Communication

Iodobenzene-Catalyzed Synthesis of α-Azidoketones and α-Thiocyanatoketones from Aryl Ketones with MCPBA as a Cooxidant

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Iodobenzene-catalyzed synthesis of α-azidoketones and α-thiocyanatoketones from aryl ketones with MCPBA as a cooxidant is described. The method is simple, rapid and practical, generating α-azidoketones and α-thiocyanatoketones from the aryl ketone without isolation of α-tosyloxyketones in good to excellent yields.

Keywords: Hypervalent iodine; α-Azidoketones; α-Thiocyanatoketones; Poly(ethylene golycol).

INTRODUCTION

α-Azidoketones are versatile organic intermediate for the synthesis of biologically important heterocyclic compounds which include oxazoles, pyrroles, and pyrazines.[1] Synthetically useful intermediates such as α-amino ketones,[2] α-azido-β-hydroxy ketones,[3] and β-amino alcohols also have been prepared from α-azidoketones.[4] The synthesis of α-azidoketones can be commonly achieved by azide-halogen exchange reactions of α-haloketones.[5] In addition, α-azidoketones have been successfully prepared from reaction of sodium azide with α-tosyloxy ketones by treatment with surfactant pillared clays[6] and triphase catalysis under ultrasound irradiation[7] in organic solvents such as chloroform or acetonitrile. Very recently, α-azidoketones have been prepared from α-diazoketones in the presence of sodium azide and cerium(III) chloride heptahydrate.[8] On the other hand, synthesis of α-azidoketones directly starting from ketones has been by far less explored. To our best knowledge, the only previous example of α-azidation of ketones was reported from our group by the reaction of α-(*p*-nitrobenzenesulfonyl)oxy ketone intermediates with sodium azide in acetonitrile.[9] α-Thiocyanatoketones can serve as valuable precursors for the preparation of many valuable heterocyclic compounds and many protocols have been developed for its preparations.[10] In similar to the α-azidoketones, the α-thiocyanatoketones are mainly prepared from the reaction of α-haloketones with thiocyanate ion in various organic solvents.[11] However, all of the known preparation methods for both α-azidoketones and α-thiocyanatoketones suffered from one or more limitations as regards tedious reaction procedure, long reaction times, and relatively low yields. Moreover, invariably all of the reported reactions were conducted in volatile toxic organic solvents.

Poly(ethylene golycol) (PEG),[12] a biologically acceptable polymer used extensively in drug delivery and in bioconjugates as tools for diagnostics has been used as a solvent medium support for various transformations.[13] In recent times ionic liquids have been in the forefront of research, and several publications and reviews have already appeared.[14] Even though ionic liquids offer some advantages, the tedious preparation of ionic liquids (and raw materials for ionic liquids) and their environmental safety is still debated. Compared with PEG, however, toxicity and environmental burden data of ionic liquids are for the most part unknown. Furthermore, the cost of ionic liquids is often more expensive than that of PEG.[15] To date some of the more important reactions have been carried out and investigated in PEG, for example, Heck reaction,[16] catalytic hydrogenations,[17] asymmetric dihydroxylation reaction,[18] Baylis-Hillman reaction,[19] Biginelli reaction,[20] Suzuki-Miyaura reaction, Stille cross-coupling reaction,[21] Wacker

reaction,[22] and asymmetric aldol reaction,[23] etc.

Hypervalent iodine(III) reagents have been used extensively in organic synthesis due to their low toxicity, ready availability and easy handling.[24] Recently, iodobenzene-catalyzed efficient α-tosyloxylation of ketones with *m*-chloroperbenzioc acid (MCPBA) and *p*-toluenesulfonic acid (PTSA) was reported to give the corresponding α-tosyloxy ketones.[25] Here, as a part of our efforts to develop greener organic reaction procedure,[26] we would like to report PhI-catalyzed α-tosyloxylation of aryl ketones to prepare α-azidoketons and α-thiocyanatoketones in PEG-400 without isolation of α-tosyloxyketones in good to excellent yields (Scheme I). Recently, study on the synthetic use of organic catalysts has become important, due to their less toxicity than that of organometallic catalysts.

RESULTS AND DISCUSSION

As shown in Scheme I, our experiments involving a one-pot procedure for the preparation of α-azidoketones (**3**) by nucleophilic substitution reactions of α-tosyloxyketones intermediates (**2**) with the azide anion in PEG-400 at room temperature was successful. The results are summarized in the Table 1. When the reaction was conducted in the classical molecular solvent, such as acetonitrile, the preparation of 2-azidoacetophenone (**3a**) needs refluxing for 2 h; however, in PEG-400, the reaction took place at room temperature for 0.5 h and gave a higher yield (Table 2). Next, we have also examined the nucleophilic substitution reactions of α-tosyloxy ketone intermediates with thiocyanate ion. The reactions worked well to give the corresponding α-thiocyanatoketones with equal efficiencies to the cases of α-azidation reactions.

A plausible reaction pathway for the present reaction is shown in Scheme II. Thus, PhI is oxidized by MCPBA in the presence of PTSA to generate [hydroxyl(tosyloxy)-imdo]benzene in situ, which then reacts with the enol form of ketone to provide α-tosyloxyketone intermediates (**2**). Nucleophilic substitution reaction of **2** with azide anion and thiocyanate ion gave the corresponding α-azidoketones and α-thiocyanatoketones (**3**).

In conclusion, we have described a novel and efficient method for the synthesis of α-azidoketones and α-thiocyanatoketones using PEG-400 as reaction medium. The important features of this procedure are enhanced reaction rate, mild reaction condition, high yield and green aspects such as avoiding hazardous organic solvents, toxic catalysts and waste, ease of recovery and reuse of this novel

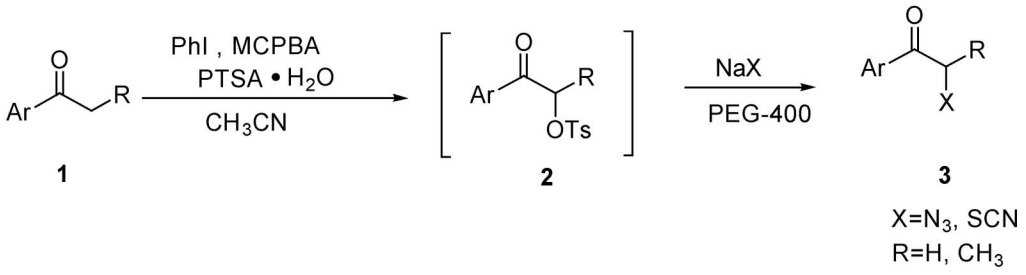
Table 1. Synthesis of α-azidoketones and α-thiocyanatoketones (**3**)

Product	Ar	R	Yield (%) of **3**	
			X=N_3	X=SCN
a	C_6H_5	H	86	85
b	4-MeC_6H_4	H	81	84
c	4-$MeOC_6H_4$	H	79	80
d	4-FC_6H_4	H	77	75
e	4-ClC_6H_4	H	80	83
f	4-BrC_6H_4	H	82	84
g	C_6H_5	Me	85	82
h	2-Furyl	H	78	80
i	2-Thienyl	H	83	81
j	2-Naphthyl	H	84	86

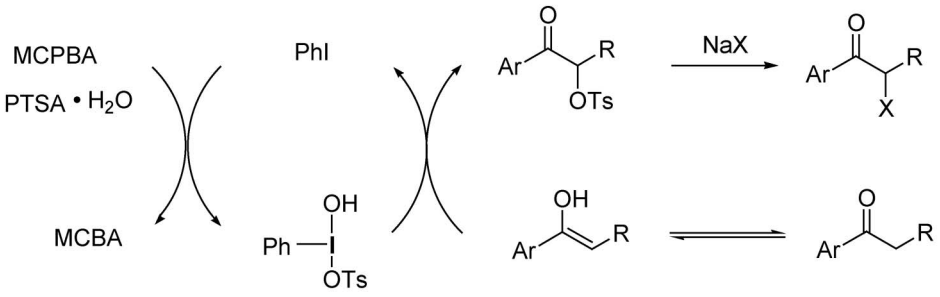
Table 2. Effect of solvent on the nucleophilic substitution of α-tosyloxy ketone intermediate with sodium azide to form 2-azidoacetophenone (**3a**)

Entry	Solvent	Reaction Temperature (℃)	Reaction Time (h)	Yield (%)
1	MeCN	80	2	75
2	[Bmim] PF_6	40	0.5	80
3	PEG-400	25	0.5	86

Scheme I



Scheme II



reaction medium.

EXPERIMENTAL SECTION

All melting points are uncorrected. The IR spectra were recorded on a Shimadzu IR-27 G spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Unity Plus 400 MHz. Chemical shifts (δ) were measured in ppm with respect to TMS. MS were obtained on a JEOL JMS D-300 instrument.

General one-pot procedure for the synthesis of α-azidoketones (3)

To a mixture of aryl ketone (**1**) (1.0 mmol), PhI (1.0 mmol), and PSTA·H_2O (1.1 mmol) in acetonitrile (20 mL) was added MCPBA (1.1 mmol) and refluxed for 1 h. After removal of acetonitrile, then PEG-400 (2 g) was added to the reaction mixture and was stirred at room temperature for 0.5 h to complete the reaction. Then the reaction mixture was extracted with EtOAc (3 × 5 mL). The extract was washed with aq sat. $NaHCO_3$ solution once and dried and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel using a mixture of ethyl acetate and n-hexane (1:4) as eluent to give **3**.

2-Azidoacetophenone (3a)

Oily compound (lit.,[27] oil). IR (neat) ν: 2104, 1695 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ : 4.86 (s, 2H), 7.47-7.52 (m, 2H), 7.62 (t, J = 7.6 Hz, 1H), 7.89-7.91 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 58.4, 127.9, 128.9, 134.1, 134.3, 193.1. MS (EI) *m/z*: 161 (M^+), 134, 106, 105.

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