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EDTA-catalyzed synthesis of 3,4-dihydroquinoxalin-2-amine derivatives by a three-component coupling of one-pot condensation reactions in an aqueous medium

Srinivasa Rao Kolla, Yong Rok Lee *

School of Chemical Engineering and Technology, Yeungnam University, Kyongsan 712-749, Republic of Korea

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ABSTRACT

This paper describes a simple and efficient one-pot synthetic approach for the preparation of biologically interesting 3,4-dihydroquinoxalin-2-amine derivatives using EDTA-catalyzed three-component reactions of *o*-phenylenediamines, carbonyl compounds, and isocyanides in an aqueous medium. This method is of great value because of its environmentally benign character, high yields, and ease of handling.

1. Introduction

Multicomponent reactions (MCRs) are generally defined as reactions where more than two starting materials react to form a product. Generally, there are three different possible classification schemes of MCRs according to reaction mechanism, components involved, or intrinsic variability.[1] The development of new MCRs is an interesting research topic in applied areas of organic, medicinal, and pharmaceutical chemistry.[2] MCRs have attracted considerable interest owing to their exceptional synthetic efficiency. Hundreds of MCRs have recently been described. These reactions play a pivotal role in the synthesis of natural and unnatural products because of their importance of therapeutic and pharmacological uses.

Isocyanide-based multicomponent reactions (IMCRs) are particularly interesting as they are more versatile and diverse than other MCRs.[3] The great potential of isocyanides for the development of multicomponent reactions lies in the diversity of bond forming processes available, functional group tolerance, and the high levels of chemo-, regio-, and stereoselectivity often observed. Moreover, there is virtually no restriction on the nature of the nucleophiles and electrophiles in IMCRs. MCRs involving isocyanides have emerged as valuable tools for the preparation of structurally diverse chemical libraries of drug-like heterocyclic compounds.[4]

Among the various classes of nitrogen-containing heterocyclic compounds, quinoxalines display a broad spectrum of biological activity.[5,6] Quinoxalines play an important role as a basic skeleton for the design of a number of antibiotics, such as echinomycin, actinomycin, and leromycin, compounds with reported inhibition of the growth of gram-positive bacteria and activity against various transplantable tumors.[7,8] Furthermore, quinoxaline derivatives show very interesting biological properties (antibacterial, antiviral, anticancer, antifungal, antihelmintic, insecticidal).[9,10] Nevertheless, development of an effective method for the synthesis of quinoxalines remains an important challenge. Accordingly, a number of synthetic strategies have been reported for the preparation of substituted quinoxalines.[11–16]

To the best of the authors' knowledge, there is no report on the synthesis of 3,4-dihyroquinoxaline-2-amines using ethylenediaminetetraaceticacid (EDTA). From known, reported reactions, a system based on Fe^{II} and EDTA in the presence of ascorbic acid and oxygen was used for the biomimetic hydroxylation of organic substrates.[17] EDTA was used in combination with $PdCl_2$ as a catalyst for the synthesis of biaryl compounds.[18] Additionally, the above combination of $PdCl_2$–EDTA was found to be an effective catalyst for the Suzuki–Miyaura cross-coupling.[19] EDTA also has the significantly superior ability to bind the Tc-tricarbonyl core $[Tc(CO)_3]$.[20] The combination of 1.0 mM of EDTA in 10% glycerol was used for the preparation of cell extracts of *Rhodococcus erythropolis* SC 13845.[21]

Reported herein is a general and convenient method for the synthesis of 3,4-dihyroquinoxaline-2-amine derivatives **4** via the

* Corresponding author. Tel.: +82 53 810 2529; fax: +82 53 810 4631; e-mail address: yrlee@yu.ac.kr (Y.R. Lee).

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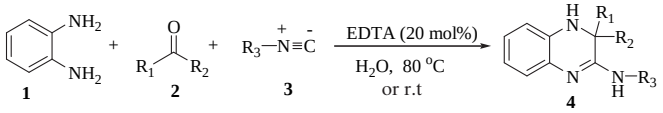
three-component condensation of *o*-phenylenediamine (**1**), ketones **2**, and isocyanides **3** in the presence of a catalytic amount of EDTA in aqueous medium at 80 °C or room temperature in good to excellent yields (Scheme 1).

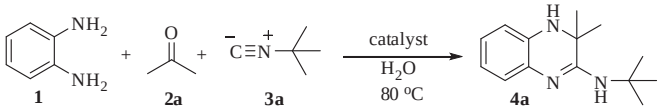


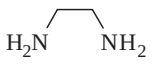
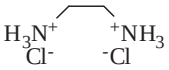
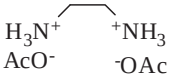
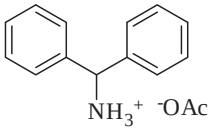
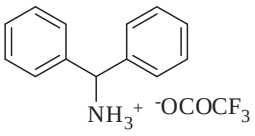
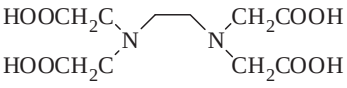
Scheme 1.

2. Results and discussion

Recently, Brønsted acids and bases have demonstrated their potential to serve as active catalysts for a variety of synthetically useful reactions in organic chemistry.[22] In particular, this lab developed a new and useful methodology for preparing a variety of benzopyrans using ethylenediamine diacetate (EDDA) as effective Brønsted acid and base catalysts.[23] As a part of an ongoing study into the synthetic efficacy of utilizing Brønsted acid and base catalysts, reactions of *o*-phenylenediamine (**1**) with acetone and *tert*-butyl isocyanide were first investigated using several Brønsted acid and base catalysts in water (Table 1). Presently, the development of environmental friendly techniques is one of the priority goals of chemical research, with water emerging as a versatile solvent for organic chemistry in recent years.[24] Water as a solvent is not only inexpensive and environmentally benign, but also gives completely new reactivities.[25] However, no combination of catalyst and ethylenediamine (20 mol %) in water at 80 °C for 12 h has provided any adducts. The use of ethylenediamine dihydrochloride and ethylenediamine diacetate gave products in 66 and 74% yields, respectively. Similarly, *o*,*o*-dipheylmethylammonium acetic acid and *o*,*o*-dipheylmethylammonium trifluoroacetic acid provided adducts in 70 and 76% yields, respectively. When we used ammonium acetate and acetic acid as catalysts, **4a** was produced in 57 and 86% yields, respectively. Interestingly, the best yield (95%) was obtained in the presence of 20 mol % EDTA.

Table 1
Reaction of **1** with **2a** and **3a** under several catalysts[a]



Entry	Catalyst	Time	Yield[b]
1	—	12	0
2		12	0
3		4	66
4		6	74
5		6	70
6		6	76
7	NH_4OAc	5	57
8	AcOH	3	86
9		4	95

[a] All reactions were carried out with 20 mol % catalyst in water at 80 °C.
[b] Yields of product **4a** after column chromatography.

Additional reactions of **1** with a variety of ketones and several isocyanides were carried out to establish generality in the presence of 20 mol % of EDTA in water. The results are summarized in Table 2. All reactions were highly regioselective with no other side reactions observed. For example, the ^1H NMR of compound **4b** showed the characteristic peaks of a methylene and methyl group at δ 1.61–1.46 (m) and 0.90 (t, J=6.6 Hz). The other methyl peaks appeared at δ 1.45 and 1.27 as singlets. To investigate the scope and limitation of this cycloaddition, three-component reactions with benzaldehyde and acetophenone were carried out. Treatment of **1** with **2f** and **3a** afforded the product **4f** in 20% yield, whereas that with **2g** gave no product. Interestingly, molecules with spirocyclic analogs were produced in good yields. However, the products of **4e**, **4l**, and **4q** were obtained in somewhat lower yield due to steric hindrance of the cycloheptanone. Three-component coupling reactions with benzyl isocyanide were also successful at room temperature. Reaction of **1** with acetone (**2a**) and benzyl isocyanide (**3d**) afforded product **4r** in 92% yield, whereas that with cyclohexanone (**2d**) gave adduct **4s** in 82%.

A possible reaction mechanism is suggested in Scheme 2. The authors contend that the EDTA could act as a Brønsted acid and base catalyst. The carbonyl group could be protonated by EDTA, which could facilitate formation of an iminium cation. Nucleophilic addition of isocyanide **3** to iminium intermediate **5**, followed by intramolecular cyclization, gave intermediate **7**, which could then be isomerized to final product **4**.

In summary, a one-pot, three-component condensation reaction of aromatic amines, various carbonyl compounds, and isocyanides was successfully applied to the synthesis of 3,4-dihydroquinoxaline-2-amine derivatives. This method further allows preparation of a class of structurally unique spirocyclic molecules. This methodology offers several advantages, including high product yield, ease of experimental procedure, environmentally benign character, and amenability to large-scale operations.

3. Experimental

3.1. General

All experiments were carried out in the aqueous layer. Merck, pre-coated silica gel plates (Art. 5554) with a fluorescent indicator were used for analytical TLC. Flash column chromatography was performed using silica gel 9385 (Merck). All ^1H and ^{13}C NMR spectra were recorded on a Bruker Model ARX (300 and 75 MHz, respectively) spectrometer in $CDCl_3$ as the solvent chemical shift. IR spectra were recorded on a Jasco FTIR 5300 spectrophotometer. HRMS spectra were carried out at the Korea Basic Science Institute on a Jeol JMS-700 spectrometer.

3.2. General procedure for the preparation of substituted 3,4-dihydroquinoxalin-2-amine

To a solution of *o*-phenylenediamine (1 mmol), ketone (2 mmol), and isocyanide (1 mmol) in 5 mL of water was added

Table 2
Additional reactions of **1** with several ketones and isocyanides[a]

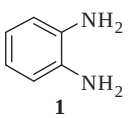
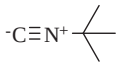
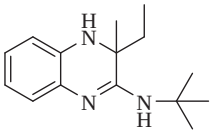
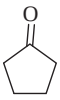
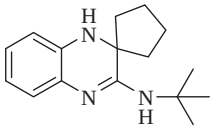
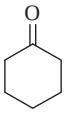
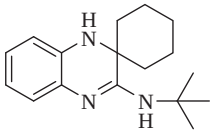
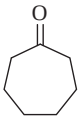
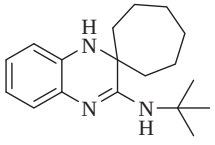
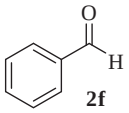
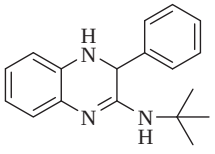
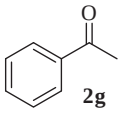
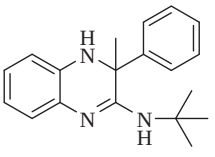
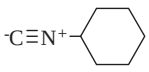
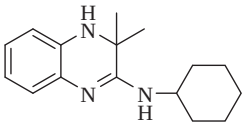
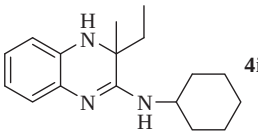
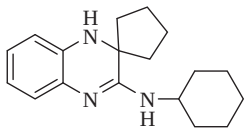
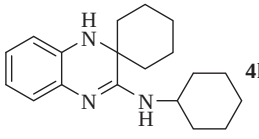
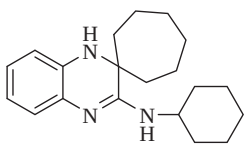
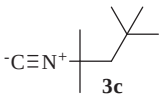
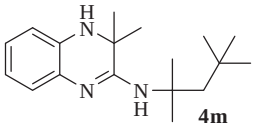
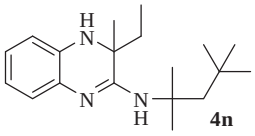
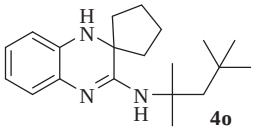
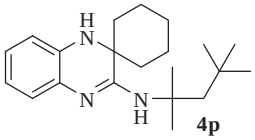
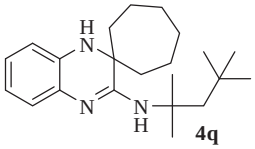
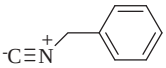
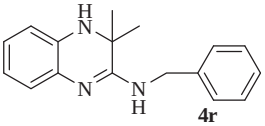
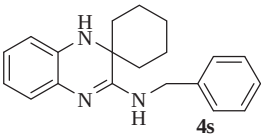
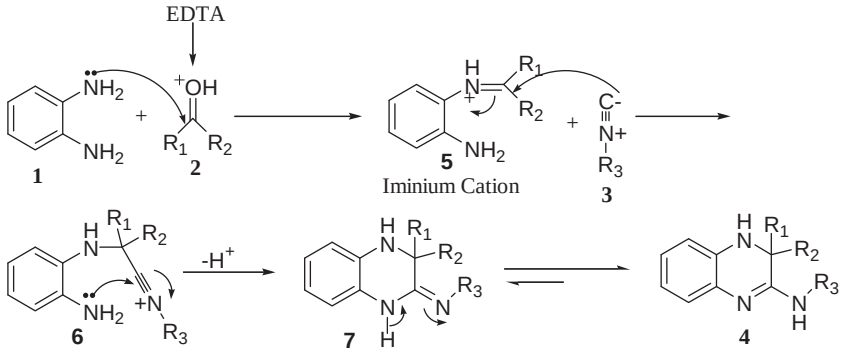
Entry	Diamine	Ketone	Isocyanide	Time (h)	Product	Yield[a,b] (%)
1	 **1**	 **2b**	 **3a**	1		**4b**	86
2		 **2c**	**3a**	1		**4c**	82
3		 **2d**	**3a**	1		**4d**	81
4		 **2e**	**3a**	2		**4e**	77
5		 **2f**	**3a**	3		**4f**	20[c]
6		 **2g**	**3a**	12		**4g**	0
7		**2a**	 **3b**	2		**4h**	92
8		**2b**	**3b**	4		**4i**	85
9		**2c**	**3b**	2		**4j**	90
10		**2d**	**3b**	2		**4k**	95
11		**2e**	**3b**	12		**4l**	74[c]

Table 2 (*continued*)

Entry	Diamine	Ketone	Isocyanide	Time (h)	Product	Yield[a,b] (%)
12		**2a**	 **3c**	3	 **4m**	93
13		**2b**	**3c**	2	 **4n**	82
14		**2c**	**3c**	2	 **4o**	80
15		**2d**	**3c**	1	 **4p**	86
16		**2e**	**3c**	2	 **4q**	72
17		**2a**	 **3d**	2	 **4r**	92[c]
18		**2d**	**3d**	3	 **4s**	82[c]

[a] All new compounds were characterized by ^{1}H and ^{13}C NMR, HRMS, and IR spectroscopy.
[b] Yield of isolated product.
[c] Reaction carried at room temperature.



Scheme 2. Proposed mechanism for the formation of product **4**.

EDTA (20 mol %). The resulting mixture was heated at 80 °C or room temperature until the completion of the reaction, as indicated by TLC (ethyl acetate/*n*-hexane). Extracted with ethyl acetate then washed with satd $NaHCO_3$ followed by brine. The organic layer was dried on Na_2SO_4, removed the solvent by rotary evaporator, and the crude product was purified by silica gel column chromatography using EtOAc/*n*-hexane as eluent to give products.

*3.2.1. Compound **4a**.* To a solution of *o*-phenylenediamine **1** (108 mg, 1 mmol), acetone **2a** (120 mg, 2 mmol), and *tert*-butyl isocyanide **3a** (83 mg, 1 mmol) in 5 mL of water was added 20 mol % of EDTA (58.5 mg). The reaction mixture was heated at 80 °C for 2 h. After completion of the reaction the crude mixture was extracted with ethyl acetate (2×25 mL) then washed with satd $NaHCO_3$ (5 mL) and followed by brine. Dried over Na_2SO_4 and removed the

solvent by rotary evaporator followed by column chromatography on silica gel using hexane/ethylacetate (9:1) gave product **4a** (220 mg, 95%) as a solid. Mp 88–90 °C; ^{1}H NMR (300 MHz): δ 7.03 (1H, m), 6.80–6.70 (2H, m), 6.52 (1H, m), 4.18 (1H, br s), 3.42 (1H, br s), 1.46 (9H, s) 1.25 (6H, s); ^{13}C NMR (75 MHz): δ 157.4, 135.4, 134.7, 123.8, 122.5, 119.3, 113.4, 51.5, 50.4, 28.9, 26.0; IR (KBr): ν 3438, 3370, 3047, 2869, 1619, 1585, 1511, 1229, 748 cm^{-1}; HRMS (*EI*) calcd for $C_{14}H_{21}N_3$: 231.1735. Found: 231.1736.

3.2.2. Compound ***4b***. To a solution of *o*-phenylenediamine **1** (108 mg, 1 mmol), 2-butanone **2b** (150 mg, 2 mmol), and *tert*-butyl isocyanide **3a** (83 mg, 1 mmol) in 5 mL of water was added 20 mol % of EDTA (58.5 mg). The reaction mixture was heated at 80 °C for 1 h. After completion of the reaction the crude mixture was extracted with ethyl acetate (2×25 mL) then washed with satd $NaHCO_3$ (5 mL) and followed by brine. Dried over Na_2SO_4 and removed the solvent by rotary evaporator followed by column chromatography on silica gel using hexane/ethylacetate (9.4:0.6) gave product **4b** (211 mg, 86%) as a solid. Mp 96–98 °C; ^{1}H NMR (300 MHz): δ 7.00 (1H, m), 6.80–6.67 (2H, m), 6.49 (1H, m), 4.14 (1H, br s), 3.47 (1H, br s), 1.61–1.46 (2H, m), 1.45 (9H, s), 1.27 (3H, s) and 0.90 (3H, t, J=6.6 Hz); ^{13}C NMR (75 MHz): δ 156.6, 135.0, 134.7, 123.7, 122.5, 118.9, 112.9, 53.5, 51.5, 31.2, 29.0, 24.1, 7.8; IR (KBr): ν 3751, 3451, 3349, 2965, 1613, 1514, 1267, 748 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{23}N_3$: 245.1892. Found: 245.1896.

3.2.3. Compound ***4c***. To a solution of *o*-phenylenediamine **1** (108 mg, 1 mmol), cyclopentanone **2c** (170 mg, 2 mmol), and *tert*-butyl isocyanide **3a** (83 mg, 1 mmol) in 5 mL of water was added 20 mol % of EDTA (58.5 mg). The reaction mixture was heated at 80 °C for 1 h. After completion of the reaction the crude mixture was extracted with ethyl acetate (2×25 mL) then washed with satd $NaHCO_3$ (5 mL) and followed by brine. Dried over Na_2SO_4 and removed the solvent by rotary evaporator followed by column chromatography on silica gel using hexane/ethylacetate (9.4:0.6) gave product **4c** (211 mg, 82%) as a solid. Mp 105–107 °C; ^{1}H NMR (300 MHz): δ 7.00 (1H, m), 6.80–6.74 (2H, m), 6.50 (1H, m), 4.16 (1H, br s), 3.61 (1H, br s), 1.80–1.68 (8H, m) 1.46 (9H, s); ^{13}C NMR (75 MHz): δ 157.1, 136.0, 135.0, 123.7, 122.2, 119.4, 113.6, 61.5, 51.4, 36.8, 28.9, 24.0; IR (KBr): ν 3461, 3298, 2959, 1591, 1516, 1216, 744 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{23}N_3$: 257.1892. Found 257.1895.

3.2.4. Compound ***4d***. To a solution of *o*-phenylenediamine **1** (108 mg, 1 mmol), cyclohexanone **2d** (200 mg, 2 mmol), and *tert*-butyl isocyanide **3a** (83 mg, 1 mmol) in 5 mL of water was added 20 mol % of EDTA (58.5 mg). The reaction mixture was heated at 80 °C for 1 h. After completion of the reaction the crude mixture was extracted with ethyl acetate (2×25 mL) then washed with satd $NaHCO_3$ (5 mL) and followed by brine. Dried over Na_2SO_4 and removed the solvent by rotary evaporator followed by column chromatography on silica gel using hexane/ethylacetate (9.4:0.6) gave product **4d** (220 mg, 81%) as a solid. Mp 106–108 °C; ^{1}H NMR (300 MHz): δ 7.01 (1H, m), 6.81–6.71 (2H, m), 6.59 (1H, m), 4.32 (1H, br s), 4.10 (1H, br s), 1.82–1.78 (2H, m), 1.63–1.55 (4H, m), 1.45 (9H, s) 1.40–1.18 (4H, m); ^{13}C NMR (75 MHz): δ 157.4, 135.5, 133.9, 123.6, 122.2, 119.3, 113.6, 51.5, 51.4, 31.6, 28.9, 25.0, 20.7; IR (KBr): ν 3435, 2928, 2859, 1612, 1574, 1512, 1219, 741 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{25}N_3$: 271.2048. Found: 271.2046.

3.2.5. Compound ***4e***. To a solution of *o*-phenylenediamine **1** (108 mg, 1 mmol), cycloheptanone **2e** (225 mg, 2 mmol), and *tert*-butyl isocyanide **3a** (83 mg, 1 mmol) in 5 mL of water was added 20 mol % of EDTA (58.5 mg). The reaction mixture was heated at 80 °C for 2 h. After completion of the reaction the crude mixture was extracted with ethyl acetate (2×25 mL) then washed with satd $NaHCO_3$ (5 mL) and followed by brine. Dried over Na_2SO_4 and removed the solvent by rotary evaporator followed by column chromatography on silica gel using hexane/ethylacetate (9.4:0.6) gave product **4e** (220 mg, 77%) as a solid. Mp 113–115 °C; ^{1}H NMR (300 MHz): δ 7.01 (1H, m), 6.80–6.69 (2H, m), 6.53 (1H, m), 4.25 (1H, br s), 3.77 (1H, br s), 1.77–1.70 (4H, m), 1.58–1.52 (8H, m), 1.45 (9H, s); ^{13}C NMR (75 MHz): δ 158.9, 135.8, 134.6, 123.9, 122.6, 119.5, 113.9, 56.1, 51.7, 36.4, 30.8, 29.2, 23.1; IR (KBr): ν 3761, 3466, 2924, 1603, 1510, 1220, 1115, 745 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{27}N_3$: 285.2205. Found: 285.2201.

3.2.6. Compound ***4f***. To a solution of *o*-phenylenediamine **1** (108 mg, 1 mmol), benzaldehyde **2f** (106 mg, 1 mmol), and *tert*-butyl isocyanide **3a** (83 mg, 1 mmol) in 5 mL of water was added 20 mol % of EDTA (58.5 mg). The reaction mixture was stirred at room temperature for 3 h. After completion of the reaction the crude mixture was extracted with ethyl acetate (2×25 mL) then washed with satd $NaHCO_3$ (5 mL) and followed by brine. Dried over Na_2SO_4 and removed the solvent by rotary evaporator followed by column chromatography on silica gel using hexane/ethylacetate (9:1) gave product **4f** (56 mg, 20%) as a solid. Mp 118–120 °C; ^{1}H NMR (300 MHz): δ 7.37–7.30 (5H, m), 7.09 (1H, m), 6.81–6.72 (2H, m), 6.49 (1H, m), 4.66 (1H, s), 3.99 (1H, br s), 3.73 (1H, br s), 1.35 (9H, s); ^{13}C NMR (75 MHz): δ 153.1, 139.9, 135.1, 134.8, 129.2, 128.8, 128.1, 124.5, 123.0, 119.7, 113.2, 57.6, 52.0, 29.0; IR (KBr): ν 3434, 3059, 2965, 1689, 1566, 1518, 1452, 1325, 1219, 1018, 761 cm^{-1}; FAB-HRMS m/z $[M+H]^+$ calcd for $C_{18}H_{22}N_3$: 280.1814. Found: 280.1817.

3.2.7. Compound ***4h***[4c]. To a solution of *o*-phenylenediamine **1** (108 mg, 1 mmol), acetone **2a** (120 mg, 2 mmol), and cyclohexyl isocyanide **3b** (110 mg, 1 mmol) in 5 mL of water was added 20 mol % of EDTA (58.5 mg). The reaction mixture was heated at 80 °C for 2 h. After completion of the reaction the crude mixture was extracted with ethyl acetate (2×25 mL) then washed with satd $NaHCO_3$ (5 mL) and followed by brine. Dried over Na_2SO_4 and removed the solvent by rotary evaporator followed by column chromatography on silica gel using hexane/ethylacetate (8.5:1.5) gave product **4h** (237 mg, 92%) as a solid. Mp 82–84 °C; ^{1}H NMR (300 MHz): δ 7.06 (1H, d, J=7.2 Hz), 6.82–6.72 (2H, m), 6.54 (1H, m), 4.28 (1H, br s), 4.04 (1H, m), 3.46 (1H, br s), 2.07–2.04 (2H, m), 1.72–1.60 (4H, m), 1.50–1.38 (2H, m), 1.28 (6H, s), 1.20–1.09 (2H, m); ^{13}C NMR (75 MHz): δ 158.0, 135.3, 134.7, 123.5, 122.6, 119.5, 113.5, 50.6, 48.3, 33.0, 25.9, 25.8, 24.7; IR (KBr): ν 3758, 3396, 2931, 2851, 2355, 1529, 1418, 1211, 743 cm^{-1}.

3.2.8. Compound ***4i***. To a solution of *o*-phenylenediamine **1** (108 mg, 1 mmol), 2-butanone **2b** (150 mg, 2 mmol), and cyclohexyl isocyanide **3b** (110 mg, 1 mmol) in 5 mL of water was added 20 mol % of EDTA (58.5 mg). The reaction mixture was heated at 80 °C for 4 h. After completion of the reaction the crude mixture was extracted with ethyl acetate (2×25 mL) then washed with satd $NaHCO_3$ (5 mL) and followed by brine. Dried over Na_2SO_4 and removed the solvent by rotary evaporator followed by column chromatography on silica gel using hexane/ethylacetate (8.5:1.5) gave product **4i** (231 mg, 85%) as a liquid. ^{1}H NMR (300 MHz): δ 7.02 (1H, d, J=7.2 Hz), 6.80–6.68 (2H, m), 6.50 (1H, d, J=7.2 Hz), 4.23 (1H, br s), 4.05 (1H, m), 3.51 (1H, br s), 2.08–2.00 (2H, m), 1.70–1.37 (8H, m), 1.30 (3H, s), 1.24–1.10 (2H, m), 0.90 (3H, t, J=7.5 Hz); ^{13}C NMR (75 MHz): δ 157.5, 135.1, 134.9, 123.5, 122.8, 119.2, 113.2, 53.9, 48.5, 33.2, 31.1, 25.9, 24.9, 24.0, 7.9; IR (Neat): ν 3455, 3363, 2927, 2852, 2353, 1612, 1578, 1515, 1453, 1196, 746 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{25}N_3$: 271.2048. Found: 271.2052.

3.2.9. Compound ***4j***. To a solution of *o*-phenylenediamine **1** (108 mg, 1 mmol), cyclopentanone **2c** (170 mg, 2 mmol), and

cyclohexyl isocyanide **3b** (110 mg, 1 mmol) in 5 mL of water was added 20 mol % of EDTA (58.5 mg). The reaction mixture was heated at 80 °C for 2 h. After completion of the reaction the crude mixture was extracted with ethyl acetate (2×25 mL) then washed with satd $NaHCO_3$ (5 mL) and followed by brine. Dried over Na_2SO_4 and removed the solvent by rotary evaporator followed by column chromatography on silica gel using hexane/ethylacetate (4:1) gave product **4j** (255 mg, 90%) as a solid. Mp 148–150 °C; ^{1}H NMR (300 MHz): δ 7.05 (1H, m), 6.80–6.72 (2H, m), 6.53 (1H, m), 4.24 (1H, m), 4.06 (1H, m), 3.64 (1H, br s), 2.06–2.02 (2H, m), 1.78–1.61 (10H, m), 1.50–1.38 (2H, m), 1.25–1.08 (4H, m); ^{13}C NMR (75 MHz): δ 157.8, 136.1, 135.1, 123.5, 122.4, 119.6, 113.7, 61.7, 48.3, 36.8, 33.0, 25.8, 24.7, 23.9; IR (KBr): ν 3429, 3264, 2931, 2855, 2354, 1568, 1511, 1311, 1200, 742 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{25}N_3$: 283.2048. Found: 283.2050.

*3.2.10. Compound **4k**.* To a solution of *o*-phenylenediamine **1** (108 mg, 1 mmol), cyclohexanone **2d** (200 mg, 2 mmol), and cyclohexyl isocyanide **3b** (110 mg, 1 mmol) in 5 mL of water was added 20 mol % of EDTA (58.5 mg). The reaction mixture was heated at 80 °C for 2 h. After completion of the reaction the crude mixture was extracted with ethyl acetate (2×25 mL) then washed with satd $NaHCO_3$ (5 mL) and followed by brine. Dried over Na_2SO_4 and removed the solvent by rotary evaporator followed by column chromatography on silica gel using hexane/ethylacetate (4:1) gave product **4k** (282 mg, 95%) as a solid. Mp 103–105 °C; ^{1}H NMR (300 MHz): δ 7.03 (1H, m), 6.82–6.72 (2H, m), 6.61 (1H, m), 4.40 (1H, m), 4.13 (1H, br s), 4.05 (1H, m), 2.06–2.02 (2H, m), 1.83–1.80 (2H, m), 1.72–1.60 (8H, m), 1.49–1.39 (4H, m); 1.25–1.09 (4H, m); ^{13}C NMR (75 MHz): δ 158.2, 135.6, 134.0, 123.4, 122.4, 119.6, 113.7, 51.8, 48.4, 33.0, 31.6, 25.8, 25.1, 24.8, 20.8; IR (KBr): ν 3396, 2927, 2853, 2352, 1511, 1295, 1168, 739 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{27}N_3$: 297.2205. Found 297.2202.

*3.2.11. Compound **4l**.* To a solution of *o*-phenylenediamine **1** (108 mg, 1 mmol), cycloheptanone **2e** (225 mg, 2 mmol), and cyclohexyl isocyanide **3b** (110 mg, 1 mmol) in 5 mL of water was added 20 mol % of EDTA (58.5 mg). The reaction mixture was stirred at room temperature for 12 h. After completion of the reaction the crude mixture was extracted with ethyl acetate (2×25 mL) then washed with satd $NaHCO_3$ (5 mL) and followed by brine. Dried over Na_2SO_4 and removed the solvent by rotary evaporator followed by column chromatography on silica gel using hexane/ethylacetate (4:1) gave product **4l** (230 mg, 74%) as a semi solid. Mp 42–46 °C; ^{1}H NMR (300 MHz): δ 7.02 (1H, d, J=7.2 Hz), 6.81–6.70 (2H, m), 6.55 (1H, dd, J=7.2 and 1.5), 4.34 (1H, m), 4.03 (1H, m), 3.82 (1H, br s), 2.04–2.01 (2H, m), 1.76–1.71 (4H, m), 1.57–1.41 (12H, m), 1.26–1.11 (4H, m); ^{13}C NMR (75 MHz): δ 159.4, 134.4, 123.3, 122.5, 119.5, 113.7, 56.0, 48.1, 36.1, 32.9, 30.5, 25.8, 24.6, 22.8; IR (Neat): ν 3454, 3046, 2922, 2855, 2347, 1578, 1506, 1189, 1096, 741 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{29}N_3$: 311.2361. Found 311.2359.

*3.2.12. Compound **4m**[4a].* To a solution of *o*-phenylenediamine **1** (108 mg, 1 mmol), acetone **2a** (120 mg, 2 mmol), and 1,1,3,3-tetramethyl butyl isocyanide **3c** (140 mg, 1 mmol) in 5 mL of water was added 20 mol % of EDTA (58.5 mg). The reaction mixture was heated at 80 °C for 3 h. After completion of the reaction the crude mixture was extracted with ethyl acetate (2×25 mL) then washed with satd $NaHCO_3$ (5 mL) and followed by brine. Dried over Na_2SO_4 and removed the solvent by rotary evaporator followed by column chromatography on silica gel using hexane/ethylacetate (9.4:0.6) gave product **4m** (267 mg, 93%) as a solid. Mp 56–58 °C; ^{1}H NMR (300 MHz): δ 7.02 (1H, m), 6.80–6.70 (2H, m), 6.52 (1H, m), 4.23 (1H, br s), 3.41 (1H, br s), 1.88 (2H, s), 1.51 (6H, s), 1.24 (6H, s), 1.01 (9H, s); ^{13}C NMR (75 MHz): δ 157.1, 135.8, 134.9, 124.0, 122.5, 119.5, 113.7, 55.8, 52.3, 50.6, 32.0, 31.8, 29.3, 26.3; IR (KBr): ν 3756, 3459, 3364, 2956, 2364, 1609, 1509, 1223, 739 cm^{-1}.

*3.2.13. Compound **4n**.* To a solution of *o*-phenylenediamine **1** (108 mg, 1 mmol), 2-butanone **2b** (150 mg, 2 mmol), and 1,1,3,3-tetramethyl butyl isocyanide **3c** (140 mg, 1 mmol) in 5 mL of water was added 20 mol % of EDTA (58.5 mg). The reaction mixture was heated at 80 °C for 2 h. After completion of the reaction the crude mixture was extracted with ethyl acetate (2×25 mL) then washed with satd $NaHCO_3$ (5 mL) and followed by brine. Dried over Na_2SO_4 and removed the solvent by rotary evaporator followed by column chromatography on silica gel using hexane/ethylacetate (19:1) gave product **4n** (247 mg, 82%) as a solid. Mp 51–53 °C; ^{1}H NMR (300 MHz): δ 7.00 (1H, d, J=7.2 Hz), 6.78–6.68 (2H, m), 6.50 (1H, d, J=7.2 Hz), 4.21 (1H, br s), 3.48 (1H, br s), 1.55 (6H, s), 1.50 (2H, s), 1.26 (3H, s), 1.01 (9H, s), 0.96–0.86 (5H, m); ^{13}C NMR (75 MHz): δ 151.9, 130.7, 130.2, 119.2, 118.0, 114.4, 108.5, 51.2, 49.0, 48.1, 27.2, 26.5, 24.5, 24.4, 19.5, 3.2; IR (KBr): ν 3462, 3354, 3046, 2955, 1616, 1512, 1224, 745 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{31}N_3$: 301.2518. Found 301.2516.

*3.2.14. Compound **4o**.* To a solution of *o*-phenylenediamine **1** (108 mg, 1 mmol), cyclopentanone **2c** (170 mg, 2 mmol), and 1,1,3,3-tetramethyl butyl isocyanide **3c** (140 mg, 1 mmol) in 5 mL of water was added 20 mol % of EDTA (58.5 mg). The reaction mixture was heated at 80 °C for 2 h. After completion of the reaction the crude mixture was extracted with ethyl acetate (2×25 mL) then washed with satd $NaHCO_3$ (5 mL) and followed by brine. Dried over Na_2SO_4 and removed the solvent by rotary evaporator followed by column chromatography on silica gel using hexane/ethylacetate (19:1) gave product **4o** (251 mg, 80%) as a liquid. ^{1}H NMR (300 MHz): δ 7.02 (1H, m), 6.79–6.71 (2H, m), 6.51 (1H, m), 4.21 (1H, br s), 3.61 (1H, br s), 1.87 (2H, s), 1.75–1.68 (8H, m), 1.52 (6H, s), 1.01 (9H, s); ^{13}C NMR (75 MHz): δ 156.8, 136.4, 135.1, 123.9, 122.2, 119.6, 113.8, 61.7, 55.7, 52.3, 36.9, 31.9, 31.8, 29.2, 24.1; IR (Neat): ν 3466, 3365, 2954, 2872, 2358, 1614, 1582, 1514, 1223, 745 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{31}N_3$: 313.2518. Found: 313.2517.

*3.2.15. Compound **4p**.* To a solution of *o*-phenylenediamine **1** (108 mg, 1 mmol), cyclohexanone **2d** (200 mg, 2 mmol), and 1,1,3,3-tetramethyl butyl isocyanide **3c** (140 mg, 1 mmol) in 5 mL of water was added 20 mol % of EDTA (58.5 mg). The reaction mixture was heated at 80 °C for 1 h. After completion of the reaction the crude mixture was extracted with ethyl acetate (2×25 mL) then washed with satd $NaHCO_3$ (5 mL) and followed by brine. Dried over Na_2SO_4 and removed the solvent by rotary evaporator followed by column chromatography on silica gel using hexane/ethylacetate (19:1) gave product **4p** (282 mg, 86%) as a liquid. ^{1}H NMR (300 MHz): δ 7.00 (1H, m), 6.81–6.71 (2H, m), 6.59 (1H, m), 4.35 (1H, br s), 4.11 (1H, br s), 1.88 (2H, s), 1.81–1.58 (5H, m), 1.51 (6H, s), 1.42–1.21 (5H, m), 1.00 (9H, s); ^{13}C NMR (75 MHz): δ 157.0, 135.8, 134.0, 123.6, 122.1, 119.4, 113.7, 55.5, 51.7, 51.5, 31.7, 31.6, 29.3, 25.1, 20.8; IR (Neat): ν 3470, 3404, 2936, 2864, 2355, 1613, 1580, 1515, 1359, 1222, 744 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{33}N_3$: 327.2674. Found: 327.2679.

*3.2.16. Compound **4q**.* To a solution of *o*-phenylenediamine **1** (108 mg, 1 mmol), cycloheptanone **2e** (225 mg, 2 mmol), and 1,1,3,3-tetramethyl butyl isocyanide **3c** (140 mg, 1 mmol) in 5 mL of water was added 20 mol % of EDTA (58.5 mg). The reaction mixture was heated at 80 °C for 2 h. After completion of the reaction the crude mixture was extracted with ethyl acetate (2×25 mL) then washed with satd $NaHCO_3$ (5 mL) and followed by brine. Dried over Na_2SO_4 and removed the solvent by rotary evaporator followed by

column chromatography on silica gel using hexane/ethylacetate (19:1) gave product **4q** (246 mg, 72%) as a solid. Mp 78–80 °C; ^{1}H NMR (300 MHz): δ 7.00 (1H, m), 6.80–6.70 (2H, m), 6.54 (1H, m), 4.26 (1H, br s), 3.78 (1H, br s), 1.89 (2H, s), 1.78–1.70 (4H, m), 1.57–1.52 (8H, m), 1.50 (6H, s), 1.01 (9H, s); ^{13}C NMR (75 MHz): δ 158.2, 135.8, 134.4, 123.7, 122.3, 119.3, 113.8, 55.8, 55.6, 52.1, 36.2, 31.7, 30.7, 29.2, 23.0; IR (KBr): 3465, 3371, 2919, 2363, 1613, 1511, 1366, 1211, 1074, 738 cm^{-1}; HRMS (EI) calcd for $C_{22}H_{35}N_3$: 341.2831. Found 341.2828.

*3.2.17. Compound **4r**.* To a solution of *o*-phenylenediamine **1** (108 mg, 1 mmol), acetone **2a** (116 mg, 2 mmol), and benzyl isocyanide **3d** (117 mg, 1 mmol) in 5 mL of water was added 20 mol % of EDTA (58.5 mg). The reaction mixture was stirred at room temperature for 2 h. After completion of the reaction the crude mixture was extracted with ethyl acetate (2×25 mL) then washed with satd $NaHCO_3$ (5 mL) and followed by brine. Dried over Na_2SO_4 and removed the solvent by rotary evaporator followed by column chromatography on silica gel using hexane/ethylacetate (4:1) gave product **4r** (244 mg, 92%) as a solid. Mp 152–154 °C; ^{1}H NMR (300 MHz): δ 7.36–7.26 (5H, m), 7.09 (1H, d, J=6.0 Hz), 6.85–6.74 (2H, m), 6.57 (1H, dd, J=7.2 and 1.5 Hz), 4.63 (3H, br s), 3.52 (1H, br s), 1.31 (6H, s); ^{13}C NMR (75 MHz): δ 158.9, 139.0, 135.1, 134.8, 128.8, 128.2, 127.6, 123.7, 123.3, 119.7, 113.8, 51.0, 45.3, 26.0; IR (KBr): ν 3340, 3292, 3026, 2964, 2920, 2370, 1606, 1568, 1528, 1486, 1210, 908, 747 cm^{-1}; HRMS m/z (M^+) calcd for $C_{17}H_{19}N_3$: 265.1579. Found 265.1578.

*3.2.18. Compound **4s**.* To a solution of *o*-phenylenediamine **1** (108 mg, 1 mmol), cyclohexanone **2d** (196 mg, 2 mmol), and benzyl isocyanide **3d** (117 mg, 1 mmol) in 5 mL of water was added 20 mol % of EDTA (58.5 mg). The reaction mixture was stirred at room temperature for 3 h. After completion of the reaction the crude mixture was extracted with ethyl acetate (2×25 mL) then washed with satd $NaHCO_3$ (5 mL) and followed by brine. Dried over Na_2SO_4 and removed the solvent by rotary evaporator followed by column chromatography on silica gel using hexane/ethylacetate (4:1) gave product **4s** (250 mg, 82%) as a solid. Mp 165–167 °C; ^{1}H NMR (300 MHz): δ 7.35–7.26 (5H, m), 7.08 (1H, d, J=7.5 Hz), 6.87–6.75 (2H, m), 6.64 (1H, dd, J=7.2 and 1.8 Hz), 4.75 (1H, br s), 4.62 (2H, s), 4.19 (1H, s), 1.89–1.86 (2H, d, J=9.3 Hz), 1.73–1.55 (4H, m), 1.46–1.38 (3H, m), 1.24–1.17 (1H, m); ^{13}C NMR (75 MHz): δ 159.0, 139.1, 135.3, 134.3, 128.8, 128.2, 127.6, 123.7, 123.1, 119.8, 114.0, 52.2, 45.6, 31.7, 25.2, 20.8; IR (KBr): ν 3448, 3399, 3019, 2933, 2856, 1610, 1574, 1524, 1485, 1294, 1242, 741 cm^{-1}; HRMS m/z (M^+) calcd for $C_{20}H_{23}N_3$: 305.1892. Found 305.1889.

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