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CAN-catalyzed syntheses of 3,4-dihydroquinoxalin-2-amine derivatives based on isocyanides

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ABSTRACT

Starting from readily available *o*-phenylenediamines **1**, ketones **2** and isocyanides **3**, a variety of highly substituted 3,4-dihydroquinoxalin-2-amine derivatives **4** were efficiently synthesized in the presence of catalytic amount of cerium(IV) ammonium nitrate at room temperature. The flexibility of this protocol also opens a new route to the structurally unique spirocyclic analogs when cyclic ketones are employed.

In the past decades, multicomponent reactions (MCRs) have drawn considerable interests owing to its exceptional synthetic efficiency.[1] Compared with conventional methods, multicomponent process exhibits high levels of efficiency and diversity, as it allows more than two simple and flexible building blocks to be combined in practical, time-saving one-pot operations. Among the known multicomponent reactions, isocyanide based MCRs (IMCRs) are particularly valuable.[2] In addition to the added diversity of bond formation and functional group tolerance, the outstanding position of IMCRs can also be traced back to the exceptional reactivity of isocyanide. As we know, no other functional group reacts with nucleophiles and electrophiles at the same atom.[3] Consequently, MCRs involving isocyanides have been widely applied to organic synthesis, especially in drug discovery.[4]

Quinoxaline derivatives are a common occurrence in many pharmacological active substances of natural or synthetic origin.[5] Many known antibiotics including echinomycin, actinomycin, and leromycin possess the basic skeleton.[6] Moreover, quinoxaline analogs also serve as dyes, organic semiconductors as well as other useful materials,[7–10] which build up the attractiveness for their syntheses. On the other hand, as the most notable one electron oxidant, cerium(IV) ammonium nitrate (CAN) has been utilized extensively for oxidative transformations. Additionally, advantages such as excellent solubility in water, inexpensiveness, ecofriendly nature, simple handling and high reactivity make CAN a powerful catalyst in organic syntheses.[11] As a continuation of our interest in lanthanide reagents and the search for potential drug structures,[12] herein we wish to report an efficient synthesis of 3,4-dihydroquinoxaline-2-amine derivative **4** catalyzed by CAN.

In our initial experiments, 4-nitro-1,2-phenylenediamine, acetone and *tert*-butyl isocyanide were employed to optimize the reaction conditions. As shown in Table 1, a series of catalysts were screened and cerium(IV) ammonium nitrate (CAN) seemed to be best choice. In the presence of catalytic amount of CAN, 3,4-dihydroquinoxaline-2-amine **4a** was afforded in 92% yield at room temperature (Table 1, entry 1).[13] A variety of substituted *o*-phenylenediamines **1**, ketones **2** and isocyanides **3** were carried out to establish the scope and the generality of the present transformation (Scheme 1) and the results were summarized in Table 2. Several structurally diversed isocyanides **3** including *tert*-butyl, cyclohexyl, benzyl and 2,6-dimethylphenyl substituted ones were firstly used and the expected products **4** were isolated in good to excellent yields (Table 2, entry 1–4). These results indicate that the excellent reactivity of isocyanide component **3** must play an important role in the whole process as the condensation of *o*-phenylenediamines **1** with 2 equiv carbonyl compounds **2** is very easy to take place.[14] In our runs, however, the reactions are quite clean and no other side reactions are observed. Various diamines **1** and ketones **2** gave satisfactory results (Table 2, entry 5–9). It was important to note that the present reaction was quite

Table 1
Optimization of reaction conditions[a]

Entry	Catalyst	Time (h)	Yield[b] (%)
1	$FeCl_3$	8	65
2	$InCl_3$	8	80
3	$Ce(NH_4)_2(NO_3)_6$	3	92
4	$ZnCl_2$	24	No reaction
5[c]	$BF_3{\cdot}Et_2O$	3	79
6	$BiCl_3$	8	85
7	$CuBr_2$	24	15
8	$Zn(OAc)_2$	24	No reaction
9	$Cu(OAc)_2$	24	No reaction

[a] Until otherwise noted, all reactions were carried out with 5 mol % catalyst in 5 mL ethanol at room temperature.
[b] Yields of product **4** after silica gel chromatography.
[c] In such case, 1 equiv $BF_3{\cdot}Et_2O$ was used.

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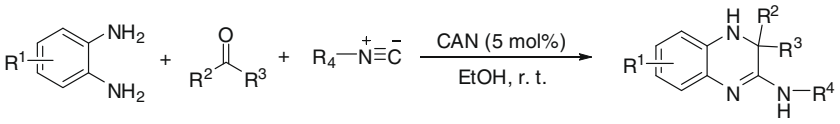
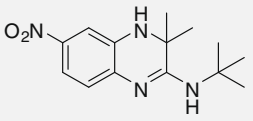
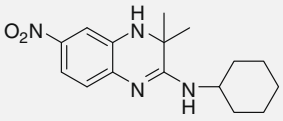
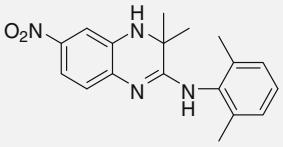
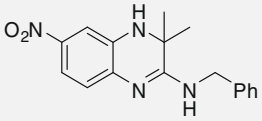
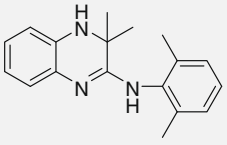
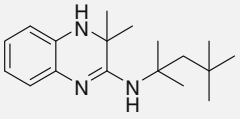
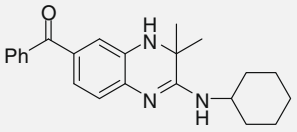
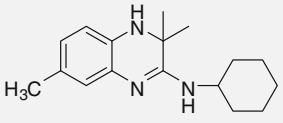
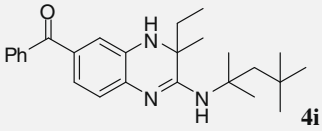
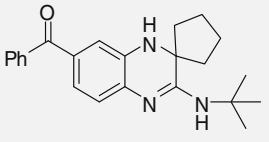


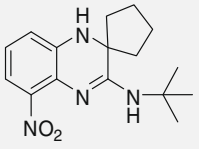
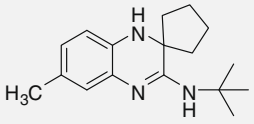
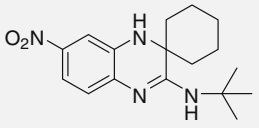
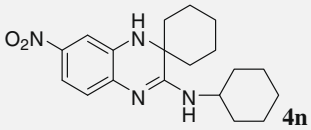
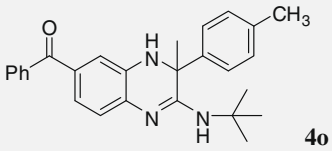
Scheme 1. Syntheses of 3,4-dihydroquinoxalin-2-amine derivatives.

Table 2
Efficient syntheses of 3,4-dihydroquinoxalin-2-amine derivatives **4**[a]

Entry	Amine **1**	Ketone **2**	Isocyanide **3**	Product **4**	Yield[b,c] (%)
1	4-Nitro-1,2-phenylenediamine	Acetone	*tert*-Butyl	 **4a**	90
2	4-Nitro-1,2-phenylenediamine	Acetone	Cyclohexyl	 **4b**	92
3	4-Nitro-1,2-phenylenediamine	Acetone	2,6-Dimethylphenyl	 **4c**	80
4	4-Nitro-1,2-phenylenediamine	Acetone	Benzyl	 **4d**	87
5	*o*-Phenylenediamine	Acetone	2,6-Dimethylphenyl	 **4e**	75
6	*o*-Phenylenediamine	Acetone	1,1,3,3-Tetramethylbutyl	 **4f**	96
7	3,4-Diaminobenzophenone	Acetone	Cyclohexyl	 **4g**	88
8	3,4-Diaminotoluene	Acetone	Cyclohexyl	 **4h**	95
9	3,4-Diaminobenzophenone	2-Butanone	1,1,3,3-Tetramethylbutyl	 **4i**	93
10	3,4-Diaminobenzophenone	Cyclopentanone	*tert*-Butyl	 **4j**	86

(*continued on next page*)

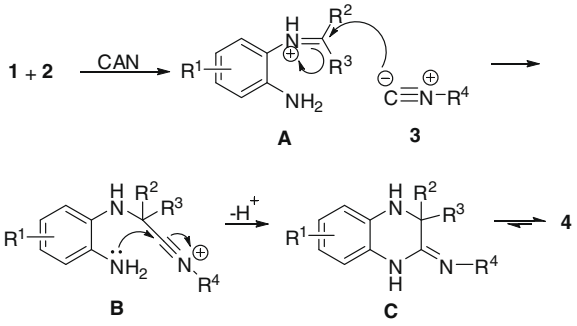
Table 2 (*continued*)

Entry	Amine **1**	Ketone **2**	Isocyanide **3**	Product **4**	Yield[b,c] (%)
11	2-Nitro-1,2-phenylenediamine	Cyclopentanone	*tert*-Butyl	 **4k**	70
12	3,4-Diaminotoluene	Cyclopentanone	*tert*-Butyl	 **4l**	62
13	4-Nitro-1,2-phenylenediamine	Cyclohexanone	*tert*-Butyl	 **4m**	91
14	4-Nitro-1,2-phenylenediamine	Cyclohexanone	Cyclohexyl	 **4n**	83
15	3,4-Diaminobenzophenone	4-Methylacetophenone	*tert*-Butyl	 **4o**	71[d]

[a] Until otherwise noted, all reactions finished within 3 h in 5 mL EtOH at room temperature.
[b] All new compounds were characterized by ^{1}H NMR, ^{13}C NMR, EA, MS and IR spectroscopy.
[c] Isolated yields.
[d] In such case, only 80% conversion was observed in 20 h.

regioselective. The ^{1}H NMR and ^{13}C NMR spectroscopy of compound **4** showed that only one isomer was produced.[15] This can be explained by the presence of electron-withdrawing nitro or benzoyl group, which controls the selectivity by deactivating the *para*-amino group. Thus the formation of iminium ion intermediate had to be initiated from the *meta*-amino group. And this rule works well for all the diamines substituted by electron-withdrawing groups. In contrast, the regioselectivity essentially turned when 3,4-aminotoluene was used. In such cases, the reactivity of para-amino group was enhanced by the electron-donating methyl group (Table 2, entry 8). Furthermore, cyclic ketones were then introduced to prepare structurally interesting spirocyclic compounds (Table 2, entry 10–14). Characterized by the quaternary carboncenter and two fused rings, to our knowledge, these compounds are usually found as subunits in natural compounds.[16,17] As shown in Table 1, the desired spirocyclic analogs **4j–n** were all efficiently afforded. Notably, somewhat lower yield (70%) and long reaction time (20 h) were observed when 2-nitro-1,2-phenylenediamine was used, which might contribute to its steric hindrance (Table 2, entry 11). In addition, aromatic ketone also underwent smooth conversion to the corresponding product **4o** with acceptable result (Table 2, entry 15). Since compound **4o** was yellow, it made detection and isolation easier.

The mechanism of the present reaction has not been unequivocally established, but a possible one is outlined in Scheme 2. Firstly, the carbonyl group could be activated by the coordination of oxygen atom with CAN, thus could facilitate the formation of iminium cation **A**.[14] The nucleophilic addition of isocyanide **3**[2a] followed by an intramolecular cyclization of **B** essentially could result in the generation of **C**, which then should be isomerized to final product **4**. Although Ce(IV) derivatives are generally employed as single electron transfer (SET) oxidants, we believe CAN serves as lewis acid in the above process same as in other carbon–carbon and carbon–heteroatom bond forming reactions.[18]



Scheme 2. Proposed mechanism for the synthesis of **4**.

In conclusion, we have disclosed an efficient strategy to synthesize highly substituted 3,4-dihydroquinoxalin-2-amine derivatives.[19] This method also allows to prepare a class of structurally

unique spirocyclic compounds. Considering the advantages such as readily available starting materials, simple operations as well as the high yields, our method will potentially find its application in organic synthesis or even in pharmaceutical industry.

Acknowledgments

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19. *Typical procedure for the synthesis of substituted 3,4-dihydroquinoxalin-2-amine* **4**: To a solution of 1 mmol *o*-phenylenediamine **1**, 1 mmol ketone **2**, 1 mmol isocyanide **3** in 5 mL ethanol, 5 mol % CAN was added quickly. The above reaction mixture was stirred at room temperature until the completion (by TLC). After usual workup, the crude product was purified by silica gel column chromatography using EtOAc–PE (1:3) as eluent to afford the pure product **4**. Selected data: *Compound* **4f**: yellow solid, mp: 59–61 °C. IR (KBr/cm^{-1}): 3459, 3360, 2951, 1615, 1513, 1226, 741. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.04–7.03 (m, 1H), 6.80–6.73 (m, 2H), 6.53–6.52 (m, 1H), 4.25 (br s, 1H, *NH*), 3.43 (br s, 1H, *NH*), 1.89 (s, 2H), 1.53 (s, 6H), 1.24 (s, 6H), 1.03 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 157.2, 135.0, 124.1, 122.7, 119.7, 113.8, 56.0, 52.4, 50.8, 32.1, 32.0, 29.4, 26.4. MS: *m*/*z* (%) = 287 (M^+, 27), 272 (11), 175 (32), 160 (100). Anal. Calcd for $C_{18}H_{29}N_3$: C, 75.21; H, 10.17; N, 14.62. Found: C, 75.36; H, 10.20; N, 14.79. *Compound* **4h**: yellow solid, mp: 153–155 °C. IR (KBr/cm^{-1}): 3446, 3353, 2960, 1636, 1562, 1480. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.76 (d, 2H, *J* = 7.0 Hz),7.53 (t, 1H, *J* = 7.0 Hz), 7.44 (t, 2H, *J* = 7.5 Hz), 7.18 (dd, 1H, *J* = 8.0 Hz), 7.14 (s, 1H), 7.02 (d, 1H, *J* = 8.0 Hz), 4.53 (br s, 1H, *NH*), 3.76 (br s, 1H, *NH*), 2.06 (d, 1H, *J* = 15.0 Hz), 1.72 (d, 1H, *J* = 15.0 Hz), 1.61–1.46 (m, 2H), 1.59 (s, 3H), 1.54 (s, 3H), 1.31 (s, 3H), 1.04 (s, 9H), 0.91 (t, 3H, *J* = 7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 196.4, 158.6, 140.3, 139.2, 134.7, 131.5, 129.9, 128.1, 123.7, 122.8, 114.6, 56.4, 53.7, 52.7, 31.9, 31.8, 31.4, 29.2, 29.0, 24.2, 8.0. MS: *m*/*z* (%) = 405 (M^+, 27), 376 (61), 264 (100), 105 (22). Anal. Calcd for $C_{26}H_{35}N_3O$: C, 77.00; H, 8.70; N, 10.36. Found: C, 77.24; H, 8.76; N, 10.56. *Compound* **4j**: yellow solid, mp: 203–205 °C. IR (KBr/cm^{-1}): 3431, 3337, 2958, 1634, 1561, 1466, 725. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.76–7.43 (m, 5H), 7.23–7.17 (m, 1H), 7.17 (s, 1H), 7.05 (d, 1H, *J* = 8.0 Hz), 4.49 (br s, 1H, *NH*), 3.88 (br s, 1H, *NH*), 1.83–1.70 (m, 8H), 1.50 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 196.4, 159.3, 141.1, 139.1, 135.1, 131.5, 131.2, 129.8, 128.0, 124.1, 122.9, 115.2, 61.7, 52.2, 37.1, 29.0, 24.0. MS: *m*/*z* (%) = 361 (M^+, 100), 305 (62), 276 (54), 105 (35). Anal. Calcd for $C_{23}H_{27}N_3O$: C, 76.42; H, 7.53; N, 11.62. Found: C, 76.17; H, 7.56; N, 11.73. *Compound* **4m**: red solid, mp: 174–175 °C. IR (KBr/cm^{-1}): 3413, 2923, 1615, 1525, 1310. ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) = 7.77 (d, 1H, *J* = 3.0 Hz), 7.46 (m, 1H), 6.83 (d, 1H, *J* = 8.5 Hz), 6.39 (s, 1H, *NH*), 6.05 (s, 1H, *NH*), 1.70–1.16 (m, 10H), 1.42 (s, 9H). ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) = 161.3, 141.9, 141.3, 135.2, 121.6, 114.2, 107.8, 51.9, 51.5, 31.2, 28.5, 24.5, 19.7. MS: *m*/*z* (%) = 316 (M^+, 100), 260 (75), 217 (77). Anal. Calcd for $C_{17}H_{24}N_4O_2$: C, 64.53; H, 7.65; N, 17.71. Found: C, 64.40; H, 7.80; N, 17.53.