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Triton-X-100: Green Media for Aza and Thia-Michael Addition

VEENA YADAV†, REKHA LAGARKHA† and RUPESH KUMAR*
Department of Chemistry, University of Delhi, Delhi-110 007, India
Fax: (91)(11)23816312; Tel: (91)(11)9818901344
E-mail: chembio005@yahoo.co.in

Triton-X-100 (non-ionic) is found to be an inexpensive and non-toxic reaction medium as well as catalyst for aza and thia-Michael addition under milder and neutral reaction conditions at room temperature. This eco-friendly protocol offers the ease of operation, avoid the use of acid and base catalysts for this conversion, no side reactions observed and moreover can be recovered and recycled.

Key Words: Michael addition, Triton-X-100.

INTRODUCTION

The development of new ways to use catalysts and the use of alternative green solvents for catalytic reactions are areas that continue to attract attention[1]. While the use of water as solvent is probably the most desirable approach, this is often not possible due to the hydrophobic nature of the reactants and the sensitivity of many catalysts to aqueous conditions[2]. Other alternatives include (a) the use of supercritical fluid media[3] that have the advantage of facile solvent removal and easy recycle but require high pressure. (b) Fluorous based systems[4] have the advantage of being highly hydrophobic and the solvents are probably innocuous but have the disadvantage of being volatile and expensive systems. (c) Ionic liquids[5] have a particularly useful set of properties, being non-volatile and virtually insoluble in water and alkanes but readily dissolving many transition metal catalysts. They are, however, very expensive. In this communication we describe the use of a simple and widely available polymer Triton-X-100 as nontoxic, inexpensive, non-ionic liquid solvents of low volatility.

The Michael reaction (discovery in 1889)[6] has been used as one of the most useful methods for effecting carbon-carbon bond formation and later has also been efficiently manipulated for carbon-sulphur and carbon-nitrogen bond forming processes[7]. Among various nucleophilic additions, the Michael addition of thiols to electron deficient alkenes constitutes a key step in biosynthesis[8] and in the synthesis of compounds with promising biological activities[9,10]. The conjugate addition of nucleophiles to electron deficient olefins is well-known in organic synthesis[11]. It is

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†Department of Chemistry, Bundelkhand University, Jhansi-284 128, India.

used extensively in the synthesis of pharmaceutical intermediates, peptide analogues, antibiotics and other biologically active molecules and drugs[12]. A number of procedures either based on activation of amines and thiols with base[13] or activation of the acceptor olefins with Lewis acids[14]. Several synthetic organic methodologies has demonstrated several inorganic salts such as zeolites[15], $Hf(OTf)_3$[16], alumina in DMF at 80 ºC[17], synthetic and natural phosphates[18], $InBr_3$[19], $Bi(NO_3)_3$[20], $Bi(OTf)_3$[21], Nafion® SAC-13[22] and $InCl_3$[23]. Ionic liquids have been introduced in place of metal catalysts for aza and thia-Michael addition reactions[24]. Previously, we have reported aza-Michael reaction of N-alkyl and N-aryl piperazine with acrylonitrile using copper nanoparticles as catalyst under mild reaction condition[25]. Recently, the utility of polyethylene glycol as non-ionic solvent for Michael addition reaction of amines to electron deficient alkenes has been reported[26]. Kamal *et al.*[27] have been reported the conjugate addition of thiols to conjugated alkenes employing polyethylene glycol as a reaction media. In this communication we describe the use of a simple and widely available polymer, Triton-X-100 (Fig. 1). Triton-X-100[28] is one of the most commonly used non-ionic surfactant for solubilizing membrane proteins during isolation of membrane-protein complexes.

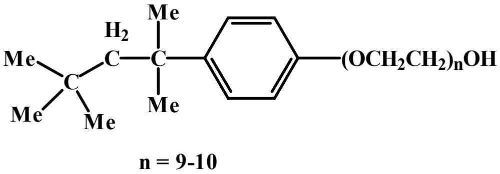


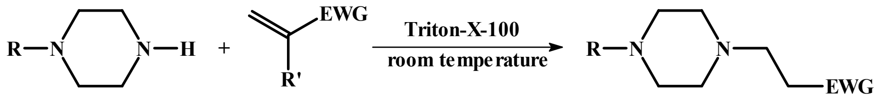
Fig. 1. Structure of Triton-X-100

Triton-X-100 has a number of benign characteristics that underlie, for example, chemically stable in most acidic and alkaline solutions, effective performance across a broad temperature range, readily biodegradable. To the best of our knowledge, Triton-X-100 had not been used as reaction media for organic transformations. It is a new green recyclable reaction medium for conjugate addition of amines and thiols to conjugated alkenes at room temperature without any use of acid-base catalysts. Such reactions do not generate any toxic waste by product.

EXPERIMENTAL

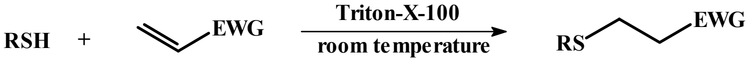
A mixture of amine/thiol (1 mmol), alkene (1.5 mmol) and Triton-X-100 (1.9 g) was placed in 25 mL round-bottomed flask. The reaction mixture was stirred at room temperature until the reaction was complete. The reaction mixture was extracted with hexane, the extract dried and concentrated under reduced pressure and resulting crude product was purified by silica column chromatography using ethyl acetate and hexane as an eluent to obtain the adduct in excellent yield (**Schemes I** and **II**). The recovered Triton-X-100 can be reused for five cycles without significant loss of activity. All organic compounds except 2-chloro-3-(4-methyl-piperazin-1-yl)-

propionitrile and 2-chloro-3-(4-methoxyphenyl-sulfanyl)-propionitrile (entry 6 and 14, respectively in Table-1), reported in literature[25-27,29,30] and are fully characterized by spectral analysis. For entry 6: ^{1}H NMR δ ($CDCl_3$, 300 MHz), 4.10 (t, J = 4.5 Hz, 1H), 3.84 (t, J = 4.8 Hz, 1H), 3.71-3.60 (m, 12H); ^{13}C NMR δ (ppm, 75 MHz), 116.1, 66.5, 60.5, 56.1, 44.2, 31.2; TOF MS ES^+ 152.18 (M-35) as parent peak and for entry 14: ^{1}H NMR δ ($CDCl_3$, 300 MHz), 7.39 (d, J = 8.5Hz, 2H), 6.81 (d, J = 8.5 Hz, 2H), 4.22 (t, J = 7.7 Hz, 1H), 3.74 (s, 3H), 3.20 (d, J = 6.9 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz), 160.4, 153.2, 135.5, 122.1, 115.6, 55.3, 29.6. MS TOF ES^+ 228.54 (M+1), 193.10 (M-35).



EWG = CN, $COCH_3$, $COOCH_3$
R' = H, Cl

Scheme-I



R = Aryl and alkyl
EWG = CN, COMe, CO_2Me

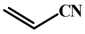
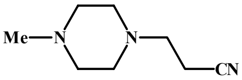
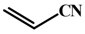
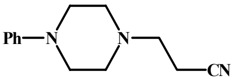
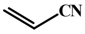
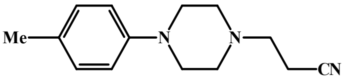
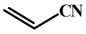
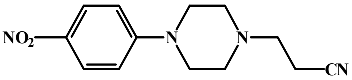
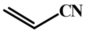
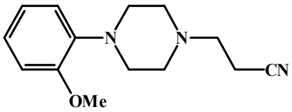
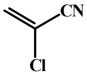
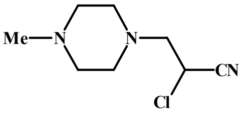
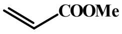
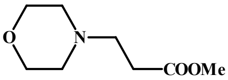
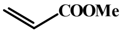
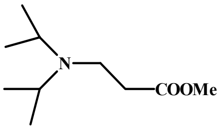
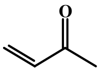
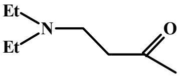
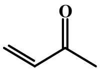
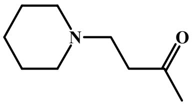
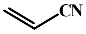
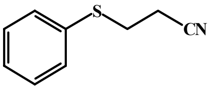
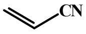
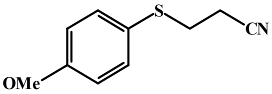
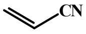
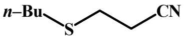
Scheme-II

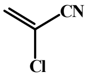
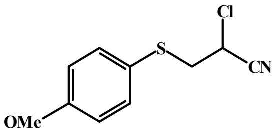
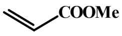
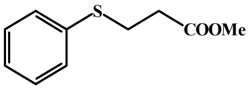
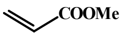
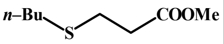
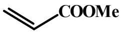
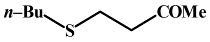
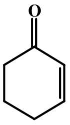
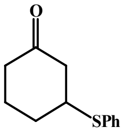
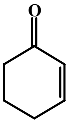
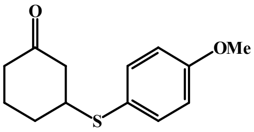
RESULTS AND DISCUSSION

The reactions of various amines and thiols with a variety of electron deficient alkenes are examined. The results are summarized in Table-1. Initially, readily available N-methyl piperazine (Table-1, entry 1) and thiophenol (Table-1, entry 11) were subjected to cyanoethylation in Triton-X-100 at room temperature for 35 min and 20 min, respectively. The corresponding product were obtained in 99 and 96 % after the standardized protocol. No by-product formation was observed. This reaction procedure is compatible with various conjugated alkenes included α,β-unsaturated ketones, nitriles and carboxylic esters. The reaction proceeds efficiently at room temperature without need for acid or base catalyst and goes to completion in short reaction time. With lower amounts of Triton-X-100, the mixing is insufficient, which results in lower yields. Similarly, at higher concentration of Triton-X-100, yields are inadequate.

In order to prove that the use of Triton-X-100 as solvent is also practical, it must be conveniently recycled with minimal loss and decomposition. Since Triton-X-100 is immiscible with aliphatic hydrocarbons, the desired product may be extracted with compounds such as cyclohexane or hexane and retained. Triton-X-100 may be reused. The solvent phase was recycled with no loss of reactivity for five cycles,

TABLE-1
AZA AND THIOLS-MICHAEL REACTION WITH ELECTRON DEFICIENT ALKENES IN TRITON-X-100[A]

Entry	Unsaturated alkenes	Product	Time (min)	Yield (%)[B]
1			35	99
2			30	99
3			30	99
4			30	99
5			30	99
6			35	96
7			35	99
8			40	94
9			35	99
10			35	99
11			20	95
12			25	92
13			40	88

14			40	87
15			30	90
16			40	85
17			40	82
18			25	92
19			30	90

[A]Reaction conditions: 1 mmol of amine, 1.5 mmol of electron deficient alkene, 1.9 g Triton-X-100, 25 ºC. [B]Isolated yield.

although a slight weight loss was observed from cycle to cycle due to degradation of Triton-X-100. The stability of Triton-X-100 under reaction conditions was studied also by the analysis of the reaction mixture by GC-MS.

A control experiment was conducted in the absence of Triton-X-100 in ether or cyclohexane and it was observed that addition of N-phenyl piperazine or thiophenol to acrylonitrile produced the corresponding product (**Schemes I** and **II**) in 18 % yield in 48 h[8].

There was no reaction in the absence of Triton-X-100. Thus, the probable mechanism for the amines to conjugated alkenes employing Triton-X-100 as recyclable reaction medium may be due to the attraction between the Triton-X-100 hydroxyl group oxygen and hydrogen attached to nitrogen of amine/sulphur of thiol, which makes the N-H/S-H bond weaker, enhancing the nucleophilicity of nitrogen/sulphur for addition to electron-deficient alkenes.

In conclusion, we have described herein a highly efficient catalyst as well as green reaction media, Triton-X-100 (non-ionic) for the Michael addition reaction of different amines and thiols with electron deficient alkenes. Triton-X-100 offers a convenient, environment friendly, thermally stable, inexpensive and recyclable reaction medium. This methodology offers significant improvements with regard to yield of products, simplicity in operation, cost efficiency and green aspects avoiding toxic catalysts and solvents. More significantly, this work clearly demonstrates the potential of Triton-X-100 as a non-ionic liquid to act as an efficient and recyclable catalyst and shows much promise for further applications.

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