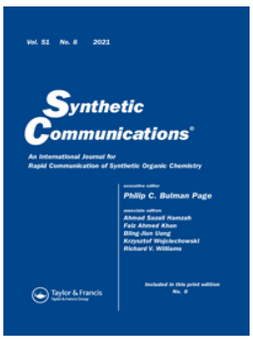

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T3P mediated intramolecular rearrangement of *o*-aminobenzamide to *o*-ureidobenzonitrile using isothiocyanates

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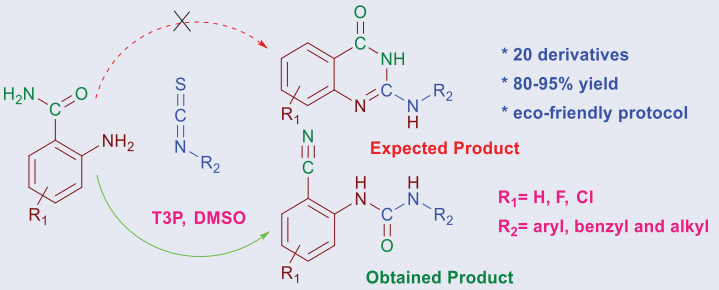
ABSTRACT

Current work describes the environmentally benign approach for the synthesis of *o*-ureidobenzonitriles, from *o*-aminobenzamides and isothiocyanates using T3P. Here, the conversion of thiourea to urea and amide to nitrile take place simultaneously via unprecedented intramolecular rearrangement. This protocol is operationally facile and offers wide variety of *o*-ureidobenzonitriles at room temperature in good to excellent yields.

GRAPHICAL ABSTRACT



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Introduction

T3P (Propane phosphonic acid anhydride) (Figure 1), is a versatile and unique reagent that is being used in many organic reactions like functional group transformations, condensation, acylation, oxidation reactions. It is an excellent dehydrating agent and coupling reagent in peptide synthesis.[1] Compared to other traditional reagents, T3P is eco-friendly, less allergic, less toxic and can be easily removed from the reaction mixture as it is highly soluble in aqueous solutions.

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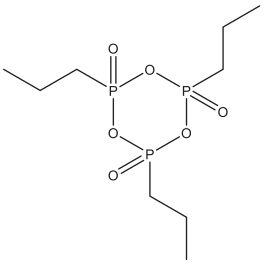


Figure 1. T3P structure.

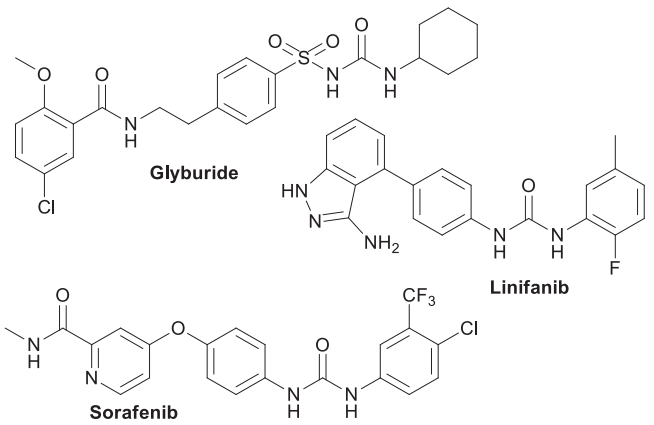
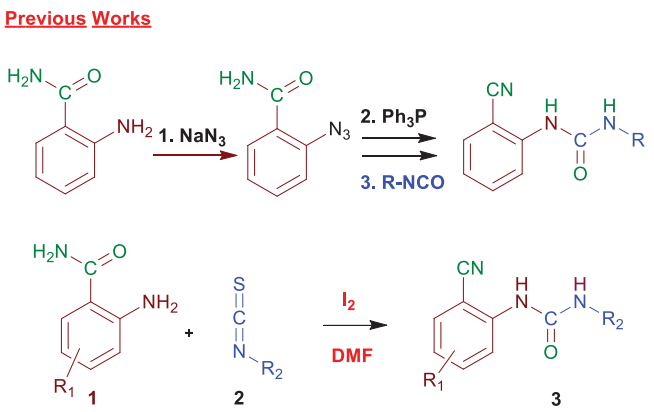


Figure 2. Bioactive molecules containing urea moiety.

Urea and its derivatives have a broad range of biochemical effects and pharmaceutical applications for their unique ability to form hydrogen bonds with proteins and receptor targets.[2,3] They also have extensive applications in agrochemicals. Some of the urea derivatives have been found to exhibit anti-diabetic, antibacterial[4a], antiviral[4b], anti-HIV[4c], anti-cancer[4d], hypnotic and sedative activities[4e]. Among those many are clinically approved drugs, such as glyburide (anti-diabetic), sorafenib and linifanib (anti-cancer) (Figure 2) bearing urea as key moiety.[5] In recent years, intense research have been focused on the design and synthesis of urea derivatives of biological interest. Traditional methods for the synthesis of urea involve the reaction of amines with isocyanate, CO and phosgene. Ureas are also synthesized using activated carbamates, carbonates, carbon monoxide, carbon dioxide at elevated temperatures.[6]

Nearly 30 pharmaceuticals containing nitrile as core motif are recommended for a diverse variety of medicinal indications.[7] Saxagliptin,[8a] cimetidine[8b] and anastrozole[8c] are the nitrile-containing drugs prescribed for the treatment of type 2 diabetes, peptic ulcer and breast cancer respectively. In addition they also have applications in dyes, agrochemicals and are also synthetic intermediates for the preparation of amines, amides, alcohols, ketones, carboxylic acids, oxazolines, some polymers and many heterocycles.[9] Therefore, the development of methods for the synthesis of nitriles is one of the most important task in organic chemistry. Nitriles are generally synthesized by the dehydration of primary amides and aldoximes. The functional group conversion of



Scheme 1. Previous works for the synthesis of *o*-ureidobenzonitriles.

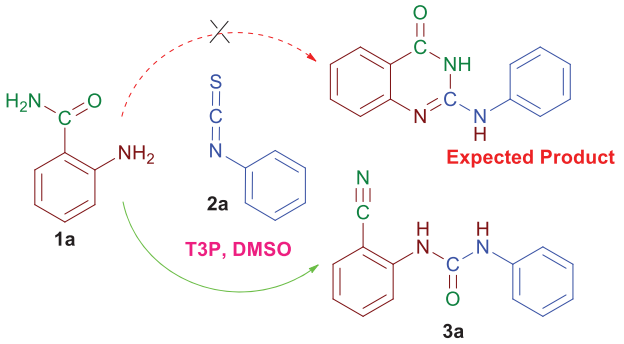
amide to nitrile is a difficult task, which requires acidic dehydrating reagents such as $POCl_3$, P_2O_5, TFAA, $TiCl_4$ or $SOCl_2$.[10] Recently, Imen Talbi et al. developed a method for the conversion of amides to nitriles using phosphorus-III reagents $P(NMe_2)_3$, PCl_3 and $P(OPh)_3$ as dehydrating agents.[11] Wan-Yin Fang and Hua-Li Qin et al. have developed some methods which are mediated by SO_2F_2 to convert primary alcohols, phenols and aldehydes into corresponding nitriles.[12]

Again, only few methods have been reported for the synthesis of *o*-ureidobenzonitriles (Scheme 1). The traditional method involves the reaction between *o*-aminobenzonitrile and isocyanates in presence of base. The method developed by Pedro Molina et al is a three steps process, starting with *o*-aminobenzamide.[13] Recently we established a new protocol using *o*-aminobenzamides and isothiocyanates catalyzed by molecular iodine.[14] All the above discussed methods have tremendous toxicological and environmental problems, suffers from narrow scope and lower yield.

Here, we are reporting a simple and straight forward method for the synthesis of *o*-ureidobenzonitriles, which has many advantages than the existing protocols. This method requires readily available inexpensive starting materials *o*-aminobenzamides, isothiocyanates, and T3P as reagent. The metal free route achieved here requires less time, works at room temperature, has easy work up procedure and exceptional functional group tolerance. The substrate scope for this method is very broad which includes phenyl, benzyl and aliphatic moieties and are synthesized in outstanding yields. Furthermore, the title compounds can serve as starting materials for many heterocycles like quinazolines and quinazolinones.[15]

Result and discussion

In continuation of our work on the synthesis of heterocycles via novel methodologies,[16] we designed a scheme to synthesis quinazolinones (Scheme 2). Initially we treated the mixture of *o*-aminobenzamide **1a** and phenyl isothiocyanate **2a** with one equivalent of T3P and DMSO in DMF solvent at room temperature for 12 h. The starting materials were consumed partially and a new non-polar spot was observed in TLC, which then isolated through column chromatography with 43% yield. Analysis of the



Scheme 2. Reaction between *o*-aminobenzamide and phenylisothiocyanate—expected and obtained products.

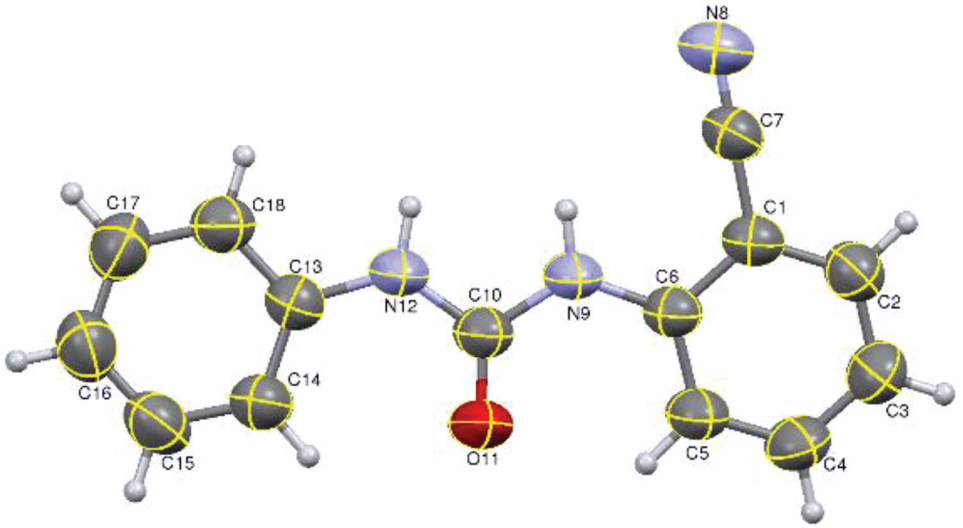
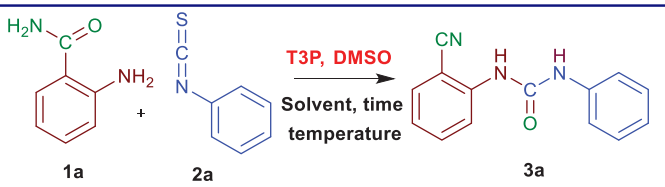


Figure 3. ORTEP diagram of 1-(2-cyanophenyl)-3-phenylurea (**3a**): CCDC number-2005876.

isolated product confirmed that, we have not got the expected product 2(phenylamino)-quinazolin-4(3H)-one but the 1-(2-cyanophenyl)-3-phenylurea, **3a** has been formed (Figure 3).

After the confirmation of structure, we initiated to optimize the reaction conditions to synthesize compound **3a** in an improved yield and the results obtained are summarized in Table 1. No desired product was observed in the absence of T3P or DMSO or both (Table 1, Entries 1–3). We then carried out the reaction using one equivalence of T3P and DMSO and obtained the product **3a** with 46% yield (Table 1, Entry 4). Increase in the loading of DMSO to 1.5, 2.0 and 2.5 equiv. and using one equiv. of T3P, yielded 68, 86 and 84% of the product respectively (Table 1, Entries 5–7). Now, by fixing DMSO quantity to 2.0 equiv., we used 0.5 and 1.5 equiv. of T3P and got 40 and 85% yields respectively (Table 1, Entries 8 and 9). So, in terms of yield, use of one equiv. of T3P and two equiv. of DMSO as additives was found to be the best among all the experimented ratios. Elapsing more time with these quantities of additives didn't

Table 1. Optimization of the reaction conditions.[a]



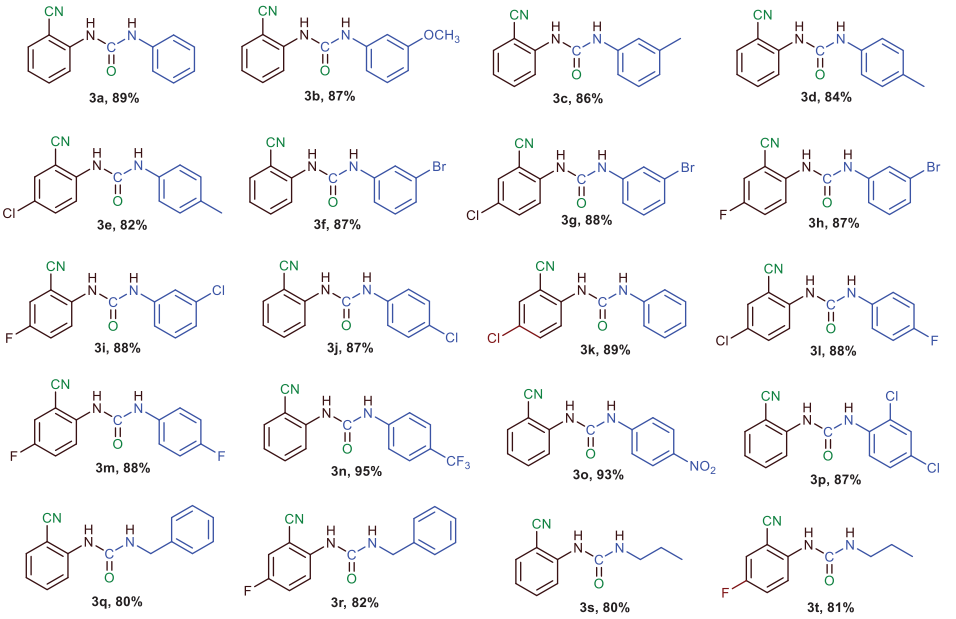
Entry	T3P (equiv.)	DMSO (equiv.)	Solvent	Temp. °C	Time h	Yield %[b]
1	0.0	0.0	DMF	rt	24	–
2	0.0	1.0	DMF	rt	24	–
3	1.0	0.0	DMF	rt	24	–
4	1.0	1.0	DMF	rt	4	46
5	1.0	1.5	DMF	rt	4	68
6	1.0	2.0	DMF	rt	4	86
7	1.0	2.5	DMF	rt	4	84
8	0.5	2.0	DMF	rt	4	40
9	1.5	2.0	DMF	rt	4	85
10	1.0	2.0	DMF	rt	10	82
11	1.0	–	DMSO	rt	4	89
12	1.0	2.0	EtOAc	rt	4	63
13	1.0	2.0	EtOH	rt	4	68
14	1.0	2.0	THF	rt	4	73
15	1.0	2.0	H_2O	rt	4	–
16	1.0	2.0	Toluene	rt	4	51
17	1.0	2.0	DMSO	40	4	71
18	1.0	2.0	DMSO	60	4	58

[a]Optimal reaction conditions: 1a (1 mmol), 2a (1 mmol) and T3P (1.0 mmol) in DMSO solvent (1 ml) at room temperature for 4 h.
[b]Isolated yield.

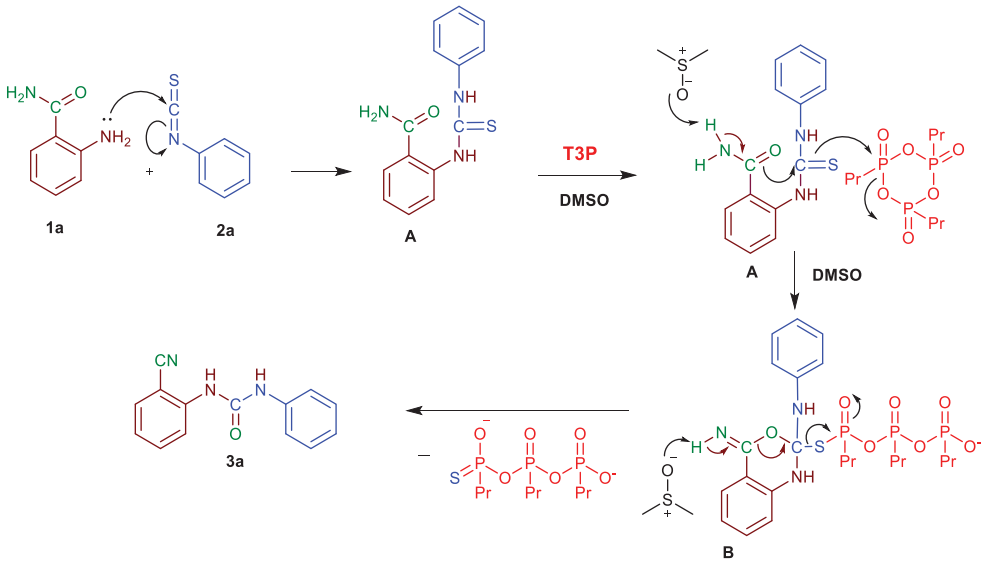
improve the yield considerably (Table 1, Entry 10). We further screened the reaction using solvents DMSO, EtOAc, EtOH, THF, H_2O and toluene (Table 1, Entries 11–16). The use of DMSO solvent, which is also an additive was found to be most favored, among the solvents employed (Table 1, Entry 11). The increase of temperature didn't facilitate the reaction in terms of yield (Table 1, Entry 17, 18). In conclusion, we found that, the reaction of *o*-aminobenzamide **(1a)** (1 mmol) and phenyl isothiocyanate **(2a)** (1 mmol) with T3P (1 mmol) in DMSO solvent at room temperature for 4 h was the ideal condition (Table 1, Entry 11) to synthesize 1-(2-cyanophenyl)-3-phenylurea, **3a**.

Using the best optimized condition, we further proceeded to synthesize a library of *o*-ureidobenzonitriles, using different combinations of *o*-aminobenzamide and isothiocyanates. We successfully synthesized twenty title compounds with excellent yields, which include phenyl, benzyl and aliphatic moieties of isothiocyanates with *o*-aminobenzamides (Table 2). The substituents on phenyl ring of isothiocyanates includes electron donating groups (–Me, –OMe), electron-withdrawing groups ($–NO_2$, $–CF_3$) and halogens (–F, –Cl, –Br). The yields of the reaction were not much dependent on the nature of the substituents as well as their positions on the benzene ring of isothiocyanates. However, in case of electron-withdrawing groups, like nitro and trifluromethyl, which are at ortho positions, the yields are a little better. This may be attributed to the fact that the electron-withdrawing groups may facilitate the nucleophilic attack of amine group of *o*-aminobenzamide on the carbon atom of isothiocyanate. The yields obtained in case of benzyl and aliphatic isothiocyanates are little less when compared to phenyl isothiocyanates. All these examples clearly illustrate the utility of the protocol for wider

Table 2. Substrate scope of the reaction.[a]



[a]Reactions were performed with 1 (1 mmol) and 2 (1 mmol) using T3P (1.0 mmol) in DMSO solvent (1 ml) at room temperature for 4 h.



Scheme 3. Plausible mechanism for the formation of *o*-ureidobenzonitrile.

applicability. We synthesized **3a** in 2.0 g scale and procured 85% yield which was 89% when synthesized in mmol scale.

A probable mechanism has been proposed for the synthesis of *o*-ureidobenzonitriles displayed in Scheme 3. The reaction between *o*-aminobenzamide **1a** and phenyl isothiocyanate **2a** first produces thiourea intermediate **A**. The interaction between T3P and sulfur atom of the thiocarbonyl group,[1c] trailed by the nucleophilic attack of carbonyl oxygen on the thiocarbonyl carbon leads to the formation of cyclized intermediate **B**. Deprotonation of amide group is done by DMSO. The unstable intermediate **B** further undergoes intramolecular rearrangement and generates stable *o*-ureidobenzonitrile **3a**.

Conclusion

Herein, we disclose a new and efficient method for the synthesis of *o*-ureidobenzonitriles under metal, ligand and acid-free conditions using nontoxic and eco-friendly reagent T3P via unique intramolecular rearrangement. The unexpected rearrangement involves the conversion of thiourea to urea and amide to nitrile simultaneously. We were able to synthesize a variety of *o*-ureidobenzonitriles, which are the precursors for the synthesis of heterocycles like quinazolines and quinazolinones. The unique reaction path observed here is employing to explore some new kind of reactions. Further extension of the substrate scope in synthesizing urea derivatives of biological interest and the study of their pharmacological and agro-chemical applications are under progress.

Experimental section

General procedure for the synthesis of o-ureidobenzonitriles (3a–3t)

The mixture of *o*-aminobenzamide (1) (1 mmol) and isothiocyanates (2) (1 mmol) was allowed to stir in DMSO solvent (1 ml) and T3P (Propane phosphonic acid anhydride solution: 50 wt. % in ethyl acetate) reagent (1 mmol, 0.7 g) at room temperature for 4 h in a round-bottomed flask. After that, the contents of the flask were poured into 15 ml of water taken in separating funnel and extracted to 15 ml ethyl acetate. The ethyl acetate extract was separated and dried over anhydrous sodium sulfate. The solvent was then removed under reduced pressure to afford corresponding crude *o*-ureidobenzonitrile (3). The crude residue thus obtained was purified by column chromatography over silica gel using 10% ethyl acetate in hexane as eluent to afford the pure o-ureidobenzonitrile with 80–95% yields.

General experimental protocols, characterization details, ^{1}H-NMR, ^{13}C-NMR and HRMS spectra of compounds and crystal analysis details are in the supporting information file.

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