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Simple and Efficient Procedure for the One-Pot Synthesis of β-Acetamido-β-aryl-propiophenones by Molecular Iodine-Catalyzed Tandem Reaction

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Simple and Efficient Procedure for the One-Pot Synthesis of β-Acetamido-β-aryl-propiophenones by Molecular Iodine–Catalyzed Tandem Reaction

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Abstract: Molecular iodine efficiently catalyzes the four-component tandem reaction of araldehydes, arylmethyl ketones, acetyl chloride, and acetonitrile to afford the corresponding β-acetamido-β-aryl-propiophenones. The new protocol gives high yields of the products, and the reactions go to completion within 10–15 min on a hot plate at 80–85°C.

Keywords: β-acetamido-β-aryl-propiophenones, acetonitrile, acetyl chloride, arylaldehydes, arylmethyl ketones, iodine

INTRODUCTION

β-Acetamido-β-aryl-propiophenones are versatile intermediates in that their skeletons exist in a number of biologically or pharmacologically important compounds.[1] The best known route for the synthesis of these compounds is the Dakin–West reaction,[2] which involves the condensation of an β-amino acid with acetic anhydride in the presence of a base via an intermediate azalactone to give the β-acetamido-β-aryl-propiophenones.

Recently, the synthesis of β-acetamido-β-aryl-propiophenones has gained acceptance and popularity among the synthetic chemist community;

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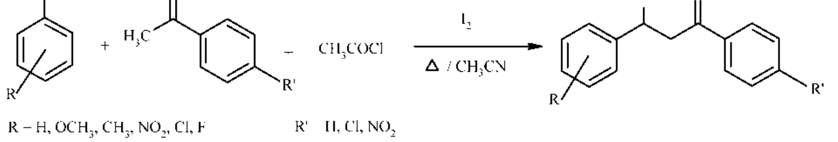
thus, the preparation of this type of molecules is of much importance. Consequently, a few methods have been reported with reagents such as silica–sulphuric acid,[3] Lewis acids,[4,5] montmorillonite K-10 clay,[6] and heteropoly acids.[7] The existing methods involve expensive reagents and strongly acidic conditions, require longer reaction duration and high temperature, and give unsatisfactory yields. The products, incompatible with other functional groups, involve cumbersome product isolation and environmental pollution. Improvements in the synthesis have been sought continuously; therefore, there is a need for simple and environmentally friendly processes for the synthesis of β-acetamido-β-aryl-propiophenones. To avoid these limitations, we started searching for new catalysts with high catalytic activity, easy availability, short reaction time, and simple workup. Molecular iodine attracted our attention. Recently, we have reported the synthesis of *N,N'*-disubstituted ureas/thioureas catalyzed by molecular iodine and α-iodoacetates from alkenes/ammonium acetate/I_2.[8]

RESULTS AND DISCUSSION

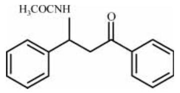
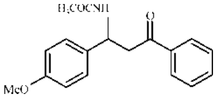
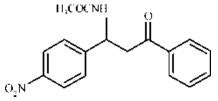
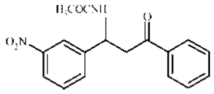
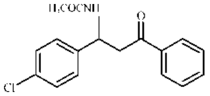
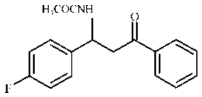
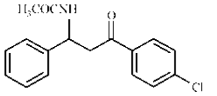
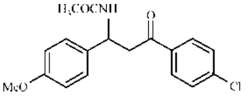
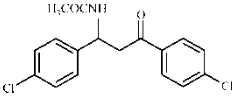
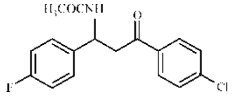
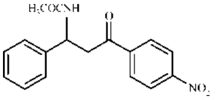
In continuation of the search for simple, nonhazardous methods for the transformations in organic synthesis using iodine, herein we report a highly versatile and efficient one-pot synthesis of β-acetamido-β-aryl-propiophenones by a four-component tandem reaction of araldehyde, arylmethyl ketone, acetyl chloride, acetonitrile, and a catalytic amount of iodine. In an experiment, the reaction mixture was taken in a 50-mL, round-bottomed flask and heated for 10–15 min on a hot plate at 80–85°C under solvent-free conditions to get β-acetamido-β-aryl-propiophenones in good to excellent yield as shown in Scheme 1.

To demonstrate the protocol, we selected 4-nitrobenzaldehyde (1 mmol) as the model substrate and treated it with acetophenone (1 mmol), acetyl chloride, and acetonitrile in the presence of iodine (0.25 mmol) for 15 min to get the desired β-acetamido-β-(4-nitrophenyl)-propiophenone in 85% yield (entry 3, Table 1). The results of the reactions of different araldehydes, arylmethyl ketones, acetyl chloride, and acetonitrile are summarized in Table 1. Several interesting features of the preparation of β-acetamido-β-aryl-propiophenones are apparent from Table 1. More important, the



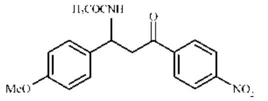
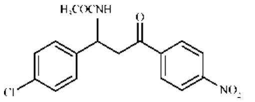
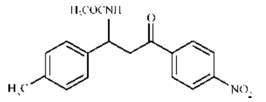
Scheme 1.

Table 1. Condensation of arylaldehydes, arylmethyl ketones, acetyl chloride, and acetonitrile to get β-acetamido-β-aryl-propiophenones

Entry	R	R′	Product[a]	Time (min)	Yield[b] (%)	Melting point (°C) Found	Melting point (°C) Reported[c]
1	H	H		10	90	102–4	104–6
2	4-OCH_3	H		15	86	116–17	115–17
3	4-NO_2	H		15	85	152	151–3
4	3-NO_2	H		15	85	112–15	112–15
5	4-Cl	H		10	85	145	146–8
6	4-F	H		10	80	110–11	109–11
7	H	Cl		10	92	114	114–15
8	4-OCH_3	Cl		10	90	124–5	125–7
9	4-Cl	Cl		15	90	140–2	141–3
10	4-F	Cl		10	88	108–10	108–10
11	H	NO_2		10	91	75–6	74–6

(*continued*)

Table 1. Continued

				Time	Yield[b]	Melting point (°C)	
Entry	R	R′	Product[a]	(min)	(%)	Found	Reported[c]
12	4-OCH_3	NO_2		13	85	87–8	87–9
13	4-Cl	NO_2		10	86	116–18	116–18
14	4-CH_3	NO_2		10	84	84–5	83–5

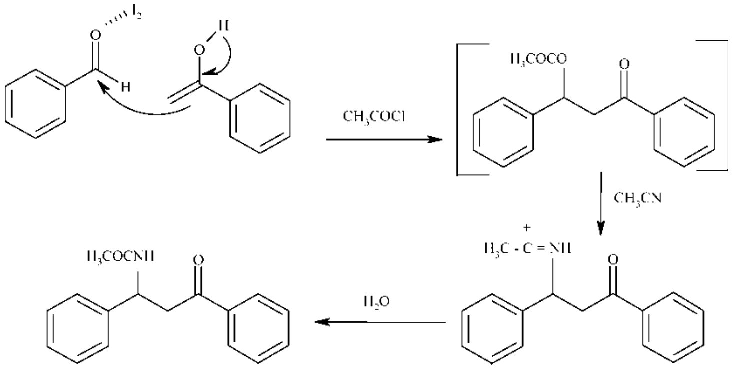
[a] All the products are known, characterized by IR and NMR spectral analysis, and compared with the authentic samples.

[b] Isolated yields.

[c] Melting points of compounds are consisted with reported values (Refs. 3, 6, and 7).

substituents such as OCH_3, Cl, F, and NO_2 are unaffected under the present reaction conditions. Further, it has been found that the conventional Lewis acids such as $ZnCl_2$, $CuCl_2$, $FeCl_3$, $NiCl_2$, $CoCl_2$, $MnCl_2$, and $AlCl_3$ have poor effect; the yields were also not satisfactory.

The mechanism may involve the enolic form of the ketone, which attacks the activated aldehyde to provide β-acetoxy ketone. The acetate group of β-acetoxy ketone is displaced by the nucleophilic nitrogen of the nitrile to provide a stable



Scheme 2.

carbocation, which may react in a Ritter fashion with water to provide the *β*-acetamido-*β*-aryl-propiophenones as shown in Scheme 2.

EXPERIMENTAL

Melting points were determined on a Büchi melting-point apparatus. IR spectra were recorded on Nicolet 400D FT-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR were recorded on 200-MHz Brucker spectrometer, and GC mass spectra on a Shimadzu GC-MS QP 5050A. Elemental analysis was performed on a Themo Finnigan Flash EA 1112 CHNS analyzer. All aralde-hydes, arylmethyl ketones, acetyl chloride, acetonitrile, and iodine were commercial products and were used without further purification.

Procedure for β-Acetamido-β-(4-nitrophenyl)-propiophenones

4-Nitrobenzaldehyde (1.51 g, 10 mmol), acetophenone (1.2 g, 10 mmol), acetyl chloride (0.3 mL), acetonitrile (2 mL), and iodine (0.25 mmol) were taken in a 50-mL, round-bottomed flask and heated at 80–85°C for 15 min. After the completion of the reaction (monitored with thin-layer chromatography, TLC), the reaction mixture was poured into ice-cold water, filtered, washed with 10% $Na_2S_2O_3$ solution, and recrystallized from EtOAc–pet. ether to afford *β*-acetamido-*β*-(4-nitrophenyl)-propiophenone (2.64 g, 85%).

Data

β-Acetamido-β-(4-nitrophenyl)-propiophenone (entry 3, Table 1): ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.16 (d, $J = 8.4$ Hz, 2H), 7.89 (d, $J = 9.6$ Hz, 2H), 7.62–7.46 (m, 5H), 7.02 (d, $J = 9.0$ Hz, 1H), 5.66 (s, 1H), 3.80 (dd, $J = 4.8$ and 17.6 Hz, 1H), 3.50 (dd, $J = 5.2$ and 17.6 Hz, 1H), 2.0 (s, 3H). ^{13}C NMR (200 MHz, $CDCl_3$): $\delta = 195.38$, 168.93, 147.34, 137.3, 135.4, 132.5, 132.49,127.8, 127.7, 127.1, 127.05, 123.35, 44.83, 42.89, 21.76; IR (KBr): 3310, 1686, 1645, 1580, 1513, 1352, 1300, 751 cm^{-1}. Anal. calcd. for $C_{17}H_{16}N_2O_4$: C, 65.38; H, 5.16; N, 9.00. Found: C, 65.19; H, 5.08; N, 8.95. MS: $m/z = 311$ (M^+).

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