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Can ultrasound substitute for a phase-transfer catalyst? Triphase catalysis and sonochemical acceleration in nucleophilic substitution of alkyl halides and α-tosyloxyketones: synthesis of alkyl azides and α-azidoketones

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Abstract

Alkyl halides and α-tosyloxyketones afford the corresponding azide derivatives upon treatment with aqueous sodium azide under triphase catalysis or ultrasound irradiation conditions. The use of surfactant pillared clay materials and sonochemistry has been compared and demonstrated in these nucleophilic substitution reactions. It appears that the use of a two-phase system in conjunction with ultrasound irradiation is the method of choice that precludes the need for a catalyst in such reactions. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Sonochemical acceleration; Triphase catalyst; Montmorillonite K 10 clay; Tetraalkylammonium bromides; Alkyl halides; α-Tosyloxyketones; Alkyl azides; α-Azidoketones

1. Introduction

The versatile reactivity and the synthetic usefulness of the azido group is well documented [1–4] and there are several methods available for the synthesis of azido compounds. The common preparative route to these molecules involves the reaction of alkyl halides with sodium azide [5–11] or lithium azide [12] in various solvents. The preparation of α-azidoketones, on the other hand, involves the oxidative addition of azide anion to silyl enol ethers [13–16], the use of α-haloketone [17] or α-nosyloxyketones [18] via the nucleophilic substitution with sodium azide. However, these methodologies often suffer from either complex procedures, long reaction times and low yields. In addition, there are usual purification problems associated with distillation [19,20] of products from the incomplete reactions since some azides decomposes rapidly with danger of explosion [21]. Consequently, we decided to undertake a systematic study of the nucleophilic substitution of

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halides and α-tosyloxy groups using aqueous sodium azide, NaN_3, under milder and efficient conditions.

We have been successful in conducting organic transformations using modified clay systems containing basic groups such as 3-aminopropyltriethoxysilane (3-APTES) and much smaller and symmetrical surfactants namely, tetramethyl-, tetraethyl- and tetrabutylammonium chlorides into the clay interlayer [22–24]. We have now extended this strategy to a practical synthesis of azides and α-azidoketones which involves triphase catalysis. The nucleophilic displacement occurs in this system that consists of a dispersed solid phase and two immiscible liquid phases containing the electrophilic and nucleophilic reagents [25] where the reagents get transferred from the liquid phase to the solid phase.

Inventing selective, efficient and eco-friendly methods for applications in complex organic synthetic manipulations constitutes a major chemical research effort. In this regard, several non-conventional methods are emerging that involve reactions in aqueous media [26,27] or those that are accelerated by exposure to microwaves [1] [29–31] or ultrasound [32–35] irradiation. These methods are now recognized as viable environmentally benign alternatives [30,31]. Although, sonication methods have been initially applied to homogeneous reactions in a variety of solvents, this approach has now evolved into a useful technique in heterogeneous reactions. A vast majority of the sonochemical applications in the synthesis deal with reactions involving metals [36,37], organic phase insoluble reagents, or their aqueous solutions [38,39]. Among the nucleophilic substitution reactions, there are only handful studies wherein ultrasound irradiation has been substituted for a phase transfer catalyst namely in the preparation of alkyl cyanide [40], synthesis of azidoacetonitrile, allylic and propargyl azides [20] and methylation of diazacoronands [41]. In view of the paucity of the data in this field [42,43], we decided to explore the viability of ultrasound as a substitute for a phase-transfer catalyst (PTC). Herein, we summarize our results on a set of catalytic systems that includes (1) triphase catalytic system under classical (reflux) condition, (2) triphase catalyst in conjunction with ultrasound irradiation at very low temperature, and finally (3) a two-phase catalyst-free system using only ultrasound irradiation.

[1] For recent reviews on microwave-assisted chemical reactions see Ref. [28].

2. Experimental

2.1. Instrumentation

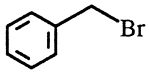
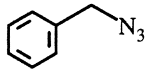
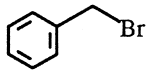
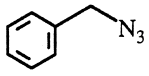
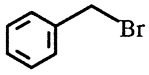
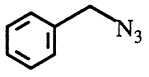
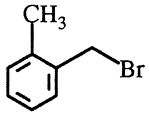
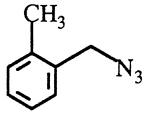
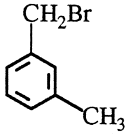
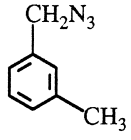
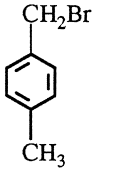
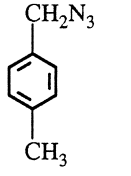
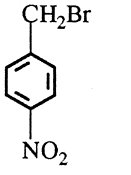
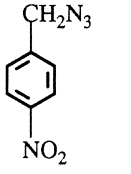
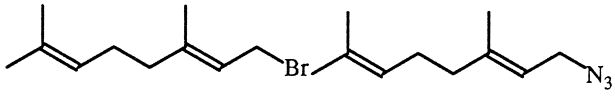
Ultrasonic processor (Heat systems-Ultrasonics, W-380) with stepped horn configuration was used for sonochemical reactions. All of the substrates and products were characterized by comparison with the literature data. ^1H and ^{13}C NMR were obtained on JEOL Eclipse 300 MHz spectrometer in $CDCl_3$ with TMS as an internal standard. Infrared spectra were recorded on a ATI Mattson FT-IR instrument.

2.2. Materials

Montmorillonite K 10 clay, tetramethyl-, tetraethyl-, tetra-*n*-butylammonium bromide and geranyl bromide were purchased from Aldrich Chemical. The rest of the chemicals or reagents were purchased from Lancaster Synthesis and were used as received without further purification. The α-tosyloxyketones were prepared by refluxing the appropriate ketone with (hydroxytosyloxy)iodobenzene in acetonitrile for 2–3 h [44]. Surfactant pillared clays were prepared by stirring sodium-exchanged clay [22–24] (6 g) in 0.2 molar solution of the corresponding surfactants for 100 h at 60–70°C. The solution was filtered, washed repeatedly with distilled water

and dried overnight in an oven (100–110°C). X-ray diffraction data shows that the spatial distance in the 001 plane increases from 9–16 Å and FT-IR spectra displays characteristic stretching frequencies of alkyl group [24]. The surfactant pillared clay material in the following experiments refer to tetramethylammonium chloride intercalated clay.

Table 1
Synthesis of alkyl azides from alkyl bromides and sodium azide under triphase catalysis and ultrasound irradiation conditions

Entry	Substrates	Product	Ref.	Time (h)	Yield[a] (%)	IR (Neat) cm^{-1}
1			[6]	6 (2.5) [3.5]	84 (87) [85]	2094
2				6	82	2094
3				6	82	2094
4			[7]	6 (2.5) [3.5]	83 (84) [84]	2095
5			[8]	6 (2.5) [3.5]	81 (80) [83]	2095
6			[9]	6 (2.5) [3.5]	83 (83) [84]	2095
7			[10]	5 (2) [3]	91 (92) [90]	2100
8			[11]	12 (4.5) [6]	93 (83) [80]	2095

[a] Yield refers to pure isolated products; the entries 2 and 3 refer the use of surfactant pillared clay that is recycled second and third time, respectively under identical conditions. Results in parenthesis are obtained using a triphase catalyst and ultrasound irradiation. Results in bracket are obtained using only ultrasound.

2.3. General procedure for the synthesis of alkyl azides using triphase catalyst

In a typical experiment, benzyl bromide (360 mg, 2.1 mmol) in hexane (3 ml) and sodium azide (180 mg, 2.76 mmol) in water (3 ml) were admixed in a round-bottomed flask. To this stirred solution, pillared clay (100 mg) was added and the reaction mixture was refluxed with constant stirring at 90–100°C until all the starting material was consumed as observed by thin layer chromatography using hexane as solvent. The reaction was quenched with water and the product extracted into ether. The ether extracts were washed with water and the organic layer dried over anhydrous sodium sulfate. The removal of solvent under reduced pressure afforded pure alkyl azides as confirmed by the spectral analysis and comparison of data with reported in literature. The clay material was retrieved from the aqueous layer by filtration, washed with organic solvent and dried overnight at 110°C for further reuse (recycled twice) without any loss in catalytic activity (entry 2 and 3 in Table 1).

2.4. General procedure for the synthesis of alkyl azides using ultrasound

In a typical experiment, benzyl bromide (360 mg, 2.1 mmol) in hexane (3 ml) and sodium azide (180 mg, 2.76 mmol) in water (3 ml) were admixed in a round-bottomed flask. To this, pillared clay (100 mg) was added and the reaction mixture was irradiated (2.5–4.5 h at 0–5°C) by immersing the ultrasound 'stepped' probe into the solution until all the starting material was consumed as observed by thin layer chromatography using hexane as solvent. The reaction was quenched with water and the product extracted into ether. The combined ether extracts were washed with water and the organic layer dried over anhydrous sodium sulfate. The removal of solvent under reduced pressure afforded pure alkyl azides.

2.5. General procedure for the synthesis of α-azidoketones using triphase catalyst

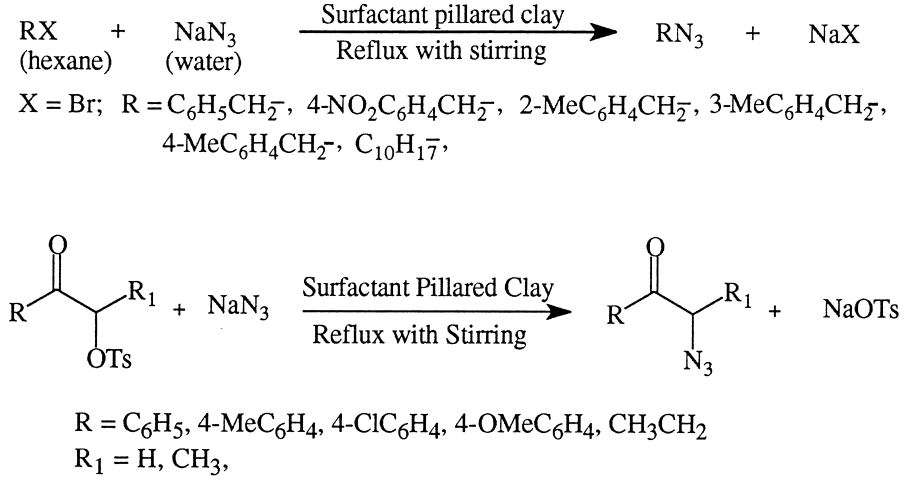
In a typical experiment, α-tosyloxyacetophenone (260 mg, 1 mmol) in chloroform (5 ml) and sodium azide (78 mg, 1.2 mmol) in water (5 ml) were admixed in a round-bottomed flask. To this stirred solution, pillared clay (100 mg) was added and the reaction mixture was refluxed with constant stirring at 90–100°C until all the starting material was consumed, as observed by thin layer chromatography using EtOAc:hexane, (1:4, v/v) as solvent. The reaction was quenched with water and the product extracted into chloroform (20 ml). The combined extracts were washed with water and the organic layer dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to afford pure α-azidoacetophenone.

2.6. General procedure for the synthesis of α-azidoketones using ultrasound

In a typical experiment, α-tosyloxyacetophenone (260 mg, 1 mmol) in acetonitrile (5 ml) and sodium azide (78 mg, 1.2 mmol) in water (5 ml) were admixed in a round-bottomed flask. This mixture was irradiated by inserting the ultrasound 'stepped' probe into the solution (10–25 min at room temperature, 25°C) until all the starting material was consumed as observed by thin layer chromatography using EtOAc: hexane, (1:4, v/v) as solvent. The reaction was quenched with water and the product extracted into chloroform (2×10 ml). The combined extracts were washed with water and the organic layer dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to afford pure α-azidoacetophenone.

3. Results and discussion

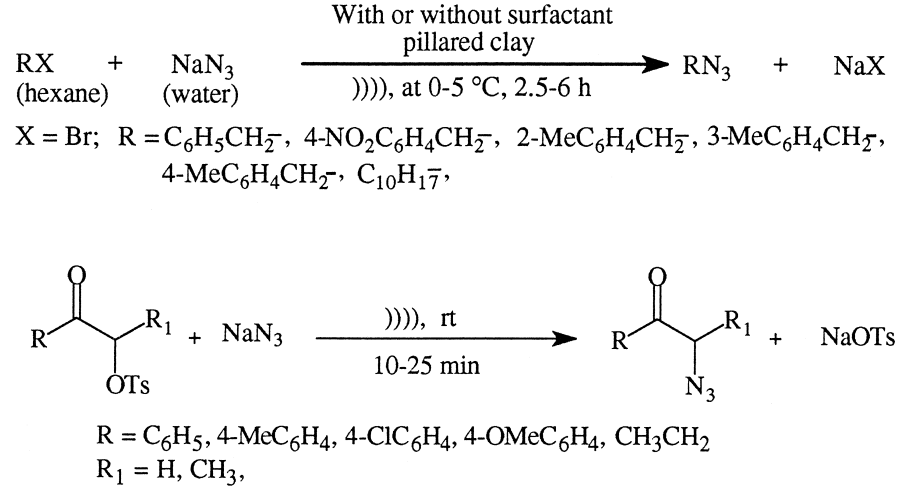
In a typical example, the alkyl bromide (in hexane) or α-tosyloxyketones (in chloroform) and aqueous NaN_3 are admixed in the molar ratio 1:1.2 and the reaction mixture is refluxed



Scheme 1.

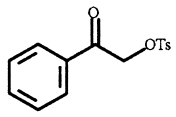
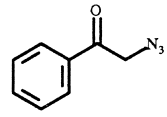
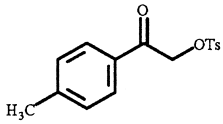
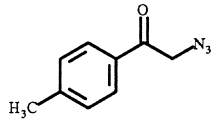
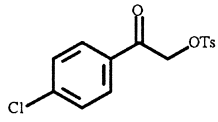
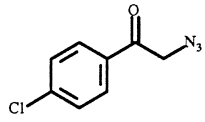
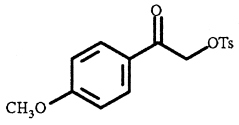
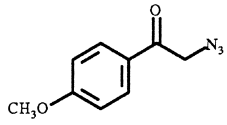
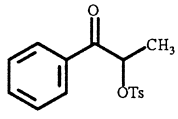
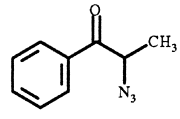
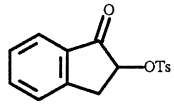
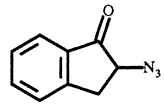
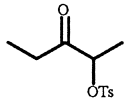
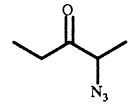
with continuous stirring in the presence of organo-clay material under classical conditions or subjected to ultrasound irradiation with or without organo-clay assembly (Schemes 1 and 2, Tables 1 and 2).

Our results for the preparation of a variety of azides under triphasic as well as ultrasound conditions are summarized in Table 1 and are exemplified by substrates such as benzyl bromide, its substituted analogues and long chain allyl bromides. Benzyl bromide bearing electron withdrawing substituents undergo the reaction at a much faster rates as compared to parent or benzyl bromide derivatives with electron releasing group appended. The reaction is very slow at room temperature (only 13% of desired product is formed after 7 days). Instead, benzyl bromide is found to produce a white polymeric material when natural montmorillonite K 10 clay is used. The reaction does not occur in the absence of the catalyst. Interestingly, the catalyst can be reused without loss in activity; we have reused the recovered clay two to three times with reproducible results (entries 2 and 3,



Scheme 2.

Table 2
Synthesis of α-azidoketones from α-tosyloxyketones and sodium azide under triphase catalysis and ultrasound irradiation conditions

Entry	Substrates	Products	Ref.	Time (min)	Yields[a] (%)	IR ν (cm^{-1})
1			[16]	90 (12)	95 (95)	2100
2			[17]	90 (10)	97 (94)	2110
3			[17]	90 (10)	93 (94)	2105
4			[17]	90 (10)	95 (96)	2120
5			[17]	120 (15)	89 (91)	2110
6			[16]	150 (25)	92 (96)	2100
7			[17]	150 (20)	88 (86)	2110

[a] Yield refers to pure isolated products and the results in parenthesis refer the use of ultrasound irradiation only.

Table 1). In the case of a long chain allyl halide (geranyl bromide, entry 8), the reaction rate is much slower and comparatively longer time is required for completion of the reaction. This may be due to the increase in the electron releasing capacity with increasing chain length and also due to restricted entry of the hydrophobic long chain allyl halides into the surfactant pillared clay interlayer. We explored the suitability of various solvents such as toluene, dichloromethane and hexane for azidation reaction of alkyl halides and found that the first two solvents are not suitable for this reaction.

The results for the preparation of α-azidoketones are summarized in Table 2 which include several α-tosyloxy substrates such as aryl- and cyclic ketones. There is essentially no difference in the reaction rate for α-tosyloxyketones bearing electron withdrawing or donating substituents. However, in the case of cyclic ketone (entry 6), the reaction rate is slower and requires comparatively longer time for the reac-

tion to be completed. We have investigated this reaction in a variety of organic solvents and found that chloroform is ideally suited for this nucleophilic substitution in terms of yield and time required for completion of the reactions.

Under ultrasound irradiation, we noticed a favorable acceleration in reaction rates when compared to classical conditions (i.e., under reflux). The addition of catalytic amount of surfactant pillared clays, further facilitated the reaction thereby indicating a synergistic effect of ultrasound on triphase catalyst system. However, the successful reaction with sonication in the absence of pillared clay (Tables 1 and 2) indicate that ultrasound can indeed substitute for a phase transfer catalyst thereby suggesting that this is the method of choice for the nucleophilic substitution reactions.

4. Conclusion

The efficiency and reusability of the triphase catalyst in nucleophilic substitution reactions is described that leads to a facile synthesis of azides and α-azidoketones in a superior and benign method. The utility of the inexpensive surfactant pillared clay materials in these synthetic protocols is compared with the reaction acceleration achieved via sonication method which indicates that sonochemical approach is a viable substitute for phase transfer catalysts. Among the three possible viable alternatives for this nucleophilic substitution reactions, we believe that the two phase system using ultrasound irradiation is the method of choice being very practical and convenient.

Acknowledgements

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