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Facile Synthesis of Polysubstituted Cyclopropanes Using α-Tosyloxyketones

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A facile synthesis of polysubstituted cyclopropanes (**5**) by the treatment of pyridinium ylides, generated *in situ* from pyridinium toslyates (**2**), with arylidenemalonitrile (**4**) is presented. Pyridinium toslyates (**2**) were obtained by reacting α-tosyloxyketones (**1**) with pyridine in benzene under reflux.

Keywords: α-Tosyloxyketones, Pyridinium tosylates, Arylidenemalononitrile.

INTRODUCTION

Cyclopropane ring has always been centre of attraction for the research community because of its strained size and unique bonding. Cyclopropane containing compounds are fascinating synthetic intermediates and building blocks for many other compounds [1-4]. In addition, cyclopropane also play a prominent role in organic synthesis as they are present in biologically active compounds and various natural compounds, such as terpenes, pheromones and fatty acid metabolite [5-8]. Moreover, activities of some biologically active compounds can be altered by incorporating this significant moiety which may prove advantageous in the field of drugs and medicines [9]. To explore the wide utility of cyclopropane in different fields, continuous efforts are going on to synthesize cyclopropane and its derivatives. To date, a number of traditional methods are available in the literature for cyclopropanation. Most common methods for synthesis of cyclopropane involve Negishi cross-coupling reactions [10], Simmon Smith reaction [11], transition metal-mediated carbene transfer from aliphatic diazo compounds to carbon-carbon double bonds [12], Michael initiated ring closure of ylides with electron-deficient olefins [13], *etc*. However, metal-free and economical synthetic methods are always in demand.

α-Halo carbonyl compounds are versatile intermediates in organic synthesis. α-Halocarbonyl compounds, such as, phenacyl bromides are well known precursors for the synthesis of a wide variety of heterocyclic compounds and α-functionalized ketones [14]. However, halocarbonyl compounds are difficult to handle, highly toxic, corrosive and associated with lachrymatory properties. Due to the hazards associated with the halogenation of ketones, the unstability and toxicity of α-haloketones, it appeared attractive to find suitable alternative to these compounds.

Synthesis of α-tosyloxyketones can easily be achieved by treating a variety of ketones with [hydroxy(tosyloxy)iodo]-benzene (HTIB, Koser's reagent) [15]. These compounds are stable, crystalline solids and provide a safe eco-friendly alternative route for synthesis of compounds conventionally prepared through α-haloketones. The ease of preparation of these substrates, their relative stability and their chemical versatility allowed the development of several methods for the construction of a variety of compounds. Prompted by above observations and our ongoing efforts in exploring the synthetic significance of hypervalent iodine reagents, we herein report a facile synthetic route to access polysubstituted cyclopropanes (**5**) by the treatment of pyridinium ylides, generated *in situ* from pyridinium toslyates (**2**), with arylidenemalonitrile (**4**). Pyridinium toslyates (**2**) were obtained by reacting α-tosyloxyketones (**1**) with pyridine in benzene under reflux.

EXPERIMENTAL

Melting points were taken in open capillaries and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1800 FT-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker 400 MHz instrument using TMS as an internal standard. The chemical shifts are expressed in ppm units downfield from an internal TMS standard. α-Tosyloxyketones (**1**) were prepared according to the procedure reported in the literature [15].

Synthesis of cyclopropane derivatives: In a 100 mL flask, an equimolar mixture of pyridinium tosylate (**2**), arylidene-

malononitrile (**4**) and triethylamine was stirred in acetonitrile at room temperature for 12-19 h. The progress of reaction was recorded by TLC. After completion, the reaction mixture was poured over ice and the separated solid was collected by filtration. The crude product, thus obtained, was recrystallized from ethanol to afford pure cyclopropane derivative **5**.

2-Benzoyl-3-phenylcyclopropane-1,1-dicarbonitrile (5a): m.p.: 119 ºC; literature m.p.: 120-121 ºC [16]; yield 82 %; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 3.91-3.93 (d, 1H, *J* = 8 Hz), 4.02-4.04 (d, 1H, *J* = 8 Hz), 7.37-7.40 (m, 2H), 7.45-7.47 (m, 3H), 7.59-7.63 (t, 2H), 7.72-7.76 (t, 1H), 8.10-8.12 (d, 2H, *J* = 8.6 Hz).

2-Benzoyl-3-(4-fluorophenyl)cyclopropane-1,1-dicarbonitrile (5b): m.p.: 152 ºC; literature m.p.: 156 ºC [16]; yield 70 %; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 3.88-3.89 (d, 1H, *J* = 7.9 Hz), 3.99-4.00 (d, 1H, *J* = 7.96 Hz), 7.59-7.63 (t, 1H), 7.63-7.73 (m, 4H), 7.75-7.78 (d, 2H, *J* = 8.6 Hz), 8.09-8.11(d, 2H, *J* = 8 Hz).

2-Benzoyl-3-(4-anisyl)cyclopropane-1,1-dicarbonitrile (5c): m.p.: 92 ºC; literature m.p.: 160-161 ºC [16]; yield 79 %; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 3.86-3.88 (d, 1H, *J* = 8.1 Hz), 3.91 (s, 3H), 3.98-4.00 (d, 1H, *J* = 8.0 Hz), 6.96-6.99 (d, 1H), 7.00-7.03 (d, 2H), 7.29-7.31 (d, 1H, *J* = 8.7 Hz), 7.58-7.68 (t, 1H), 7.71-7.73 (t, 1H), 7.89-7.93 (d, 2H), 8.09-8.11 (d, 1H, *J* = 8.6 Hz).

2-Benzoyl-3-(4-bromophenyl)cyclopropane-1,1-dicarbonitrile (5d): m.p.: 164 ºC; literature m.p.: 169-170 ºC [16]; yield 71 %; ^{1}H NMR (400 MHz, $CDCl_3$) δ, ppm): 3.89-3.91 (d, 1H, *J* = 8), 4.00-4.02 (d, 1H, *J* = 8), 7.19-7.21 (d, 2H, *J* = 8), 7.21-7.26 (m, 4H), 7.60-7.64 (t, 1H), 8.10-8.12 (d, 2H, *J* = 8.0 Hz).

2-Benzoyl-3-(4-chlorophenyl)cyclopropane-1,1-dicarbonitrile (5e): m.p.: 170 ºC; literature m.p.: 175-176 ºC [16]; yield 90 %; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 3.88 (d, 1H, *J* = 7.8 Hz), 3.99 (d, 1H, *J* = 7.8 Hz), 7.33 (t, 2H), 7.44 (d, 2H, *J* = 7.2 Hz), 7.61 (t, 2H), 7.74 (t, 1H), 8.10 (d, 2H, *J* = 6.6 Hz).

2-(4-Anisyl)-3-(4-methylbenzoyl)cyclopropane-1,1-dicarbonitrile (5f): m.p.: 80-83 ºC; yield 66 %; IR (ν_{max}, cm^{-1}): 3436, 1672, 1254, 1216, 847, 828; ^{13}C NMR (100 MHz, δ, ppm): 15.29, 29.70, 35.50, 37.83, 83.38, 112.35-111.13, 113.45, 127.80, 129, 130.98, 131.85, 132.82, 133.95, 136.19, 141.18, 158.29, 165.60, 187.67; ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm) 2.43 (s, 3H), 3.84 (s, 3H), 3.91-3.93(m, 2H), 6.95-6.96 (d, 2H, *J* = 11.6 Hz), 7.26-7.30(m, 2H), 7.73-7.76 (d, 2H, *J* = 12.9 Hz), 7.94-7.97 (d, 2H, *J* = 12.9 Hz); *m/z* 323 (M^+).

2-(4-Chlorophenyl)-3-(4-nitrobenzoyl)cyclopropane-1,1-dicarbonitrile (5g): m.p.: 198-199 ºC; literature m.p.: 201 ºC [16]; yield 80 %; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 3.70 (2d, 2H, *J* = 9.0 Hz), 7.50-7.54 (m, 3H), 7.84-7.87 (d, 2H), 7.9 (d, 2H), 8.12-8.14 (d, 2H, *J* = 8.4 Hz).

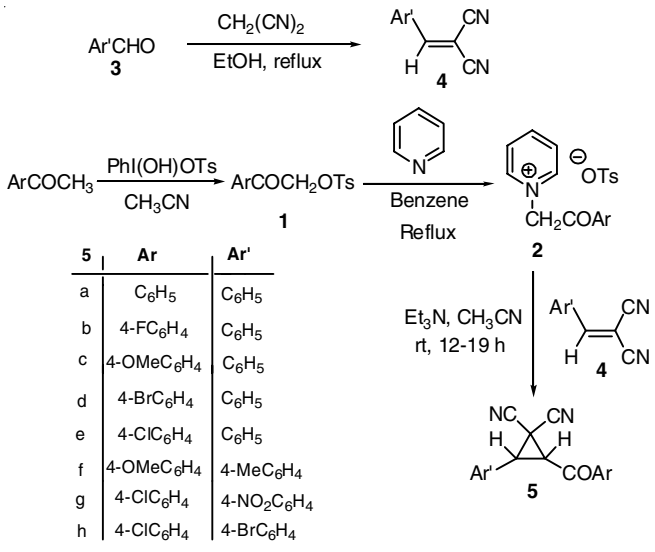
2-(4-Bromobenzoyl)-3-(4-chlorophenyl)cyclopropane-1,1-dicarbonitrile (5h): m.p.: 203-204 ºC; yield 85 %; IR (ν_{max}, KBr, cm^{-1}): 3438, 1682, 1258, 1219, 846, 833; ^{13}C NMR (100 MHz, δ, ppm): 15.27, 29.37, 29.70, 35.53, 37.80, 111.08, 111.82, 127.77, 129.67, 129.61, 129.71, 130.09, 131.00, 132.84, 133.94, 187.60; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 3.87-3.93 (2d, 2H), 7.30-7.33 (d, 2H, *J* = 8.4 Hz), 7.44-7.60 (d, 2H, *J* = 8.4 Hz), 7.75-7.78 (d, 2H, *J* = 10.8 Hz), 7.95-7.98 (d, 2H, *J* = 8.6 Hz); *m/z* 385 (M^+).

RESULTS AND DISCUSSION

As described earlier, α-haloketones and α-tosyloxyketones behave analogously in most of their reactions. Prakash and Aneja [17] demonstrated the synthetic equivalency of these compounds by achieving successful synthesis of useful thiazole derivatives. Other significant reports highlighting the synthetic equivalency of α-tosyloxyketones and α-haloketones are, (i) isolation of synthetically useful furocoumarins by the reaction of α-tosyloxyketones with 4-hydroxycoumarin [18], (ii) diastereoselective synthesis of differently substituted *trans*-2,3-dihydrofuro[3,2-*c*]-coumarins [19] and (iii) synthesis of polysubstituted oxazoles *via* decarboxylative oxidative cyclization of primary amino acids and α-tosyloxyketones [20].

Wang *et al.* [16] reported the synthesis of polysubstituted cyclpropanes by the reaction of pyridinium ylide, generated by the reaction of α-haloketones and pyridine, with aromatic aldehydes and acetonitrile derivatives. Keeping in view the above observations that α-haloketones and α-tosyloxyketones behave analogously in most of their reactions, it was anticipated that the reaction of α-tosyloxyketones (**1**) with pyridine might result into pyridinium tosylates, which can be used to generate pyridinium ylides that might afford polysubstitued cyclopropanes (**5**) on treatment with arylidene-malonitrile (**4**).

To determine the fate of the above proposal, α-tosyloxyacetophenone (**1a**), obtained by the reaction of acetophenone and Koser's reagent (HTIB), was allowed to react with pyridine in refluxing benzene. N-phenacylpyridinium tosylate (**2a**), thus obtained, was reacted with benzylidenemalonitrile (**4a)** in the presence of weak base, triethylamine, at room temperature in acetonitrile as solvent (**Scheme-I**). Completion of the reaction was confirmed by TLC using petroleum ether and ethyl acetate. The spectroscopic studies established the synthesis of 2-benzoyl-3-phenylcyclopropane-1,1-dicarbonitrile (**5a**) in 82 % yield.



5	Ar	Ar'
a	C_6H_5	C_6H_5
b	4-FC_6H_4	C_6H_5
c	4-OMeC_6H_4	C_6H_5
d	4-BrC_6H_4	C_6H_5
e	4-ClC_6H_4	C_6H_5
f	4-OMeC_6H_4	4-MeC_6H_4
g	4-ClC_6H_4	4-$NO_2C_6H_4$
h	4-ClC_6H_4	4-BrC_6H_4

Scheme-I

The formation of cyclopropane **5a** from this reaction is an encouraging observation because such cyclopropanes are important precursors for the synthesis of variety of compounds. So, it was considered worthwhile to assess the generality of

this approach for the synthesis of differently substituted cyclopropanes. Accordingly, substituted α-tosyloxyketones (**1**) were treated with pyridine to give pyridinium tosylates (**2**). Pyridinium tosylates (**2**) were then reacted with arylidenemalonitrile (**4**) to afford corresponding polysubstituted cyclopropanes (**5**) in moderate to good yields (**Scheme-I**). Structures of the cyclopropanes (**5**) were established on the basis of thorough analysis of their spectral data.

Conclusion

The results obtained from the present study offer an easy and eco-friendly approach for the synthesis of polysubstituted cyclopropanes (**5**). These results reveal that α-tosyloxyacetophenones can be used as synthetic equivalents to α-haloketones towards reactions with pyridine derivatives. The most remarkable feature of this approach is that it avoids the use of highly lachrymatory phenacyl halides.

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