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Original Research article

Iron(III)Phospahte-Catalyzed Condensation Reaction of Amines with Cyclohexyl Isocyanate and Aldehydes under Environmentally Condition

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ABSTRACT

In this paper, synthesis of 4-aryl-3-cyclohexyl-4,5-dihydro-1*H*-benzo[f][1,3,5]triazepin-2(3H)-one and *N*′,*N*′′-1,2-phenylenebis*N*-cyclohexylurea are reported by condensation reaction of amines with cyclohexyl isocyanate and aldehydes using iron(III)phosphate as catalyst under environmentally friendly conditions.

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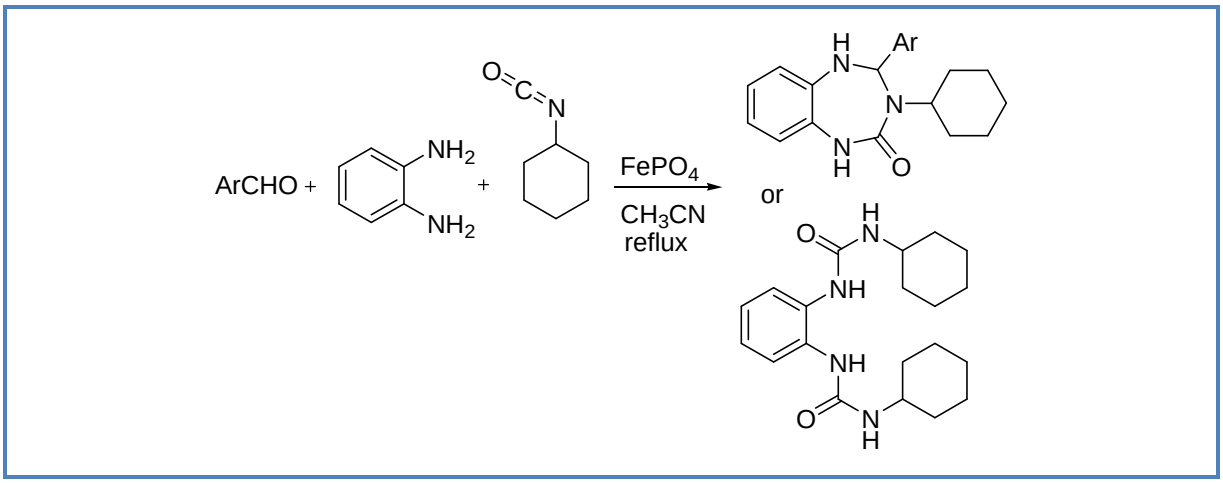
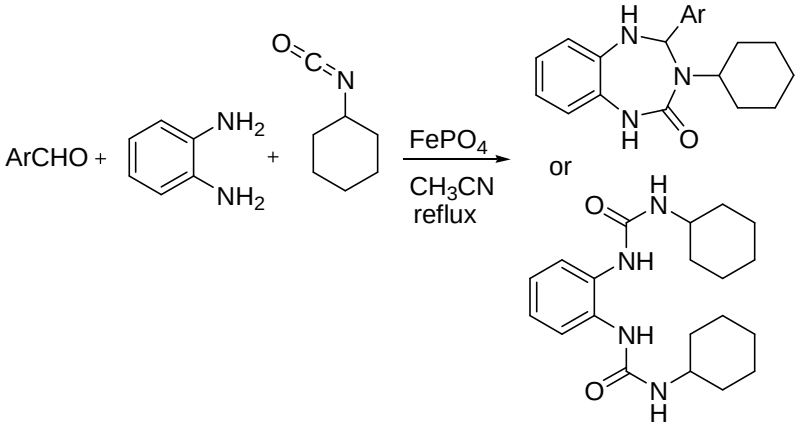
Graphical Abstract



Introduction

Iron(III)phosphate which is cheap, safe and available reagent has also been employed for the selective oxidation of CH_4 to CH_3OH, [1] benzene to phenol, [2] one-pot synthesis of dihydropyrimidinones and thiones, [3] one-pot three component synthesis of 2,4,5-trisubstituted imidazoles, [4] synthesis of 1,2,4,5-tetraarylated imidazoles, [5] acetylation of alcohols and phenols with acetic anhydride, [6] synthesis of bis(indolyl)methanes, [7] synthesis of *N*-substituted pyrroles [8] and synthesis of 2-disubstituted benzimidazoles [9]. Dicyclohexylurea (DCU) analogous are also of considerable interest with diverse bioactivities [10]. Various amino acid conjugates of DCU, 2-[((2-3-benzoyl-1,3-dicyclohexylureido)-2-oxoethyl)amino]-3-(4-substituted phenyl) propanoic acids were synthesized and reported to possess good antioxidant and anti-inflammatory activities [11]. In addition, a series of novel 1-substituted-1,3-dicyclohexylurea analogous of long chain carboxylic acids have been synthesized as potent antimicrobial agents [12]. Furthermore, the synthesized DCU analogous such as benzoyl-*N*,*N*'-dicyclo hexyl urea, *N*,*N*'-dicyclohexyl-*N*-3,5-dinitro benzoyl urea and *N*,*N*'-dicyclohexyl-*N*-[(E)-3-phenylacryloyl] urea were found to possess free radical scavenger activity [13]. Benzotriazepines comprise an interesting class heteroaromatic compounds because of their significant biological and pharmaceutical properties such as antibacterial, antiviral, psychotropic and antimalarial properties [14]. With the recent emergence of combinatorial chemistry and high speed parallel synthesis, the multi-component reactions (MCRs) have witnessed a resurgence of interest [15]. Easily automated one-pot reactions, such as Ugi, [16] Passerini, [17] and Petasis [18] reactions are powerful tools for producing diverse arrays of compounds, often in one step and high yield. In this regards, and following our previous research to

introduce catalytic protocols for the synthesis of heterocyclic compounds using eco-friendly catalysts, [19] herein synthesis of 4-aryl-3-cyclohexyl-4,5-dihydro-1*H*-benzo[f][1,3,5]triazepin-2(3H)-one and *N'*,*N''*-1,2-phenylenebis*N*-cyclohexylurea are reported by condensation reaction of amines with cyclohexyl isocyanate and aldehydes using iron(III)phosphate as a catalyst under environmentally friendly conditions (Scheme 1).

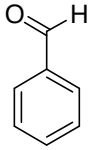
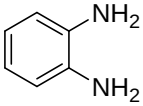
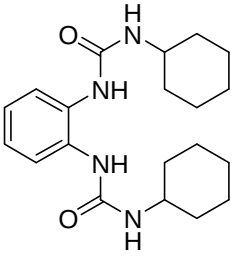


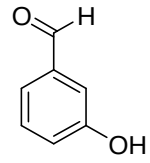
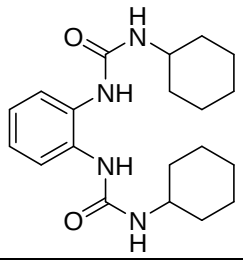
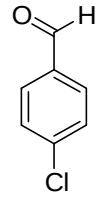
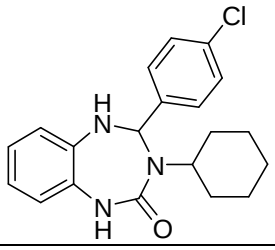
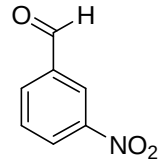
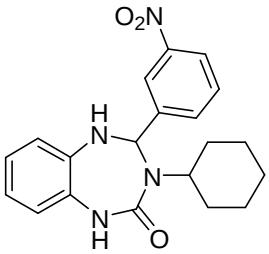
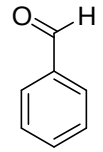
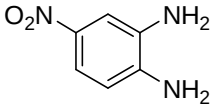
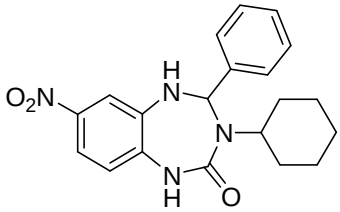
Scheme1.Condensation reaction between aldehydes, cyclohexyl isocyanate and *o*-phenylenediamines

Results And Discussion

In the same reaction condition, the reaction of amines and cyclohexyl isocyanate with aromatic aldehydes were carried out. When benzaldehyde and 3-OH-benzaldehyde were subjected in model reaction, *N'*,*N''*-1,2-phenylenebis*N*-cyclohexylureawere obtained (entries 1, 2; Table 1). These reactions revealed that 3-OH-benzaldehyde and benzaldehyde have not contributedin reaction and condensation reaction has just occurred between cyclohexyl isocyanate and *o*-phenylenediamine. 4-aryl-3-cyclohexyl-4,5-dihydro-1*H*-benzo[f][1,3,5]triazepin-2(3H)-one was synthesized by the rest of aromatic aldehydes such as 3-chlorobenzaldehyde and 3-nitro benzaldehyde as well as condensation reaction 4-nitro-1,2-phenylene diamine, benzaldehyde and cyclohexyl isocyanate (entries 3, 4, 5, Table 1).

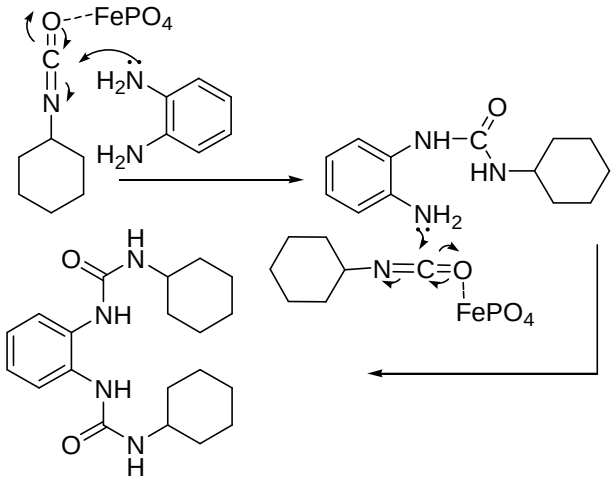
Table 1. Condensation reaction of amines with cyclohexyl isocyanate and aldehydes using iron(III)phosphate

Entry	Aldehyde	Amines	Product	Yield%	m.p.(℃)
1				88	187-188

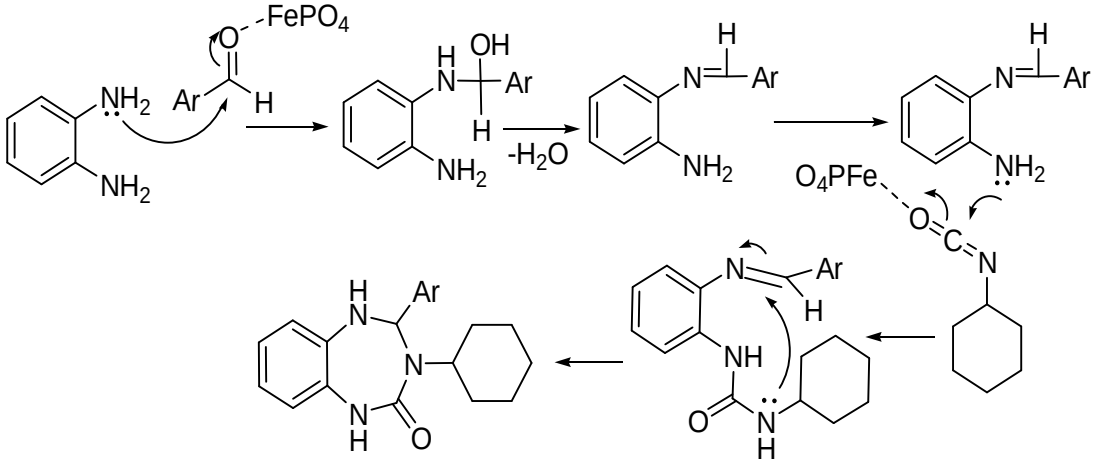
2		"		85	200-204
3		"		88	189-190
4		"		80	190-191
5				85	230-232

Proposed mechanism for the synthesis *N*′,*N*′′-1,2-phenylenebis*N*-cyclohexylureahas been shown in Scheme 2.

Scheme 2. Suggested mechanism for the synthesis *N*′,*N*′′-1,2-phenylenebis*N*-cyclohexylurea



The mechanism for the synthesis 4-aryl-3-cyclohexyl-4,5-dihydro-1H-benzo[f][1,3,5]triazepin-2(3H)-one have been also proposed in Scheme 3. Nucleophilic attacking of NH_2 from diamine 1 to $FePO_4$-activated aromatic aldehyde gave imine intermediate 3. Afterwards, the other NH_2 of 3 attacked $FePO_4$-activated cyclohexyl isocyanate to form intermediate 4. Intramolecularn ucleophilic attacking 4 resulted 4-aryl-3-cyclohexyl-4,5-dihydro-1H-benzo[f] [1,3,5]triazepin-2(3H)-one 5.



Scheme 3. Proposed mechanism for the synthesis 4-aryl-3-cyclohexyl-4,5-dihydro-1H-benzo[f] [1,3,5]triazepin-2(3H)-one using $FePO_4$

Experimental

Melting points were measured using the capillary tube method with an electro thermal 9200 apparatus. IR spectra which were recorded on Perkin Elmer FT-IR spectrometer did scanning between 4000–400cm^{-1}. ^{1}HNMR spectra were obtained on Bruker DRX- 300 MHZ NMR instrument. Chemical shifts are reported in parts per million(S) relative to tetramethylsilane (δ=0.0) as internal standard. Analytical TLC of all reactions was performed on Merck precoated plates (silica gel 60 F-254 on aluminum). All starting materials purchased from Merck and Acros Company. GC/Mass spectra were recorded on an Agilent 6890 GC Hp-5 capilary 30 m×530 µm×1.5 µm nominal operating at 70 eV.

Condensation reaction of *o*-phenylenediamine with cyclohexyl isocyanate and aldehydes uses iron(III)phosphate. General procedure. In two neck flask, *o*-phenylenediamine (2.0 mmol), cyclohexyl isocyanate (2.0 mmol) and aromatic aldehyde (2.0 mmol) were mixed with CH_3CN (5 ml) and refluxed for 4 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture of reaction was filtered off and the catalyst was removed. Evaporated of solvent obtained a solid product. The residue was purified by dichloromethane and *n*-hexane.

Physical and spectra data

N',*N'''*-1,2-phenylenebis*N*-cyclohexylurea (Table 1, Entry 1, 2):mp:187-188. IR spectrum, ν, cm^{-1}:3338,1644. ^{1}H NMR spectrum, δ, ppm (*J*, Hz):7.65(s, 2H, Ar), 7.45 (s, 2H, Ar), 6.91(s, 2H, NH), 6.41(s, 2H, NH), 3.4 (brs, 2H, CH), 1.79-1.15(m, 20H, cyclohexyl). ^{13}C NMR spectrum, δ, ppm:154.4, 128.1, 124.6, 121.7, 49.5, 33.2, 28.0, 22.5. GC/Mass(70 ev):358.24[M^+]. Elem. Anal. For $C_{20}H_{30}N4O_2$, calculated C, 67.01; H, 8.44; N, 15.63. FoundC, 67.00; H, 8.40; N, 15.6.

4-(4-cholorophenyl)-3-cyclohexyl-4,5-dihydro-1H-benzo[f][1,3,5]triazepin-2(3H)-one (Table 1, Entry 3):mp:89-190 °C,IR spectrum, ν, cm^{-1}:3309,1644. ^{1}HNMR spectrum, δ, ppm (*J*, Hz):8.53(s, 1H, NH), 8.25 (d, *J*=9Hz, 1H, Ar), 7.85(d, *J*=6Hz, 1H, Ar), 7.59(d, *J*=3Hz, 1H, Ar), 7.47(d, *J*=3Hz, 1H, Ar), 7.12-7.15(m, 1H, Ar), 6.43(s, 1H, NH), 5.3-5.12(m, 1H, CH), 4.55-4.53(d, *J*=6Hz, 1H, CH), 2.05-1.09(m, 10 H, CH_2). ^{13}CNMR spectrum, δ, ppm:158.7, 139.2, 137.1, 128.6, 122.2, 120.2 117.0, 111.2, 107.4, 72.0, 50.0, 31.1, 28.0, 22.8. GC/Mass (70 ev): 355. Elem. Anal. For $C_{20}H_{22}ClN_3O$, calculated C, 67.50; H, 6.23; N, 11.81. Found C, 67.45; H, 6.12; N, 11.77.

3-Cyclohexyl-4-(3-nitrophenyl)-4,5-dihydro-1H-benzo[f][1,3,5]triazepin-2(3H)-one Table 1, Entry 4):mp:190-191 °C, IR spectrum, ν, cm^{-1}:3309, 1643. ^{1}H NMR spectrum, δ, ppm (*J*, Hz):8.7(s, 1H, NH),8.64 (s, 1H, NH), 8.33-8.22(m, 1H, Ar), 7.60-7.51(m, 1H, Ar), 5.21(s, 1H, NH), 4.68(s, 1H, CH), 3.64(s, 1H, CH), 1.18-2.03(m, CH_2). ^{13}C NMR spectrum, δ, ppm:158.6, 148.2, 139.7, 134.1, 129.5, 125.2, 123.2, 122.4, 120.1, 117.3, 113.7, 71.0, 60.0, 31.1, 28.0, 22.7. GC/Mass (70 ev):366 [M^+]. Elem. Anal. For $C_{20}H_{22}N_4O_3$, calculated C, 65.56; H, 6.05; N, 15.29. Found; C, 65.47; H, 6.01; N, 15.18.

3-Cyclohexyl-7-nitro-4-phenyl-4,5-dihydro-1H-benzo[f][1,3,5]triazepin-2(3H)-one Table 1, Entry 5):mp:230-232 °C, IR spectrum, ν, cm^{-1}:3384, 1607. ^{1}H NMR spectrum, δ, ppm (*J*, Hz):8.85(m, H, NH), 8.34-7.70(m, 4H, Ar), 6.76(s, 1H, NH), 5.06(s, 1H, CH), 1.94-1.08(m, 10H, cyclohexyl). GC/Mass (70 ev):366.17. ^{13}C NMR spectrum, δ, ppm:158.7, 144.7, 140.6, 138.2, 128.5, 127.1, 126.1, 123.2, 109.5, 107.4, 72.0, 50.0, 31.1, 28.0, 22.7. GC/Mass (70 ev):366 [M^+]. Elem. Anal. For$C_{20}H_{22}N_4O_3$, calculated C, 65.56; H, 6.05; N, 15.29. Found; C, 65.47; H, 6.01; N, 15.18.

Conclusion

In summary, synthesis of unpresedented of 4-aryl-3-cyclohexyl-4,5-dihydro-1*H*-benzo[f][1,3,5]triazepin-2(3H)-ones was introduced in the presence of aromatic aldehydes, amines and cyclohexyl isocyanate using iron(III)phosphate as a catalyst. Relatively, short reaction time, use of solid, green and reusable catalyst, high yields,easy procedure and work up are the other feature of this protocol.

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