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A green and facile approach for the synthesis of *N*-monosubstituted ureas in water: Pd catalyzed reaction of arylcyanamides (an unexpected behavior of electron withdrawing groups)

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ABSTRACT

The Fe_3O_4 magnetic nano-particles were prepared, coated with tetraethyl orthosilicate (TEOS), functionalized with 3-chloropropyltrimethoxysilane (CPTMS), further functionalized with 2,2′-(piperazine-1,4-diylbis(methylene) dianiline (PDMD) and the corresponding Pd complex synthesized as a novel nano-magnetic heterogeneous catalyst (Fe_3O_4@SiO_2@CPTMS@PDMD@Pd) to be used for the synthesis of various *N*-monosubstituted ureas in water.

Also, in another attempt to see the effect of HCOOH, the hydration reaction of arylcyanamide was carried out in the presence of HCOOH (water + 98% HCOOH) which had two effects: it decreased the amount of the Pd catalyst from 40 to 30 mg, and the reaction condition was changed from the reflux condition to room temperature.

Interestingly, the arylcyanamides with electron withdrawing groups influence the course of the reaction and need more reaction times for completion which is an unexpected behavior, probably due to the high electron density around the central carbon atom of the nitrile group.

1. Introduction

Urea derivatives have been synthesized by a number of methods and used for treatment of a range of tumors [1–6]. Urea-based pro-drugs have been reported as candidates for melanocyte-directed enzyme pro-drug therapy which the drug will be released upon exposure to tyrosinase [7]. Some corresponding urea derivatives have been also reported as protein tyrosine kinases inhibitors to become potential anticancer drugs [8]. For these reasons, the synthesis of urea and their functionalized derivatives is of high interest. For instance, L. Fu and coworker designed and synthesized a novel series of ureas containing pyrimidinyl group. Some of the prepared compounds showed potential cytotoxicity against several human cancer cell lines. From the structure–activity relationships we may conclude that introduction of a sulfide bridge between phenyl and pyrimidinyl rings would be critical for their biological activities [9].

Also, aryl urea is an interesting entity for many medicinal chemists to explore its various biological activities. For example Umadevi and coworkers synthesized few compounds by condensing urea, thio- urea and thiosemicarbazide with phenol and substituted aromatic aldehyde (Scheme 1, compounds **1** to **5**). These compounds were further evaluated for antibacterial activity *in vivo* against Bacillus subtilis, Salmonella aureus, Salmonella typhi and Shigella dysentry. Ampicillin was taken as standard drug. These compounds show significant antibacterial activity [10].

The hydrolysis of cyanamide to urea by different catalysts has been investigated for a long time [11–16], since the *N*-monosubstituted ureas are found in many natural products and were used in pharmaceutical and agrochemical industry, biological chemistry, and agrochemical industry [17–20]. Some researchers have devoted their careers to find the better procedure for the synthesis of ureas. For example, D. P. Fairlie and coworkers synthesized the guanidine and urea Ligands through amination and hydration of a cyanamide ligand bound to Pt(II), Os(III), and Co(III) [21]. F. Briganti and coworkers prepared urea from the hydration reaction of cyanamide by the use of carbonic anhydrase catalyst [22]. P.-L. Fabre and coworkers prepared the [Pd(en)(3,4-(NC(O)NH_2)sq)]-0.5H_2O complex and observed the unusual hydration of the cyanamido ligand [23]. The three-dimensional structure of a possible intermediate in the hydration reaction of cyanamide to urea catalyzed by human carbonic anhydrase II (hCAII) has been determined by S. Mangani and coworkers via the cryocrystallographic techniques [15].

However, hydration of cyanamides suffers from various disadvantages such as low yields, long reaction times, the use of

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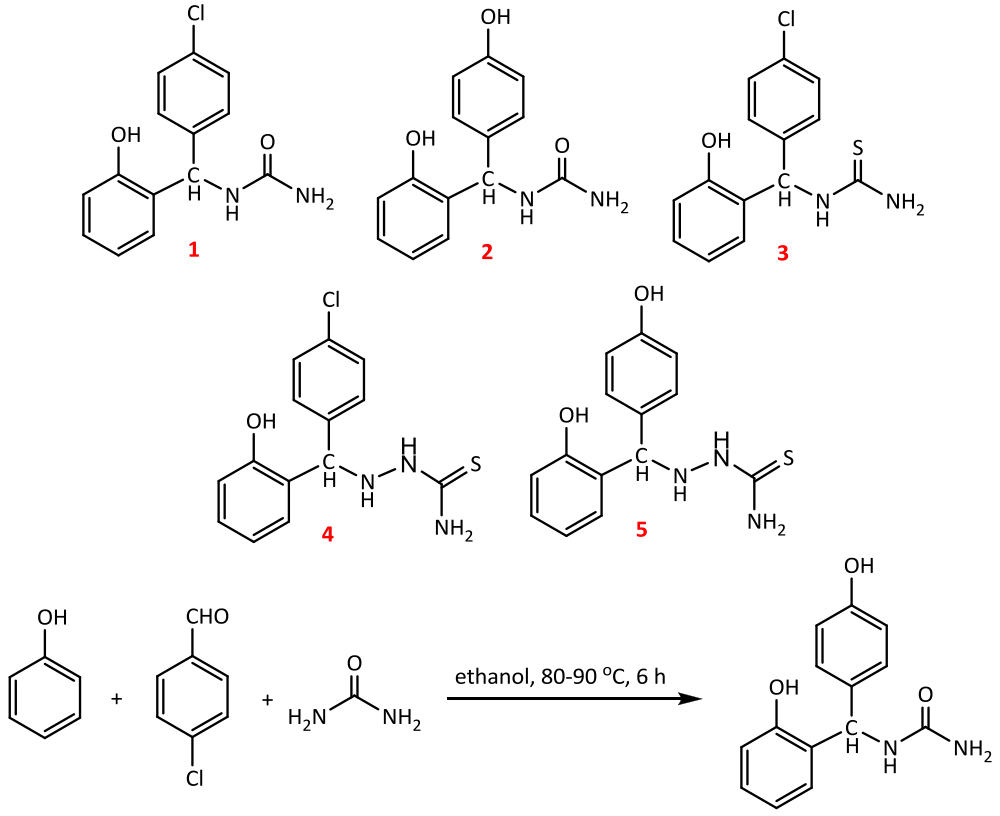
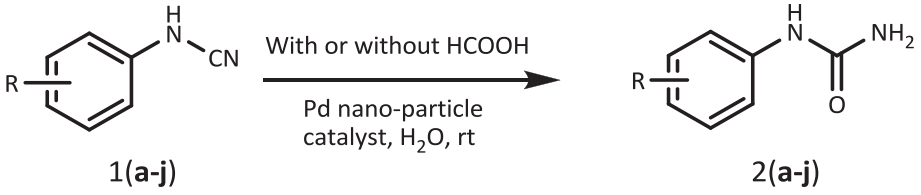


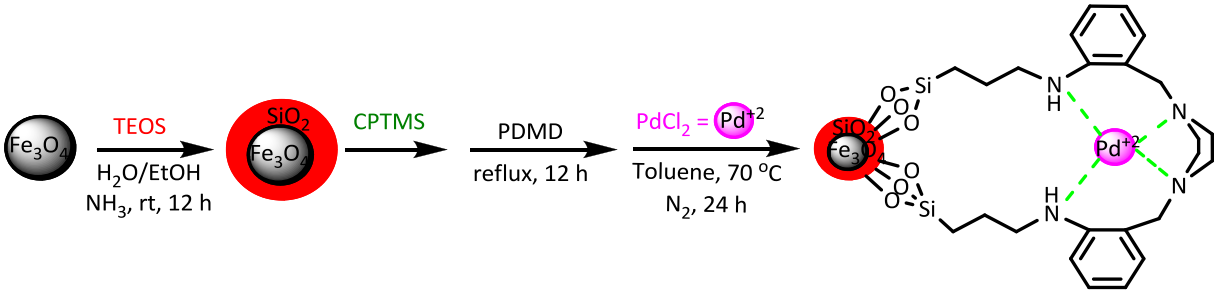
Scheme 1. Synthesis of some medicinal ureas.

corrosive base or acids, the use of the toxic organic solvents, application of the expensive, toxic and dangerous reagents or catalysts and tedious work-up [24–28]. Therefore, it is desirable to develop an efficient and green method for the preparation of *N*-monosubstituted ureas that reduce or eliminate the problems.

The use of magnetic nanoparticle catalysts has a significant growth during the past decade since nanoparticles have a large surface-to-volume ratio compared to bulk materials [29–31]. Also, their use are in accord with the principles of green chemistry due to their minimum chemical wastes, energy efficiency, improved economy and easy separation since the system is heterogeneous. Among the various magnetic nanoparticles, Fe_3O_4 is the most widely used magnetic substance for catalyst supported which is less toxic than their metallic counterparts [32]. For example, a magnetic nanoparticle conjugated mesoporous nanocatalyst (Fe_3O_4@SBA-15) with a high surface area was synthesized by A. Bhaumik and co-workers via the chemical conjugation of Fe_3O_4 nanoparticles with functionalized mesoporous SBA-15. The



Scheme 2. Synthesis of the *N*-monosubstituted ureas.



Scheme 3. Synthesis of the Pd nano-particle catalyst.