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One-Pot, Four-Component Reaction of Aryl Aldehydes, Aryl Ketones, Phosphorus Trichloride, and Acetonitrile Catalyzed by Acetyl Chloride: Synthesis of β -Acetamido Ketones

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Abstract: The one-pot, four-component reaction of aryl aldehydes, aryl ketones, phosphorus trichloride, and acetonitrile, catalyzed by acetyl chloride, affords β -acetamido ketones in good to excellent yields. Silicaphosphine (silphos), [P(Cl)_{3-n}(SiO₂)_n], can also be used effectively as a solid-supported reagent instead of phosphorus trichloride.

Keywords: β -acetamido ketones, Dakin–West reaction, phosphorus trichloride, silicaphosphine, silphos

During the past few years, multicomponent reactions (MCRs) have proved to be remarkably successful in generating molecular complexity in a single-synthetic-step operation.^[1] These processes consist of two or more synthetic steps, which are performed without isolation of any intermediates, thus reducing time and saving both energy and raw materials. MCRs are powerful tools in modern drug-discovery processes and allow fast, automated, and high-throughput generation of organic compounds.^[2] Furthermore, a field of increasing interest is the synthesis of useful synthetic building

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Synthesis of β -Acetamido Ketones

blocks via MCR chemistry. For this reason, the discovery of novel MCRs is of interest.^[3-5]

The Dakin-West reaction is the best known route for the synthesis of β -acetamido ketones.^[6,7] These compounds are versatile intermediates, in that their skeletons exist in a number of biologically or pharmacologically important compounds.^[8,9] A few catalysts have already been applied for the synthesis of β -acetamido ketones using this method, including different transition-metal triflates, BF₃, CuCl₂, BiCl₃, LaCl₃, LiClO₄, InCl₃, ^[10] CoCl₂, ^[11] montmorillonite K-10 clay, ^[12] H₂SO₄/SiO₂, ^[13] heteropoly acids, ^[14] BiOCl, ^[15] ZrOCl₂ · 8H₂O, ^[16] and silica sulfuric acid. ^[17] The role of these acidic catalysts has been reported to be activation of the carbonyl group of the aldehyde toward the addition of acetonitrile^[11,12] or toward the attack of the enole of aryl ketone.^[10] Having in mind that phosphorus trichloride is capable of accepting the electron pair of oxygen and activating the carbonyl group toward the nucleopholic attacks, we decided to investigate the reaction of aryl aldehydes, aryl ketones, acetonitrile, and acetyl chloride in the presence of this compound as catalyst. We started our investigation by carrying out the reaction of 4-chlorobenzaldehyde, acetophenone, acetylchloride, and acetonitrile. Thus, a mixture of 3 mmol of 4-chlorobenzaldehyde, 3 mmol of acetophenone, 3 mmol of phosphorus trichloride, and 3 mmol of acetyl chloride was stirred in boiling acetonitrile as solvent for 60 min. The reaction progress was monitored by thin-layer chromatography (TLC). After the workup of the reaction, we obtained the desired β -acetamido ketones 3 in 90% yield. The structure of the product was deduced by comparison of its ¹H and ¹³C NMR and IR spectra with those of authentic compounds.^[12] To obtain the best reagent ratio and reaction condition, we carried out this reaction with different amounts of acetyl chloride and phosphorus trichloride. The obtained results are shown in Table 1. As indicated in Table 1, no reaction was observed in the absence of acetyl chloride or phosphorus trichloride

Entry	CH ₃ COCl amount (mol%)	PCl ₃ amount (mol%)	Time (min)	Yield (%)
1	0	100	240	a
2	100	0	240	a
3	10	100	60	73 ^b
4	20	100	60	85^{b}
5	20	110	60	90^{b}
6	20	110	300	$75^{b,c}$

Table 1. Four-component reaction between 4-chlorobenzaldehyde, acetophenone, phosphorus trichloride, and acetonitrile catalyzed by acetyl chloride

^aOnly starting materials were obtained after the workup of the reaction. ^bIsolated yield.

^cThe reaction is carried out at room temperature.

	ArCHO + Ar'COC	$H_3 + PCl_3$ (or silphos)	CH ₃ COCl CH ₃ CN, 80° C, 1hr	-NHCOCH ₃ =0 3
Entry	Ar	Ar'	Product ^a	Yield $(\%)^b$ (PCl ₃ ^c /silphos ^d)
1	C ₆ H ₅	C ₆ H ₅	H ₃ COC- _{NH O}	90/93
2	3-NO ₂ C ₆ H ₄	C ₆ H ₅		93/90
3	$4-NO_2C_6H_4$	C_6H_5	H ₃ COC-NH O	88/85
4	4-ClC ₆ H ₄	C_6H_5	H ₃ COC- _{NH O}	90/85
5	2-ClC ₆ H ₄	C_6H_5		90/85
6	4-CH ₃ OC ₆ H ₄	C_6H_5	H ₃ COC-NH O H ₃ CO	85/90
7	C_6H_5	4-NO ₂ C ₆ H ₄	H ₃ COC- _{NH O}	94/95
8	C ₆ H ₅	$4-BrC_6H_4$	H ₃ COC- _{NH O}	92/90
9	C ₆ H ₅	4-ClC ₆ H ₄	H ₃ COC- _{NH O}	89/83
10	4-NO ₂ C ₆ H ₄	4-NO ₂ C ₆ H ₄	H ₃ COC-NH O O ₂ N NO ₂	93/88

Table 2. One-pot condensation of aryl aldehydes, aryl ketones, phosphorus trichloride (or silphos), and acetonitryl to give the corresponding β -acetamido ketones

(continued)

Entry	Ar	Ar'	Product ^a	Yield $(\%)^b$ (PCl ₃ ^c /silphos ^d)
11	3-NO ₂ C ₆ H ₄	$4-NO_2C_6H_4$		91/88
12	$4-NO_2C_6H_4$	4-BrC ₆ H ₄		90/93
13	3-NO ₂ C ₆ H ₄	4-BrC ₆ H ₄	H ₃ COC- _{NH O} O ₂ N	88/84
14	$4-FC_6H_4$	4-NO ₂ C ₆ H ₄	H ₃ COC- _{NH O} F	87/92
15	4-ClC ₆ H ₄	$4-NO_2C_6H_4$		88/90
16	4-CH ₃ C ₆ H ₄	$4-NO_2C_6H_4$	H ₃ COC- _{NH O} H ₃ C	92/94
17	4-CH ₃ OC ₆ H ₄	$4-NO_2C_6H_4$		89/90
18	4-ClC ₆ H ₄	4-BrC ₆ H ₄	H ₃ COC _{NH O}	90/85
19	4-FC ₆ H ₄	4-ClC ₆ H ₄	H ₃ COC _{NH O}	89/83
20	CH ₃ CH ₂	$4-NO_2C_6H_4$	H ₃ COC _{NH O} H ₃ CH ₂ C	22/31

Table 2. Continued

^{*a*}All products were characterized by comparing their ¹H NMR, ¹³C NMR, and IR spectra with reported compounds.^[11,12]

^bIsolated yield.

^{*c*}All reactions were carried out in 15 mL, of boiling acetonitryl for 1 h with starting material ratio of PCl_3 -aldehyde-ketone- $CH_3COCl = 3.3:3:3:0.6$.

^{*d*}All reactions were carried out in 15 mL of boiling acetonitryl for 1 h with 1.8 g of silphos, 3 mmol of aldehyde, 3 mmol of ketone, and 0.6 mmol of CH₃COCl.

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(entries 1 and 2). However, acetyl chloride can be used in catalytic amounts (Table 1, entry 4). In all of the previously reported investigations on fourcomponent Dakin–West reaction, acetyl chloride has been used in excess amounts (usually 3-4 equivalents).^[13-17] Contrary to our expectation, when we used phosphorus trichloride in catalytic amounts, we could only obtain the desired Dakin–West products in low yields, and the major isolated compounds were the starting aldehyde and ketone. The best amount of phosphorus trichloride was found to be 1.1 equivalents. Considering these observations, we can say that in this reaction phosphorus trichloride acts as a reagent and acetyl chloride is catalyst.

To investigate the scope of this method for synthesizing β -acetamido ketones, we carried out the reaction with different aryl aldehydes and aryl ketones. The results are summarized in Table 2. Several functional groups such as nitro, chloro, bromo, and methoxy were compatible with this procedure. Aliphatic aldehydes can also be used, but the yield is low (Table 2, entry 20).

Being successful in carrying out the reaction with phosphorus trichloride, we decided to investigate the effectiveness of the newly introduced silicaphosphine (silphos), [P(Cl)_{3-n}(SiO₂)_n], as a solid-supported reagent to synthesize β -acetamido ketones. The introduction of supported reagents for bringing about various chemical transformations has provided an attractive option for organic synthesis.^[18] Such reagents not only modify the reactivity but also may impart product selectivity, enhanced reaction rates, cleaner reaction products, and operational simplicity.^[19,20] Silphos has been recently introduced as an efficient reagent or catalyst for some organic transformations, including halogenation of alcohols,^[21] formylation and acetylation of alcohols and amines,^[22] and conversion of epoxides to alkenes or β -bromoformates.^[23]

To investigate the effectiveness of silphos, we first carried out its reaction with 4-chloro benzaldehyde and acetophenone in the presence of acetyl chloride in acetonitrile as solvent. Silphos was easily prepared by the reaction of phosphorus trichloride and silica gel as reported in the literature.^[21] The reaction was carried out by stirring a mixture of 4-chlorobenzaldehyde, acetophenone, acetyl chloride, and silphos in boiling acetonitrile. The reaction was completed after an hour in refluxing acetonitrile as indicated by thin-layer chromatography (TLC), and the product was obtained in 93% yield. The amount of silphos and acetyl chloride was optimized for this reaction. The best result was obtained by using 0.6 g of silphos with 1 mmol each of p-chlorobenzaldehyde and acetophenone and 0.2 mmol of acetyl chloride in 15 mL of refluxing acetonitrile. This optimized condition was used for the reaction of other aldehydes and ketones. Aromatic aldehydes or acetophenones both with electron-withdrawing and electron-releasing groups underwent smooth transformation to the corresponding β -acetamido ketones in high to excellent yields (Table 2). However, no product was isolated in the absence of silphos or acetyl chloride.



Scheme 1.

Although we did not investigate the reaction mechanism, one reasonable possibility is shown in Scheme 1.

In conclusion, we have developed a one-pot, four-component reaction of phosphorus trichloride, aryl aldehydes, aryl ketones, and acetonitrile for synthesis of β -acetamido ketones by the Dakin–West reaction. The reaction can also be carried out with simply prepared and filterable silphos instead of harder-to-handle phosphorus trichloride. The advantages of this method are easily available starting materials, short reaction times, easy and clean workup, and excellent yields.

GENERAL PROCEDURE FOR PREPARATION OF β -ACETAMIDO KETONES

A solution of aryl aldehyde (3 mmol), aryl ketone (3 mmol), phosphorus trichloride (3.3 mmol), and acetyl chloride (0.6 mmol) in acetonitrile (15 mL) was stirred at reflux temperature for an hour. The mixture was poured into 50 mL of ice water (when silphos was used, the reaction mixture was filtered into ice water, and the mass on filtering paper was washed with

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30 mL of 1:1 mixture of acetonitrile/water into ice water). The solid product was filtered, washed with ice water, and recrystallized from ethyl acetate/n-hexane to give the pure product. All products were identified by comparing their melting point and their NMR and IR values with those of authentic samples.^[12,13]

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