

Regioselective Synthesis of Indanones

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Abstract: The degree of hydrolysis of polyphosphoric acid (PPA) has a crucial effect on the regioselectivity of the PPA-mediated synthesis of indanones. It was found that the regioselectivity can be switched by employing PPA with either a high or low content of P_2O_5 . This methodology was used for the regioselective synthesis of a range of electron-rich indanones, including a natural sesquiterpene.

Key words: indanones, polyphosphoric acid, electrophilic aromatic substitution, total synthesis, regioselectivity

Indanones are an important class of compounds due to their widespread occurrence in natural products and the biological activity associated with both natural and synthetic indanones. For example, indanones belonging to the Pterosin sesquiterpene family exhibit antimicrobial,¹ antispasmodic² and cytotoxic activity,³ while the synthetic indanocine shows antiproliferative activity⁴ (Figure 1). The development of chemo- and regioselective synthetic methodology toward indanones is therefore of considerable importance.

The main methods for the synthesis of indanones are (intramolecular) Friedel–Crafts acylation,⁵ Nazarov cyclization,⁶ and various transition-metal-catalyzed ring-closing reactions.⁷ Indanones can also be accessed by the one-pot reaction of α,β -unsaturated carboxylic acids with benzene derivatives using polyphosphoric acid (PPA).^{8,9} This protocol is frequently used in our laboratory for the synthesis of indanones, which serve as building blocks en route to overcrowded alkenes.¹⁰ The main advantage of this method is the use of simple substrates that are often commercially available. However, the lack of control over the regioselectivity severely decreases the efficiency of the indanone synthesis. In some cases, these reactions generate mixtures of regioisomers that are difficult to separate, while in other cases, certain regioisomers cannot be accessed at all with this method.

We envisioned that the P_2O_5 content in PPA can be a key control parameter in the selective alkylation versus acylation in the PPA-mediated synthesis of indanones.¹¹ A change in the regioisomer ratio, depending on the polyphosphoric acid concentration, has been observed for a perimidine heterocycle.¹²

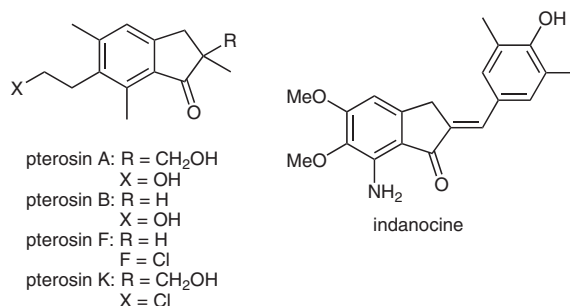
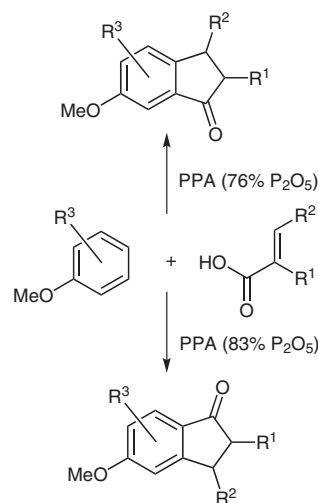


Figure 1 Natural and synthetic indanones with biological activity



Scheme 1 Regioselective synthesis of two indanone isomers depending on the P_2O_5 content in PPA

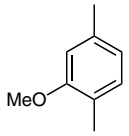
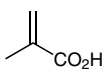
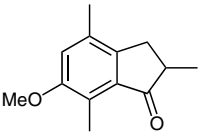
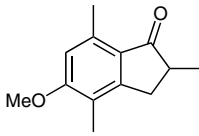

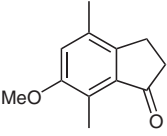
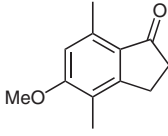
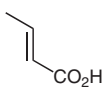
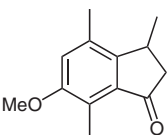
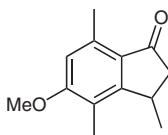
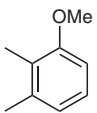
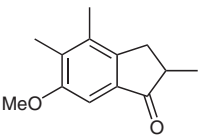
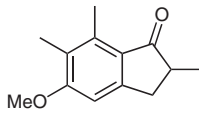
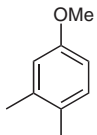
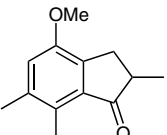
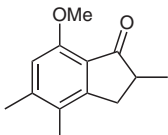
In this letter, the effect of the P_2O_5 content in PPA on the regioselectivity for the synthesis of indanones is examined. It was found that the regioselectivity can be effectively switched, depending on the degree of hydrolysis of PPA (Scheme 1). A mechanistic rationale is given for the observed change in regioselectivity, together with supporting ^{31}P NMR spectroscopic studies. Additionally, the natural product sesquiterpene **19a** and its unnatural regioisomer **19b** were synthesized selectively by using the developed protocol to demonstrate its synthetic value.

The condensation of 2,5-dimethylanisole (**1**) with methacrylic acid (**2**) was conducted by using PPA with two different concentrations, 76% P_2O_5 (Table 1, entry 1) and 83% P_2O_5 (entry 2). At 100 °C, both reactions went to full conversion within four hours. To our surprise, it was found that the regioselectivity of this reaction completely

switched from >95% in favor of **3a** to >95% in favor of **3b**. To examine the generality of this finding, several substrates were tested; the results are summarized in Table 1. In all cases, it was shown that the PPA concentration has an effect on the regioselectivity, although this was more pronounced in some cases than in others. It appears that PPA with a low P₂O₅ content promotes the formation of the indanone isomer having the electron-donating group *meta* to the carbonyl functionality, whereas PPA with a high P₂O₅ content favors the formation of the indanone

with electron-donating group *ortho* or *para* to the carbonyl functionality. Substitution in either the α - or β -position of the unsaturated carboxylic acid promotes the formation of the isomer with the methoxy group in the 5-position (entries 1–6). Various indanones with different substitution patterns are accessible with this method (entries 7–10), but the use of electron-poor benzene derivatives resulted in very low yields and were therefore not investigated further.

Table 1 Scope of the Reaction

Entry	Reactant	Reactant	Condition ^a	Product I	Product II	Ratio I/II ^b	Yield (%) ^c
1			A			>95:5	64
	1	2		3a	3b		
2	1	2	B	3a	3b	<5:95	61
3	1		A			>95:5	63
		4		5a	5b		
4	1	4	B	5a	5b	60:40	58
5	1		A			25:75	81
		6		7a	7b		
6	1	6	B	7a	7b	<5:95	88
7		2	A			50:50	82
	8			9a	9b		
8	8	2	B	9a	9b	<5:95	78
9		2	A			85:15	52
	10			11a	11b		
10	10	2	B	11a	11b	15:85	51

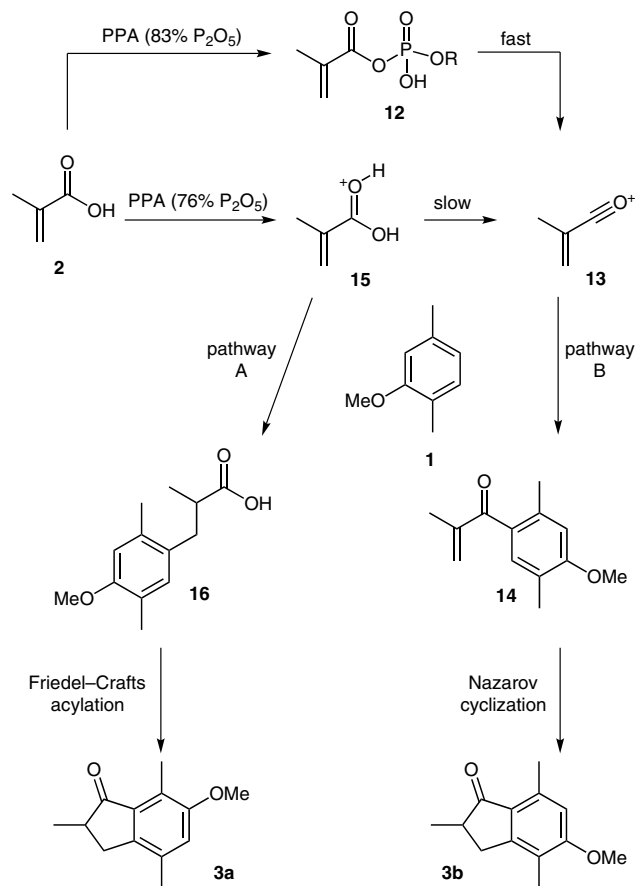
^a Condition A: 100 °C, PPA (76% P₂O₅); Condition B: 100 °C, PPA (83% P₂O₅).

^b The regioisomer ratio was determined by analysis of the crude product with ¹H NMR spectroscopy.

^c Isolated yield.

A ^{31}P NMR experiment was conducted to gain more insight into the change in regioselectivity of this reaction. Analysis of a mixture consisting of 5 wt% methacrylic acid (**2**) in PPA (83% P_2O_5) at 80 °C by ^{31}P NMR spectroscopy indicated the formation of several species, which were identified as phosphoric anhydrides of methacrylic acid. The formation of mixed anhydride was not detected when PPA (76% P_2O_5) was employed (see the Supporting Information). These results are consistent with an earlier investigation on the ratio of benzoic acid and phosphoric anhydride in PPA of various concentrations.¹³ Based on these results, together with the fact that PPA (83% P_2O_5) promotes the formation of the indanone with the methoxy group at the 5-position, while PPA (76% P_2O_5) promotes the formation of the isomer with the methoxy substituent at the 6-position, the mechanism shown in Scheme 3 is proposed. At high PPA concentration (83% P_2O_5), methacrylic acid (**2**) forms the mixed anhydride **12**, which dehydrates to form the acylium ion **13**. Arene **1** undergoes acylation via the acylium ion **13**. The resulting intermediate **14** gives indanone **3b** through acid-catalyzed Nazarov cyclization (pathway B). At low PPA concentration, it is proposed that the formation of the acylium ion is considerably slower because of the lower acidity of the medium¹⁴ and the fact that the mixed anhydride is not formed. At this point, arene **1** will react through a competing pathway. The arene adds to the unsaturated carboxylic acid in a 1,4-fashion to give intermediate **16**. This type of addition is consistent with the observation that a methyl substituent in the α -position of the unsaturated carboxylic acid disfavors this reaction, presumably because of electronic effects¹⁵ (see Table 1, entries 1–4). Subsequent intramolecular Friedel–Crafts reaction of **16** yields indanone **3a** (pathway A). The intermediates **14** and **16** were never observed, even when the reaction did not reach full conversion, which is indicative of the fact that the intramolecular reaction is faster than the intermolecular reaction, for both reaction pathways. Unsaturated carboxylic acids substituted at the β -position mainly react through pathway B, even with PPA with low P_2O_5 content.

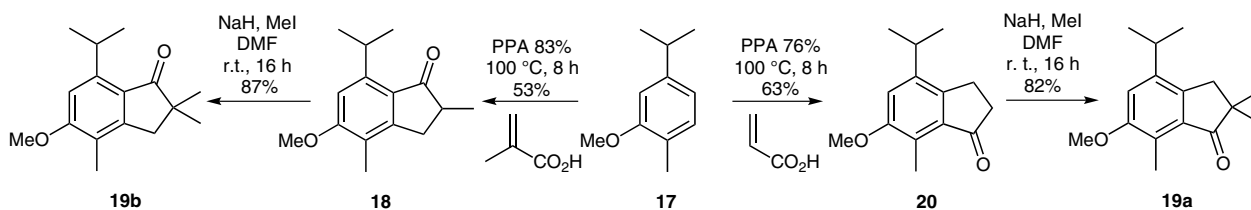
As an application of the reactions described above, we show that the natural product **19a** and its unnatural regioisomer **19b** can both be synthesized from the same starting material in two steps with full regioselectivity. Sesquiterpene **19a** was isolated from an unnamed soft-coral *Primnoeides* sp.¹⁶ The only total synthesis of this compound was reported in 1997 and consisted of five steps (17% overall yield) starting from carvacrol methyl



Scheme 3 Proposed reaction pathways for the formation of **3a** (pathway A) and **3b** (pathway B).

ether **17**.¹⁷ Beginning with the same precursor **17**, the indanone skeleton was constructed with the methoxy substituent at the 5- and 6-position by using high concentrated PPA and low concentrated PPA, respectively (Scheme 2). Methylation at the α -position of the ketone by using MeI afforded both isomers **19a** (52% over two steps) and **19b** (46% over two steps) in only two steps, which is a considerable improvement on the previously reported synthesis.

In conclusion, the effect of the PPA concentration on regioselectivity for the synthesis of indanones was examined. It was found that the theoretical P_2O_5 content in PPA has a profound effect on the selectivity of this reaction and that this can be exploited for the regioselective synthesis of indanones. The explanation for the change in selectivity is attributed to the fact that at high PPA concentration



Scheme 2 Total synthesis of sesquiterpene **19a** and its unnatural regioisomer **19b**

mixed phosphoric anhydrides are formed with the substrate, whereas at low PPA concentration this does not occur. This is, as far as we know, the first synthetic methodology in which the degree of hydrolysis of PPA was used as a way to control the regioselectivity of a PPA-mediated reaction. The developed procedure allows facile and selective access to electron-rich indanones, as was demonstrated by the synthesis of a natural sesquiterpene **19a**.

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Supporting Information for this article is available online at <http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083>.

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