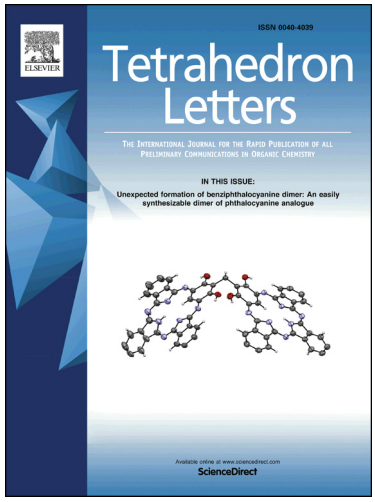

Cobalt-catalyzed isocyanide insertion cyclization to dihydrobenzoimidazotriazins

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PII: S0040-4039(17)31256-X
DOI: https://doi.org/10.1016/j.tetlet.2017.09.088
Reference: TETL 49358

To appear in: *Tetrahedron Letters*

Received Date: 17 July 2017
Revised Date: 25 September 2017
Accepted Date: 29 September 2017

Please cite this article as: Ahmadi, F., Mirzaei, P., Bazgir, A., Cobalt-catalyzed isocyanide insertion cyclization to dihydrobenzoimidazotriazins, *Tetrahedron Letters* (2017), doi: https://doi.org/10.1016/j.tetlet.2017.09.088

Graphical Abstract

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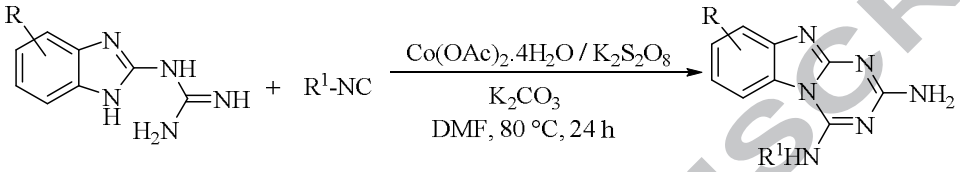

Tetrahedron Letters
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Cobalt-catalyzed isocyanide insertion cyclization to dihydrobenzoimidazotriazins

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Isocyanide insertion
Cobalt-catalyzed isocyanide insertion
Benzoimidazotriazine
Triazine

ABSTRACT

We have developed an isocyanide insertion reaction for the synthesis of dihydrobenzo[4,5]imidazo[1,2-a][1,3,5]triazins and imidazol-quinoxaline-5-carboxamides utilizing cobalt catalyst. Cobalt-catalyzed system is inexpensive and more acceptable from industrial point of view.

Introduction

Triazines are planar six-membered benzene-like systems with three nitrogens.[1] Among triazine isomers (1,2,3-triazine, 1,2,4-triazine and 1,3,5-triazine), the 1,3,5-triazine is more considered duo to its unique structure and chemical and therapeutical properties.[2] For example, 1,3,5-triazine-thiazolidine-dione **I** and triazine dimer **II** have been reported as DPP-4 inhibitors with antibacterial activity for the treatment of type 2 diabetes[3] and antileishmanial agent,[4] respectively (Fig. 1). Furthermore, 4-(4-aminopyrazolotriazin-8-yl)benzamide **III** has been nominated as a highly potent and selective inhibitors of tyrosine threonine kinase.[5] The antiproliferative activity of fluorinated 1,2,4-triazolo[1,5-a][1,3,5]triazines against lung cancer A549 and breast cancer MDA-MB-231 cell lines has been established.[6] In addition, some 1,3,5-triazines containing varied functionalities are particularly prominent in many histamine H4 receptor ligands,[7] human DNA topoisomerase IIα inhibitors,[8] A1 adenosine receptor antagonists,[9] escherichia coli dihydrofolate reductase inhibitors[10] and anti cancer agents.[11] Benzimidazole triazines **IV** and **V** have been described as mammalian target of rapamycin (mTOR) inhibitor[12] and dual PI3K/Mtor inhibitor,[13] respectively (Fig. 1). 2, 4 or 6-Amino-1,3,5-triazin derivatives such as furazil, tretamine and dioxadet have been known as anticancer drugs.[14] Although there are several conventional methods for the synthesis of 1,3,5-triazine such as heterocyclization of biguanides or their analogues with β-keto esters, aldehydes, ketones and ortoesters,[15] the introduction of new methods is still of much interest.

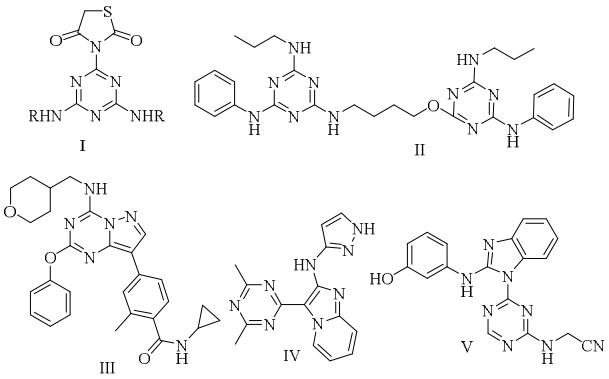

Fig. 1. Some of potent pharmacological agents with 1,3,5-triazine nuclei

New and modern synthetic methodologies that afford simple access to a broad range of functionalized heterocycles are critically important in advanced medicinal and combinatorial chemistry as they allow providing compound libraries and expanding the available drug-like compounds. The transition metal-catalyzed C-N bond formation followed by intramolecular cyclization has received broad attention recently compared to traditional methods for the heterocyclic synthesis.[16-20] The other important and modern strategy for the heterocycles synthesis is

Keywords: Isocyanide insertion, Cobalt-catalyzed isocyanide insertion, Benzoimidazotriazine, Triazine.

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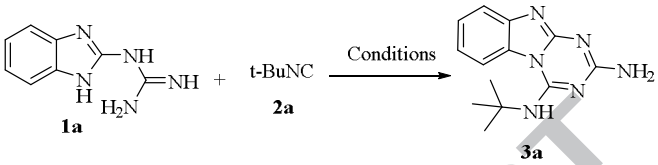
isocyanide insertion cyclization.[21] Isocyanide insertion cyclization gives an atom economical, simple and direct synthetic strategy to complex and structurally diverse molecules using simple substrate.[22] The isocyanide insertion cyclization reaction is the metal-catalyzed direct insertion of isocyanide into a heteroatom/carbon-hydrogen or carbon-hologen bond to give an imidoylative intermediate which subsequently undergoes an intramolecular nucleophilic reaction to give a heterocycle.[21-23] Among previous reports, palladium catalyzed isocyanide insertion cyclization with C-X (X=H, Br or I) bond are very common[21b-h] and low cost metal catalyzed direct isocyanide insertion reaction into the active N–H bonds are rare.[21i-k] Therefore, the expansion of more inexpensive catalyst systems for isocyanide insertions cyclization is more desirable. Ji and coworkers reported cobalt catalyst isocyanide insertion reactions to amine based bisnucleophiles for the synthesis of 2-aminobenzimidazoles, 2-aminobenzothiazoles, and 2-aminobenzoxazoles.[21J] The cobalt-catalyzed isocyanide insertion reaction to form amino methylidyneaminiums and guanidines was developed by this group.[24,25] Very recently, we reported cobalt-catalyzed isocyanide insertion cyclization for the synthesis of benzoimidazoquinazolines.[26] Herein, we wish to report a new approach for the synthesis of dihydrobenzoimidazotriazins by Co-catalyzed isocyanide insertion cyclization.

Result and discussion

The starting point of our study was the reaction of benzo[d]imidazol-guanidine[15b] **1a** and *t*-buthyl isocyanide **2a** as a model reaction in the presence of $Pd(OAc)_2$ and potassium carbonate as base in DMF at 80 °C (Table 1, entry 1). The reaction had some side products and the desired product **3a** was separated in 22 % isolated yield after 24 h. When the model reaction was performed in the presence of $K_2S_2O_8$ as oxidant (entry 2), a satisfactory improvement in the isolated yield was observed. We also checked the another oxidant like Ag_2O and Ag_2CO_3 (entries 3,4), but unfortunately no improvement was detected even after 48 h. Therefore, we decided to change the catalyst. When we changed the catalyst to $Co(OAc)_2.4H_2O$, surprisingly high conversion was observed after 24 h in DMF and in the presence of the $K_2S_2O_8$ (entry 5). Then, we checked the efficiency of $NiCl_2$ as catalyst in the reaction and conversion was less than $Co(OAc)_2.4H_2O$ after 24 h (entry 6). So, $Co(OAc)_2.4H_2O$ was chosen as the best catalyst for the reaction. After screening the solvents such as PhMe, 1,4-dioxane, MeCN and H_2O (entries 7-10), DMF was found to be the most suitable reaction media, providing benzo[4,5]imidazo-triazine (**3a**) in 63% isolated yield in the presence of $Co(OAc)_2.4H_2O$ (10 mol%), K_2CO_3(1eq) and $K_2S_2O_8$ (1eq) at 80 °C. To optimize the reaction temperature, we also performed several experiments at 60, 80 and 100 °C (entries 5, 11 and 12). As can be seen from Table 1, the most suitable reaction temperature was 80 °C (entry 5). The $K_2S_2O_8$ played a crucial role in this reaction and when this reaction was carried out without $K_2S_2O_8$, the yield of the product was 27% (entry 13).

Then, the scope of the isocyanide insertion reaction cyclization was examined using several substituted benzoimidazol-guanidines containing both electron-withdrawing and electron-donating group **1** with various isocyanides **2** under the optimized reaction conditions and the expected products **3** were obtained in 48-75% isolated yields[27] (Scheme 1). It should be mentioned that high conversion (>80%) were obtained by using optimal reaction condition and to gain more isolated yields we used different purification methods. The column chromatography was the best purification method and the pure products were isolated in 50-75% yield. When unsymmetrically substituted benzoimidazol-guanidine with methyl-substituted group (**1b**) was treated with isocyanides, an inseparable regioisomeric mixture was obtained in moderate isolated yields (Scheme 1, entries **3b** and **3e**).

Table 1 Optimization of the reaction conditions[a]



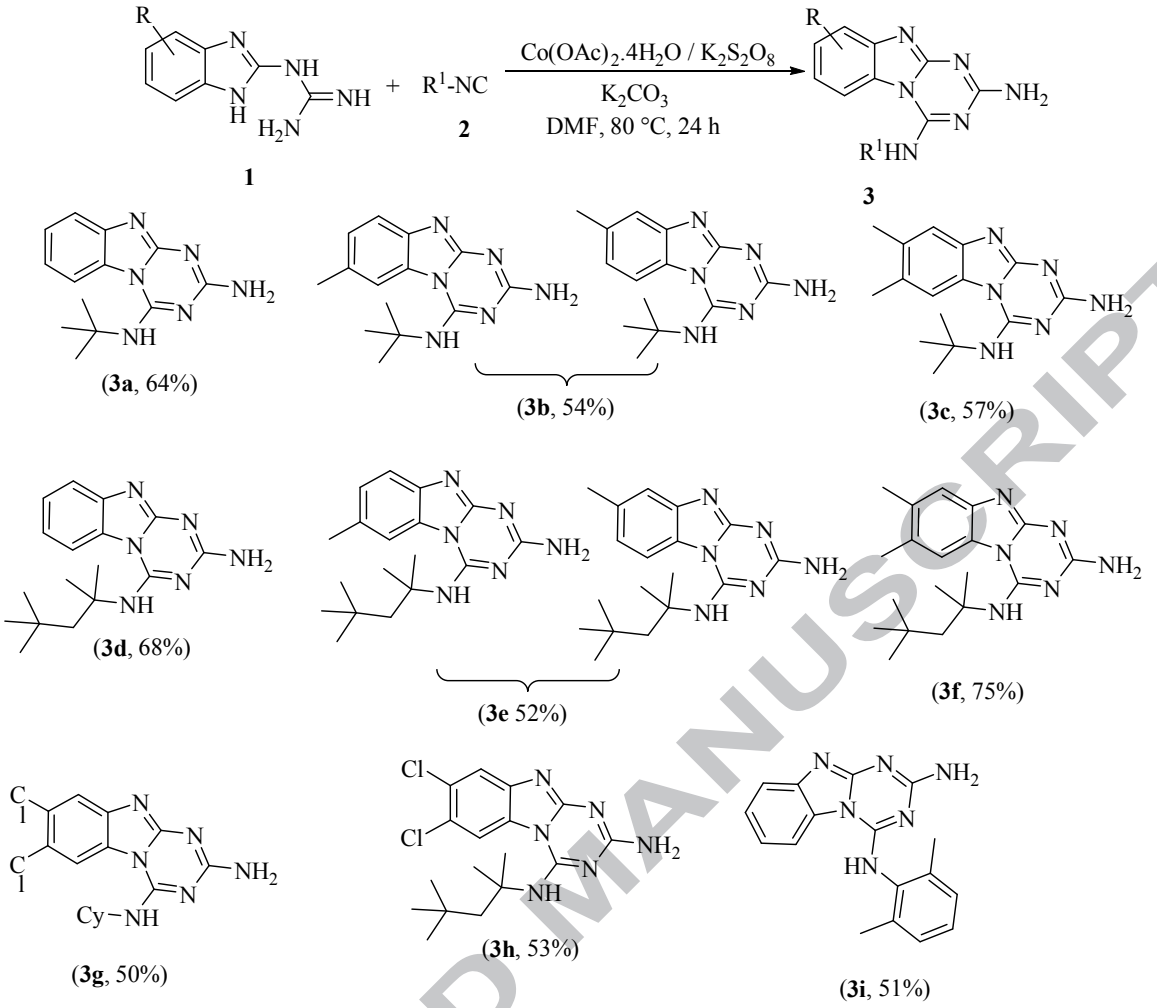
1a **2a** **3a**

Entry	Solvent	Oxidant	Catalyst	Yield (%)[b]
1	DMF	-	$Pd(OAc)_2$	22
2	DMF	$K_2S_2O_8$	$Pd(OAc)_2$	50
3[c]	DMF	Ag_2O	$Pd(OAc)_2$	37
4[c]	DMF	Ag_2CO_3	$Pd(OAc)_2$	46
5	DMF	$K_2S_2O_8$	$Co(OAc)_2.4H_2O$	63
6	DMF	$K_2S_2O_8$	$NiCl_2$	37
7	H_2O	$K_2S_2O_8$	$Co(OAc)_2.4H_2O$	trace
8	$PhCH_3$	$K_2S_2O_8$	$Co(OAc)_2.4H_2O$	56
9	1,4-Dioxane	$K_2S_2O_8$	$Co(OAc)_2.4H_2O$	51
10	CH_3CN	$K_2S_2O_8$	$Co(OAc)_2.4H_2O$	51
11[d]	DMF	$K_2S_2O_8$	$Co(OAc)_2.4H_2O$	44
12[e]	DMF	$K_2S_2O_8$	$Co(OAc)_2.4H_2O$	64
13	DMF	-	$Co(OAc)_2.4H_2O$	27

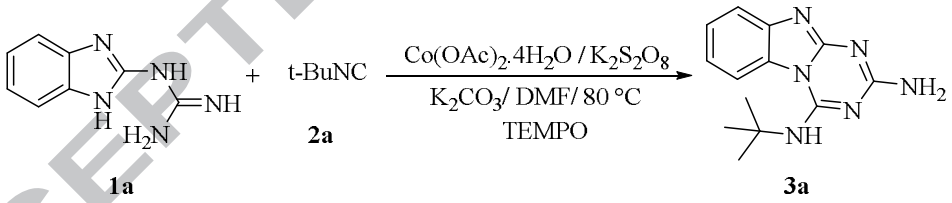
[a]benzo[d]imidazol-guanidine 1a (0.5 mmol), *t*-BuNC (0.75 mmol), K_2CO_3 (0.5 mmol), oxidant
(0.5 mmol), catalyst (10 mol%), solvent (2.0 mL), 80 °C.
[b] Isolated yields. [c]Reaction time = 48 h. [d]Reaction temperature = 60 °C.
[e]Reaction temperature = 100 °C.

The structures of products **3** were fully characterized by IR, ^{1}H NMR, ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis. The mass spectrum of **3a** showed the molecular-ion peak at *m/z* 256. The IR spectrum of **5a** exhibited absorption bands due to imine groups at 1633 and 1546 cm^{-1} and broad absorption bands for the NH and NH_2 groups was observed at 3429 and 3151 cm^{-1}. The ^{1}H-NMR spectrum of **5a** consisted of singlet signal for the t-buthyl group (δ_H 1.57 ppm) and two broad resonances for the NH and NH_2 groups (δ_H 6.68 and 7.01 ppm). The aromatic hydrogens give rise to characteristic signals in the aromatic region of the spectrum. The ^{1}H-decoupled ^{13}C-NMR spectrum of **3a** showed 11 distinct signals, in agreement with the proposed structure.

To achieve more information about the reaction mechanism, a control radical trapping experiment was conducted using TEMPO as a radical scavenger to trap possible radical intermediates (Scheme 2). Surprisingly, no considerable change took place and the desired product **3a** produced in 53 % yields, thus indicating the ionic mechanism.



Scheme 1. The synthesized benzo[4,5]imidazo[1,2-a][1,3,5]triazines



Scheme 2. TEMPO trapping control experiment

On the basis of the literature reports[21k,25] and TEMPO trapping experiments, two possible ionic pathways mechanism is suggested in Figure 2. In the Path A, cobalt acetate reacts with isocyanide to form isocyanide coordinated cobalt(II) complex **I**. Then, under the basic condition, reaction of imidazol guanidine **1** with **I** gave **III**. The other plausible pathway for the formation of **III**, involves a direct reaction of the cobalt(II) acetate and **1** to give complex **II**. Then, isocyanide insertion reaction resulted **III** (Figure2, path B). After the formation of **III**, two different insertions into Co-complex **III** are possible to generate intermediate **IV or V**. Co(II) complex **IV** can be easily oxidized to result cobalt(III)-complex **VI** or **VII**. The intermediates **VI or VII** subsequently undergo reductive elimination to afford the desired product **3**. Doing some control test showed that Path B is more possible (see supporting information)

Encouraged by this success, the brimonidine **4** was used as a versatile compound for isocyanide insertion reaction. Brimonidine is a drug used as eye drops under the brand names Alphagan and Alphagan-P to treat open-angle glaucoma or ocular hypertension, and as a gel, Mirvaso, for facial skin redness in rosacea.[28] When this reaction was carried out with birmonidine **4**, it was interesting that the desired product **5** was obtained in trace, while N-(alkyl)-6-((4,5-dihydro-1H-imidazol-2-yl)amino)quinoxaline-5-carboxamide **6** was produced under the same reaction conditions (Scheme 3).

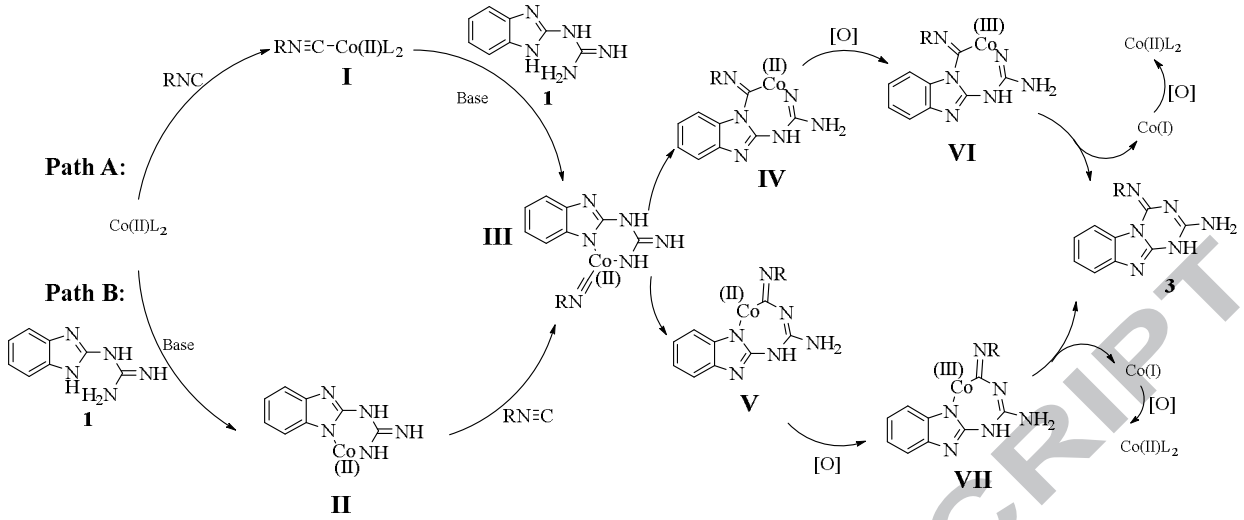
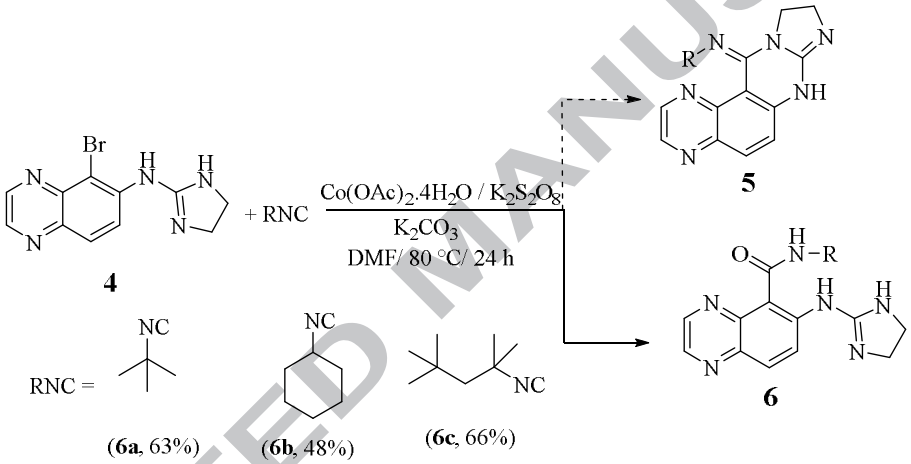


Figure 2. Plausible reaction mechanism



Scheme 3. Isocyanide insertion reactionof Birmonidine

In this article, for the first time, an efficient and practical cobalt-catalyzed isocyanide insertion cyclization of 1-(1*H*-benzo[d]imidazol-2-yl)guanidines and isocyanides for the synthesis of dihydrobenzo[4,5]imidazo[1,2-a][1,3,5]triazins is developed. Cobalt-catalyzed reaction of brimonidine with isocyanide resulted in the formation of imidazol-2-yl-amino quinoxaline-5-carboxamides. Further expansion of the reaction scope and synthetic applications of this methodology are in progress in our laboratory.

Acknowledgments

We gratefully acknowledge 読nancial support from the Research Council of Shahid Beheshti University.

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27. General procedure for the synthesis of N^4-(tert-butyl)benzo[4,5]imidazo[1,2-a][1,3,5]triazine-2,4-diamine (**3a**): A mixture of 1-(1H-benzo[d]imidazol-2-yl)guanidine (0.5 mmol), *t*-buthyl isocyanide (0.75 mmol), $Co(OAc)_2.4H_2O$(0.05 mmol), K_2CO_3 (0.5 mmol) and $K_2S_2O_8$(0.5 mmol) in DMF was stirred overnight at 80 ^oC. After the completion of the reaction, the solvent was removed and the residue was purified by column chromatography over silica gel using Ethyl acetate/MeOH (9:1) as eluent to give the desired product **3a**. Cream powder (64%); mp 248–250 ^oC. IR (KBr) (mmax/ cm^{-1}): 3429, 3151, 2965, 2906, 1633, 1546. MS (EI, 70 eV) m/z: 256 (M^+).^{1}H NMR (300 MHz, DMSO-δ_6) δ_H (ppm) 7.71 (1H, d, $^3J_{HH}$ = 9.0 Hz, H–Ar), 7.45 (1H, d, $^3J_{HH}$ = 9.0 Hz, H–Ar), 7.30 (1H, t, $^3J_{HH}$ = 9.0 Hz, H–Ar), 7.14 (1H, t, $^3J_{HH}$ = 9.0 Hz, H–Ar), 7.01 (2H, s, NH_2), 6.68 (1H, s, NH), 1.57 (9H, s, *t*Bu). ^{13}C NMR (75 MHz, DMSO-δ_6): δ_C (ppm) 162.2, 155.4, 151.4, 144.8, 126.4, 124.9, 119.3, 117.2, 113.6, 53.6, 28.8. Anal. Calcd for $C_{13}H_{16}N_6$: C, 60.92; H, 6.29; N, 32.79%. Found: C, 60.81; H, 6.35; N, 32.72.
7,8-dimethyl-N^4-(2,4,4-trimethylpentan-2-yl)benzo[4,5]imidazo[1,2-a] [1,3,5]triazine-2,4-diamine (**3f**). Cream powder (75%); mp 255-257 ^oC. IR (KBr) (mmax/ cm^{-1}): 3489, 3118, 2919, 1646, 1600. MS (EI, 70 eV) m/z: 340 (M^+). ^{1}H NMR (300 MHz, DMSO-δ_6) δ_H (ppm) 7.50 (1H, s, H–Ar), 7.25 (1H, s, H–Ar), 6.91 (2H, bs, NH_2), 6.31 (1H, s, NH), 2.36 (3H, s, CH_3), 2.30 (3H, s, CH_3), 2.08 (2H, s, CH_2),1.63 (6H, s, CH_3), 0.99 (9H, s, CH- *t*Bu). ^{13}C NMR (75 MHz, DMSO-δ_6): δ_C (ppm) 161.4, 155.0, 151.0, 143.2, 133.1, 127.5, 124.5, 118.0, 113.5, 57.2, 50.4, 31.9, 31.6, 29.6, 20.3, 20.3. Anal. Calcd for $C_{19}H_{28}N_6$: C, 67.03; H, 8.29; N, 24.68%. Found: C, 67.16; H, 8.21; N, 24.58.
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Research Highlight

- Synthesis of dihydrobenzoimidazotriazins
- Synthesis of imidazol-2-yl-amino quinoxaline-5-carboxamides
- Cobalt-catalyzed isocyanide insertion cyclization reaction
- Cobalt-catalyzed direct insertion of isocyanide into the two N-H active bonds