, s, CH$_3$); 3.86 (3H, s, CH$_3$O); 7.08 (2H, d, *J* = 8.8, H-3,5 Ar); 7.14–7.23 (2H, m, H-5,6 Ind); 7.36–7.42 (1H, m, H-7 Ind); 7.54 (1H, d, *J* = 15.3, α-CH); 8.02 (1H, d, *J* = 15.3, β-CH); 8.00–8.04 (1H, m, H-4 Ind); 8.11 (2H, d, *J* = 8.8, H-2,6 Ar); 11.81 (1H, s, NH).

(*E*)-3-(2-Methyl-1*H*-indol-3-yl)-1-(naphth-2-yl)prop-2-en-1-one (4e). Yield 80 mg (70%), yellow powder, mp 238–239°C. IR spectrum, ν, cm^{-1}: 3179, 1699, 1599, 1564, 1456, 1434, 1284, 1260, 743. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.65 (3H, s, CH$_3$); 7.08–7.24 (2H, m, H-5,6 Ind); 7.37 (1H, d, *J* = 7.8, H-7 Ind), 7.53–7.63 (2H, m, H Naphth); 7.65 (1H, d, *J* = 15.1, α-CH); 7.93 (1H, d, *J* = 7.5, H Ar); 7.97 (1H, d, *J* = 8.5, H Ar); 8.02 (1H, d, *J* = 7.8, H Ar); 8.10 (1H, d, *J* = 15.1, β-CH); 8.10 (1H, dd, *J* = 8.7, *J* = 1.4, H Naphth); 8.15 (1H, d, *J* = 7.8, H Naphth); 8.69 (1H, s, H-1 Naphth); 11.69 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 11.9; 109.3; 111.5; 114.1; 120.3; 121.2; 122.1; 124.4; 125.9; 126.7; 127.6; 128.2 (2C); 129.1; 129.6; 132.4; 134.7; 136.0; 136.2; 137.9; 144.3; 188.5. Found, %: C 81.08; H 5.60; N 4.35. C$_{22}$H$_{17}$NO·0.75H$_2$O. Calculated, %: C 81.33; H 5.74; N 4.31.

(*E*)-3-(2-Methyl-1*H*-indol-3-yl)-1-(thiophen-2-yl)prop-2-en-1-one (4f). Yield 57 mg (61%), orange powder, mp 197–198°C. IR spectrum, ν, cm^{-1}: 3222, 2919, 1619, 1533, 1452, 1272, 710. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.62 (3H, s, CH$_3$); 7.09–7.18 (2H, m, H-5,6 Ind); 7.21 (1H, t, *J* = 4.2, H Th); 7.36 (1H, d, *J* = 15.5, α-CH); 7.32–7.37 (1H, m, H-7 Ind); 7.79 (1H, d, *J* = 4.8, H Th); 7.92 (1H, d, *J* = 7.3, H-4 Ind); 7.99 (1H, d, *J* = 15.5, β-CH); 7.99–8.04 (1H, m, H Th); 11.66 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 11.9; 109.0; 111.5; 113.8; 120.2; 121.2; 122.1; 125.8; 128.7; 131.7; 133.8; 136.1; 137.0; 144.2; 146.4; 181.3. Found, %: C 71.64; H 4.86; N 5.38. C$_{16}$H$_{13}$NOS. Calculated, %: C 71.88; H 4.90; N 5.24.

(*E*)-3-(5-Methoxy-2-methyl-1*H*-indol-3-yl)-1-phenylprop-2-en-1-one (4g). Yield 69 mg (68%), yellow powder, mp 190–191°C. IR spectrum, ν, cm^{-1}: 3244, 2982, 2921, 1635, 1544, 1278, 695. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.60 (3H, s, CH$_3$); 3.87 (3H, s, CH$_3$O); 6.75 (1H, dd, *J* = 8.7, H Ind); 7.24 (1H, d, *J* = 8.7, H Ind); 7.31 (1H, d, *J* = 2.2, H-4 Ind); 7.35 (1H, d, *J* = 15.3, α-CH); 7.47–7.59 (3H, m, H Ph), 7.97–8.04 (3H, m, H Ph); 11.53 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 12.0; 55.5; 103.2; 109.0; 110.6; 112.0; 113.8; 126.6; 127.8; 128.5; 130.9; 131.9; 137.8; 138.9; 144.2; 154.9; 188.7. Found, %: C 78.23; H 5.86; N 5.05. C$_{19}$H$_{17}$NO$_2$. Calculated, %: C 78.33; H 5.88; N 4.81.

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