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Tris-ureas as versatile and highly efficient organocatalysts for Michael addition reactions of nitro-olefins: Mechanistic insight from in-situ diagnostics

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ABSTRACT

Tris(2-aminoethyl)-amine, TREN based tris-ureas (**1a–1d)** and tris-thiourea (**1e**) have been explored towards a wide range of catalytic Michael addition reactions. These tris-ureas, **1a–1d** efficiently catalyze the addition reaction of β-nitro styrenes (**2a–2d**) with various nucleophiles such as β-ketoesters (**3a–3c**), 1,3-dicarbonyl compound (**3d**), a cyanoester (**3e**) and a nitroester (**3f**) under ambient conditions to produce corresponding nitro alkanes in high yields. Pentafluorophenyl attached tris-urea, **1d** is found to be the most effective catalyst in the series that yields 78–98% products conversion. In case of the reaction between β-nitro styrenes and malononitrile (**3g**) in presence of **1d**, 2-amino-5-nitro-4,6-diphenylcyclohex-1-ene-1,3,3-tricarbonitriles are also isolated as a minor product along with the corresponding Michael adduct. The added advantage of bridge-head nitrogen center in tris-urea organocatalysts, **1a–1d** has been established by studying analogous benzene platform based tris-ureas (**1f, 1g, 1h)** in similar experimental conditions. Furthermore, a plausible reaction mechanism has also been established based on in-situ ^{1}H NMR kinetic studies.

1. Introduction

Organocatalysis has emerged as one of the most rapidly growing and promising areas in synthetic organic chemistry. The advantages of organocatalysis consist of their operational simplicity, ready availability, low cost, and low toxicity, which confers a huge direct benefit in the production of pharmaceutical intermediates [1]. In current research, organocatalytic strategies include formation of temporary covalent bond through enamine or iminium catalysis [2], hydrogen bonding interaction through urea or thiourea catalysis [3], pi-stacking interactions [4], Brønsted acid base interactions [5] and ion-pair interactions by phase transfer catalysts [6], etc. Combinations of different strategies may lead to an unexpected synergistic effect to develop better organocatalysts. The Michael reaction of nitro-olefins represents a convenient route to nitroalkanes which are versatile intermediates in organic synthesis [7]. This reaction has been well studied using different organocatalysts and it has emerged as one of the most efficient and powerful tools to C—C bond formation. Several organocatalysts like modified amines and diamines [8], substituted thiourea [9] functionalized L-proline [10], squaramide [11](a)–(e), and other asymmetric version of catalysts [11](f) are also reported.

In recent times, TREN based tripodal ureas/thioureas have been extensively studied in the area of anion recognition chemistry upon manipulating the hydrogen bonding ability of ureas/thioureas [12]. These receptors generally create a C_{3v}-symmetric cleft for guest species where hydrogen atoms of three urea/thiourea moieties are directed towards the inner cavity. Apart from these urea/thiourea moieties in such receptors, a bridge-head nitrogen atom (tertiary N center) is located close proximity to the cleft bound guest. Herein we explore such tris-ureas (Scheme 1) as effective catalytic scaffolds towards the Michael addition reaction of nitro-olefins with various carbon nucleophiles. To the best of our knowledge this represents the first report on the Michael addition reaction by tripodal tris-urea as organocatalyst. Moreover, control experiments have been carried out to justify the involvement of bridge-head nitrogen center of tris-ureas in the catalytic activity and in-situ ^{1}H NMR kinetic studies to establish a plausible reaction mechanism.

2. Results and discussion

2.1. Selection of tris-ureas as catalysts

A judicious choice of scaffold is indeed very important towards the development of a new generation organocatalysts. Our choice

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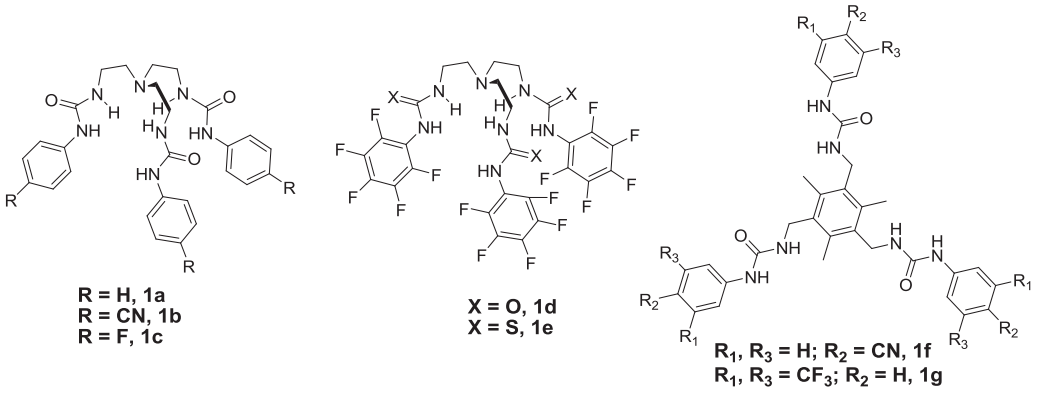


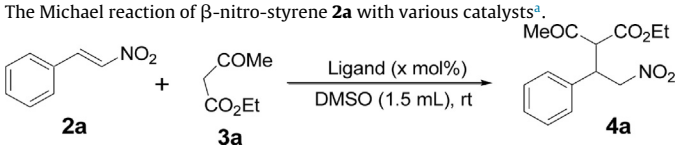
Scheme 1. TREN and mesitylene based tripodal tris-ureas.

of TREN based tripodal tris-ureas towards Michael addition reaction between nitro-olefins and different carbon nucleophiles are based on, (i) tris-ureas produce a microenvironment by forming C_{3v}-symmetric clefts or dimeric capsular assemblies [12]. In cases of anionic guest, acidic H-atoms of urea NH are directed towards the center of the cavity [12]. Thus, orientation of multiple urea protons of the catalysts might favor activation of the incoming guests like nitro-olefins in case of the Michael addition reaction through multiple hydrogen bonding interactions, (ii) presence of bridge-head *N*-center in the catalytic scaffold can also play a synergistic role in such addition reaction. Thus, it would be interesting to have a new generation organocatalysts with tris-urea receptors having bridge-head *N*-center in the scaffold, (iii) further scope to tune the catalytic activity by changing the substituent on the attached aryl unit to the urea center to study the Michael addition reactions with closely related catalysts.

2.2. Efficacy of functionalized tripodal tris-urea catalysts

Various tren-based ureas and thiourea derivatives **1a–1e** have been synthesized following the literature procedures to examine the effect of substituents on the aryl moieties attached to urea linkage [12]. Then the evaluation of catalytic activities of **1a–1e** towards the Michael addition of various carbon nucleophiles to nitro-olefins are undertaken. We have carried out the Michael reaction of β-nitro-styrene **2a** with 1.5 equiv. of ethylacetoacetate **3a** as model reaction with different catalysts loading (Table 1). The screening study has been carried out in DMSO due to insolubility of catalysts in other solvents like THF, MeOH, DCM, etc. We have also carried out selected Michael addition reactions with all the catalysts (**1a–1e**) in different heterogeneous reaction medium (Soluble substrate + insoluble catalyst). However, in all the cases no product is formed. This suggests that the reaction is going only through homogeneous medium. The reaction in the presence of phenyl analogue, **1a** (5 mol%) provides 60% yield of the desired Michael adduct **4a** after 5 h of reaction (entry 1, Table 1). Replacement of the catalyst with **1b** containing 4-cyano phenyl and **1c** with 4-flluoro phenyl groups improve the yields up to 67% (entry 2, Table 1) and 70% (entry 3, Table 1), respectively. Interestingly, pentaflurophenyl substituted catalyst **1d** dramatically increases the yield up to 95% within 4 h (entry 4, Table 1). The catalyst **1d**, bearing five fluoride atoms shows the highest catalytic activity. This could be due to the enhancement of the overall acidity of urea N–H groups. Gratifyingly decreasing the catalyst loading by employing 2 mol% of the catalyst **1d**, the reaction proceeds well and we find 82% yield after 4 h of reaction (entry 5, Table 1) and the reaction is completed after 6 h where **4a** is isolated in 95% yield, as diastereomeric mixtures (entry 6, Table 1). It is important to mention that some racemic and unselective versions of the Michael addition of nitro-styrene have been reported by using different metal/base catalysis [13], heterogeneous catalytic systems [14], organic bases [15], etc. Remarkably, in most of the cases there are some difficulties on the basis of high catalyst loading, limited substrate scope, and undefined mechanism of such reaction. However, here we could explore the Michael reaction with low catalyst loading towards a variety of substrates along with the plausible mechanism which are discussed latter. The catalytic activity of **1d** towards the Michael addition reaction decreases in DMF where product **4a** is isolated in 60% yield after 15 h. When thiourea analogue of **1d** i.e., pentafluorophenyl substituted tris-thiourea, **1e** (5 mol%) is chosen as catalyst, the catalytic activity of the reaction between **2a** and **3a** in DMSO decreases significantly. In this case, a trace amount of the desired product is detected after 15 h of reaction by TLC (entry 7, Table 1). Since **1e** is also soluble in

Table 1
The Michael reaction of β-nitro-styrene **2a** with various catalysts[a].



Entry	Ligand (mol%)	Time (h)	Yield (%)[b]
1	**1a** (5)	5	60
2	**1b** (5)	5	67
3	**1c** (5)	5	70
4	**1d** (5)	4	95
5	**1d** (2)	4	82
6	**1d** (2)	6	95
7	**1e** (5)	15	Trace

[a] the reaction was conducted with **2a** (1 equiv.), **3a** (1.5 equiv.), and DMSO(1.5 mL) in the presence of various catalysts at room temperature.
[b] isolated yield.