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Article

An Efficient Protocol for Facile Synthesis of New 5-Substituted-1*H*-Tetrazole Derivatives Using Copper-Doped Silica Cuprous Sulfate (CDSCS) as Heterogeneous Nano-Catalyst

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A facile and highly efficient protocol for synthesis of new 5-substituted-1*H*-tetrazoles derivatives using copper-doped silica cuprous sulfate (CDSCS) is described. In this method, the cycloaddition reaction of sodium azide with structurally diverse nitriles involving bioactive *N*-heterocyclic cores exploiting CDSCS in refluxing H_2O/*i*-PrOH (1:1, v/v) furnishes the corresponding 5-substituted-1*H*-tetrazoles in good to excellent yields (up to 93%). The influence of parameters effective in progress of reaction including solvent type, temperature and catalyst was studied and discussed. In this protocol, CDSCS was proved to be an efficient heterogeneous nano-catalyst to easily achieve the new tetrazole derivatives. The advantages of CDSCS in current protocol known are its cheapness, thermal and chemical stability, ease of recyclability and reusability for several consecutive runs without significant decline in its reactivity.

Keywords: azide, CDSCS, cycloaddition, nitrile, 1*H*-tetrazole

Introduction

Tetrazole and its derivatives are an important class of *N*-heterocyclic compounds exhibiting widespread applications.[1,2] Tetrazoles are extensively applied in different industries as instance: stabilizers in photography and photo imaging,[3,4] explosives in rocket propellants,[5-7] chelating agents in coordination chemistry,[8,9] plant growth regulators, herbicides, fungicides in agriculture,[3,10] and anti-wears and frictions in lubricants.[11] Additionally, tetrazoles can be served as bioisosteres for the carboxylic acids.[12-14] Replacing a carboxyl group with tetrazolyl moiety extensively improves the metabolic stability, bioavailability and cell permeability of a drug molecule.[15,16] When increase in the lipophilicity factor (log P) for a drug molecule involving carboxylic moiety is desired, one can replace the carboxylic moiety with tetrazole as a more lipophilic bioisostere. Consequently, tetrazoles are widely applied in synthesis of many well-known drugs like losartan,[17-19] candesartan,[18,19] zolarsartan[18,19] and valsartan.[17] In addition, tetrazoles exhibit varied biological activities such as antihypertensive,[17-21] antibacterial,[22,23] antifungal,[24,25] anticonvulsant,[26] anti-inflammatory,[27,28] antitubercular,[29] anticancer,[30] antineoplastic,[31] antiallergic,[32-34] and antiviral[35] especially anti-HIV[36] activities.

The synthesis of tetrazole and its derivatives has attracted considerable attention since the broad utilities found for tetrazoles. In this context, the different preparative methods have been emerged so far.[37,38] Among them, the [3 + 2]-cycloaddition reaction of nitriles with azides is a well-known and most extensively studied and used procedure for synthesis of diverse 5-substituted-1*H*-tetrazoles.[39,40] In this regard, several homogeneous reagents or catalysts have been developed to synthesize 5-substituted-1*H*-tetrazoles.[41,42] Although these methods exhibit some advantages to access 1*H*-tetrazoles, their scale up synthesis are restricted by one or more disadvantages such as harsh reaction conditions, low yields, long reaction times, the use of strong Lewis acids, the *in situ* generation of HN_3 as a highly dangerous volatile material with a great risk of eruption and toxicity, production of the stable metal-tetrazole complexes, the use of expensive and toxic metals or solvents, tedious work-up procedure and failure to undertake the recovery or reusability of the catalyst.

Nowadays, heterogeneous catalysts have gained considerable attention due to both economic and environmental standpoints. The successful applications of heterogeneous systems in various organic transformations

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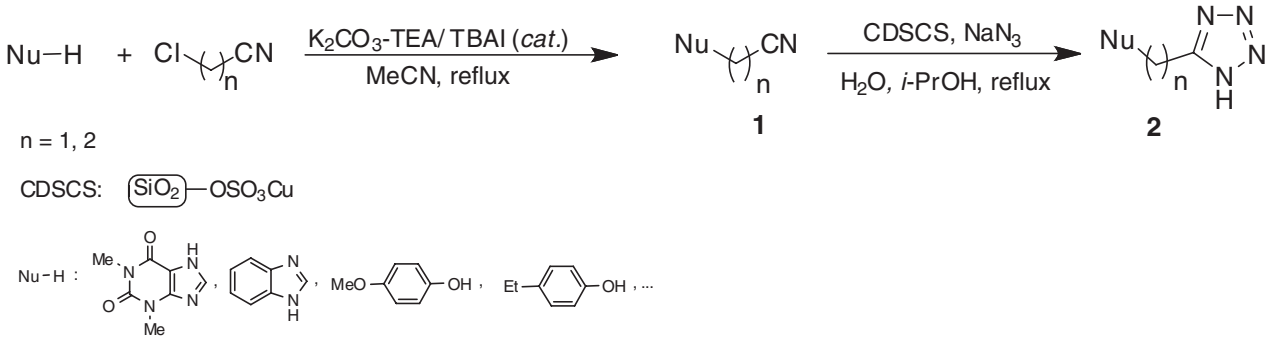
are well documented. Employing the heterogeneous catalysts often leads to the simple experimental procedures, mild reaction conditions, recovery and reusability of the catalyst, the minimization of undesirable chemical wastes, and the production of large quantities of products by using a small amount of catalyst. Thus, the exploit of heterogeneous catalysis has an exact superiority over homogeneous catalyst. In recent decade, some heterogeneous catalytic systems were developed to promote the synthesis of 5-substituted-1*H*-tetrazoles;[43-55] nevertheless, drawbacks are usually accompanied with these heterogeneous catalysts comprising: (*i*) the strong acidic nature of some catalysts that largely aggravates the release of dangerous HN_3; (*ii*) the use of weakly bonded or none-bonded metal salts supported on mineral supports which normally lead to desorption of active metal species during the reaction progress or work-up procedure; (*iii*) the formation of stable metal-tetrazole complexes that makes the tedious work-up procedure and (*iv*) the thermal or chemical instability. Thus, the employment of a heterogeneous catalyst that obviates the above drawbacks is of particular interest.

Silica-based catalysts offer several advantages like cheapness, mild reaction conditions, high yields and selectivity, non-corrosive properties, ease of handling and preparation. In addition, they could be easily removed from the reaction mixture, recovered, and reused by a simple flash filtration. Recently, we have reported the synthesis, characterization, and application of copper-doped silica cuprous sulfate (CDSCS) as a novel and efficient heterogeneous nano-catalyst for the Cu^{I}-catalyzed 'Click' synthesis of 1,4-disubstituted 1,2,3-triazoles[56] and also 3,5-disubstituted isoxazoles.[57] In light of the unique biological activities of tetrazoles and also in continuation of our ongoing research in utilizing CDSCS in organic synthesis,[56-58] we herein report a practical and environmentally benign catalytic protocol for efficient synthesis of 5-substituted-1*H*-tetrazole derivatives using CDSCS (Scheme 1). In this synthesis, the desired nitriles **1** were primarily achieved by the reaction of diverse nucleophiles with 2-chloroacetonitrile or 3-chloropropanenitrile in the presence of an equimolar mixture of triethylamine (TEA)-K_2CO_3 and catalytic amount of tetrabutylammonium iodide (TBAI) in MeCN at reflux condition. Then, to access tetrazoles **2**, the cycloaddition reaction of nitriles **1** with sodium azide was carried out utilizing CDSCS in H_2O/*i*-PrOH at reflux condition.

Results and Discussion

The first step of this synthetic approach was initiated by the preparation of the essential nitriles **1**. In this context, various nucleophiles comprising azole derivatives, purine and pyrimidine nucleobases and phenols underwent the *N*- or *O*-alkylation reaction with 2-chloroacetonitrile or 3-chloropropanenitrile through the S_N2-type reaction. The reaction of the selected nucleophiles with above chloronitriles was carried out using TEA-K_2CO_3 (1:1) in the presence of TBAI (cat.) in refluxing MeCN (anhyd.) to gain **1**. Afterward, to assess the optimized reaction condition for [3 + 2]-cycloaddition of **1** with NaN_3, the influence of various parameters including temperature, solvent, and catalyst was studied. In this regard, the cycloaddition reaction of 2-(1*H*-benzo[*d*]imidazol-1-yl)acetonitrile (**1a**) with NaN_3 was selected as a sample reaction.

To progress the reaction efficiently, the choice of an appropriate solvent is crucial. Among tested solvents, the use of water has attracted enormous interest in organic transformations, since water is a cheap, clean, and universal solvent exhibiting extraordinary physical properties and enviro-economic benefits.[59] In this regard, the model reaction was carried out in an aquatic media at room temperature. However, the corresponding tetrazole **2a** was obtained only in 19% yield (Table 1, entry 1). To increase the reaction yield, the model reaction was investigated at varied temperatures (Table 1). As indicated in Table 1, the use of pure water at different temperatures failed to afford the satisfactory results even at reflux condition. This can be attributed to the lack of solubility of nitrile **1a** in pure water. Consequently, the influence of several 1:1 (v/v) solutions



Scheme 1. CDSCS catalyzed synthesis of 5-substituted 1*H*-tetrazoles.

Table 1. Effect of solvent and temperature on the model reaction[a]

1a **2a**

entry	Solvent	T / °C	time / h	Yield[b] / %
1	H_2O	r.t.	24	19
2	H_2O	50	10	28
3	H_2O	60	7	39
4	H_2O	70	7	42
5	H_2O	80	5	50
6	H_2O	reflux	4	58
7	H_2O/*i*-PrOH[c]	r.t.	18	62
8	H_2O/*i*-PrOH[c]	reflux	4	93
9	H_2O/Me_2CO[c]	reflux	6	40
10	H_2O/DMF[c]	reflux	7	46
11	H_2O/DMSO[c]	reflux	7	49
12	H_2O/NMP[c]	reflux	6	53
13	H_2O/HMPA[c]	reflux	7	50
14	H_2O/THF[c]	reflux	8	81
15	THF	reflux	12	46
16	*i*-PrOH	reflux	5	60

[a]Reaction conditions: nitrile (0.01 mol), NaN_3 (0.015 mol), CDSCS (0.05 mol%), solvent (50 mL); [b]isolated yield; [c]1:1 (v/v).

of H_2O with some water miscible organic solvents were examined (Table 1).

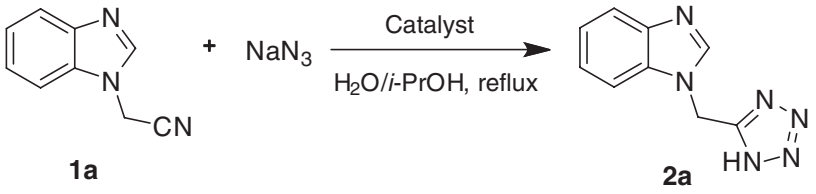
As indicated in Table 1, a solution of H_2O/*i*-PrOH (1:1, v/v) was found to be the most appropriate solvent for synthesis of tetrazole derivatives in the presence of CDSCS (Table 1, entry 8). Therefore, this solvent was used for all subsequent reactions. Employing H_2O/tetrahydrofuran (THF) (1:1, v/v) solution afforded the corresponding tetrazole in 81% yield after 8 h (Table 1, entry 14). Moreover, the combination of water with other miscible solvents like acetone, dimethylformamide (DMF), dimethyl sulfoxide (DMSO), *N*-methylpyrrolidone (NMP), and hexamethylphosphoramide (HMPA) yielded the moderate amount of product (Table 1, entries 9-13). In addition, when THF and/or *i*-PrOH were used separately as a solvent, **2a** was obtained in 46 and 60% yields, respectively (Table 1, entries 15, 16). Also, in an attempt to carry out the reaction in H_2O/*i*-PrOH (1:1, v/v) solution at r.t. **2a** was produced in 62% yield after 18 h (Table 1, entry 7).

It is well understood that cycloaddition reaction between nitrile and azide is very slowly achieved in the absence of a suitable catalyst and thus it is unsuitable for large scale synthesis. In this connection, the choice of an efficient catalyst is critically essential for progress of the reaction. To investigate the catalytic potency of CDSCS, the effect of different catalysts was studied and compared with CDSCS (Table 2). To this end, we examined the potency of several heterogeneous or homogeneous catalysts including Lewis and proton acids, solid supports, and ammonium salts which are often applied in synthesis of tetrazole derivatives. As the results in Table 2 indicate, higher yield of **2a** in shorter reaction time were observed utilizing CDSCS in comparison with other tested catalysts. The use of other catalysts yielded **2a** in moderate to reasonable amounts in variable times.

The optimized stoichiometric ratio of nitrile/sodium azide to access **2a** using CDSCS (0.05 mol%) was determined to be 1:1.5.

The generality and versatility of current protocol was screened by applying the optimized condition to various structurally diverse nitriles **1a-1o** (Table 3). Due to Table 3, CDSCS proved to be a convenient and efficient heterogeneous nano-catalyst for cycloaddition reaction of sodium azide with different nitriles tethered to bioactive cores. As shown in Table 3, nitriles bearing azole derivatives (Table 3, entries 1-4, 10, 11), xanthine (Table 3, entry 9), purine and pyrimidine nucleobases (Table 3, entries 5 and 6) were employed to produce their corresponding 5-substituted-1*H*-tetrazole derivatives in good to excellent yields. Moreover, nitriles involving amine (Table 3, entry 12), cyclic amides (Table 3, entries 7 and 8), and phenols (Table 3, entries 13-15) underwent

Table 2. Comparing the influence of different catalysts with CDSCS in synthesis of **2a**[a]



1a **2a**

entry	Catalyst	time / h	Yield[b] / %
1	TBAF[c]	24	40
2	NH_4Cl[c]	24	59
3	$Et_3N.HCl$[c]	12	75
4	$FeCl_3$–SiO_2[c]	24	54
5	CDSCS[d]	4	93
6	amberlyst-15[c]	24	30
7	HCl[c]	24	48
8	silica sulfuric acid[c]	12	79
9	Cu_2O[c]	10	67
10	$CuFe_2O_4$[c]	12	70
11	Zeolite[d]	24	52
12	$ZnBr_2$[c]	5	67
13	ZnO[c]	15	53
14	$AlCl_3$[c]	10	72
15	TMSCl[c]	12	41
16	$H_3PW_{12}O_{40}$[e]	8	50

[a]Reaction conditions: nitrile (0.01 mol), NaN_3 (0.015 mol), catalyst, H_2O/*i*-PrOH (50 mL); [b]isolated yield; [c]an equimolar amount was used; [d]0.05 mol%; [e]1 mol%.

cycloaddition reaction with azide to obtain the desired tetrazole derivatives. The structures of all synthesized compounds were confirmed by ^1H and ^{13}C NMR, elemental analysis, mass and infrared (IR) spectroscopy techniques.

The applicability of the present protocol in preparative scale was also examined. In this context, the cycloaddition reaction of nitrile **1a** with NaN_3 was performed on a 100-mmol scale. Interestingly, **2a** was obtained in an excellent yield (89%) after 4 h which is comparable to smaller scale synthesis (Table 3, entry 1).

The recoverability and reusability of the catalyst is an important issue from different aspects like commercial applications and environmental concerns. In this connection, the reusability of CDSCS was investigated for sample reaction (Table 4).

The separation of the catalyst from the reaction media was conducted using a sintered glass funnel. The catalyst was then washed with ethyl acetate (2 × 15 mL) and dried in a vacuum oven at 90 ºC for 20 min. The catalyst was sequentially applied for 5 runs without the addition of the fresh catalyst to the reaction media. As shown in Table 4, the catalyst can be reused for many consecutive times without considerable decline in its catalytic activity. To determine the amount of leached Cu from CDSCS, the copper content of catalyst was determined using inductively coupled plasma (ICP) analysis for both fresh and reused catalyst (after 5 runs). Based on the ICP results, the leached Cu was found to be 0.014%, which is negligible.

Conclusions

In conclusion, we have described a convenient protocol for facile and high yield synthesis of the new structurally diverse 5-substituted-1*H*-tetrazoles utilizing CDSCS as a highly efficient heterogeneous nano-catalyst. CDSCS was proved to be a useful catalyst for cycloaddition reaction of sodium azide with different nitriles involving bioactive cores in H_2O/*i*-PrOH (1:1, v/v) at reflux condition, which affords the corresponding tetrazole derivatives in good to excellent yields. The use of ecofriendly solvent, the reusability of the catalyst, the simplicity of the process, cheapness, and applicability in preparative scale are benefits that can be mentioned for current synthetic protocol.

Experimental

General

All chemicals were purchased from either Fluka or Merck. Reactions were followed by TLC using

Table 3. Synthesis of 5-substituted-1*H*-tetrazole derivatives using CDSCS[a]

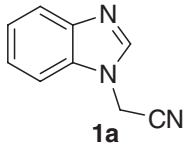
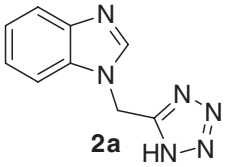
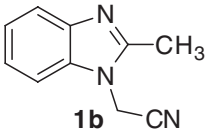
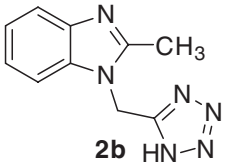
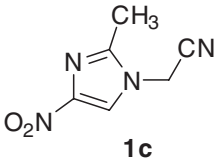
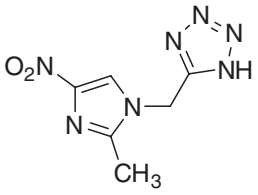
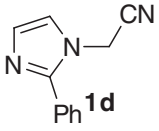
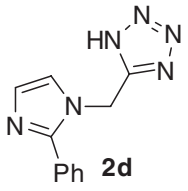
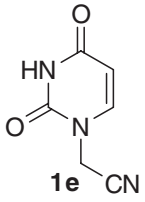
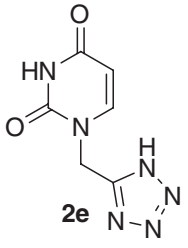
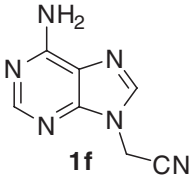
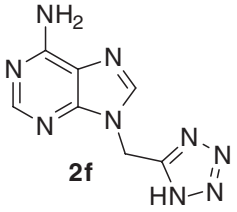
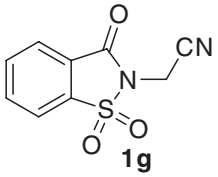
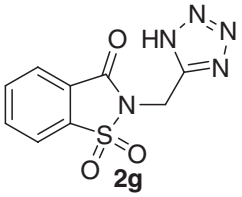
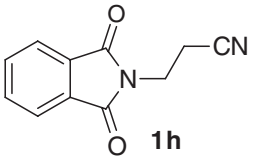
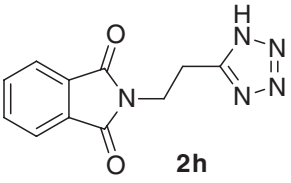
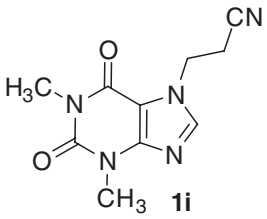
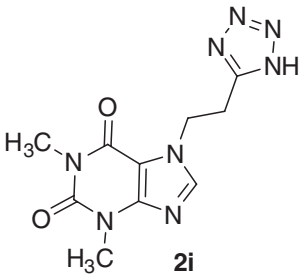
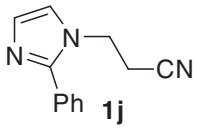
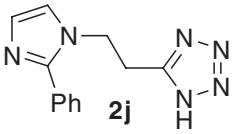
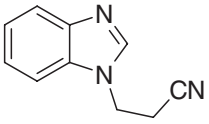
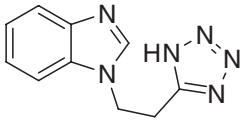
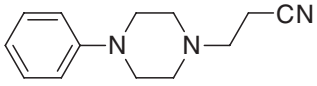
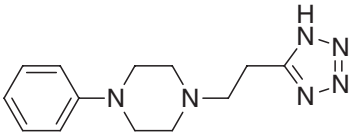
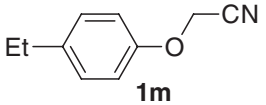
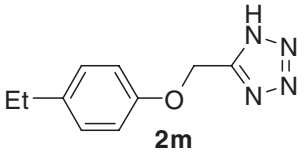
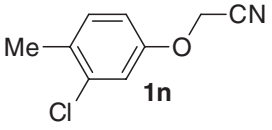
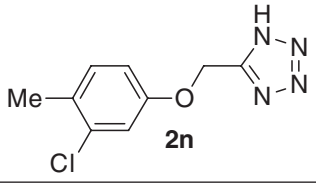
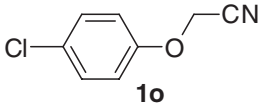
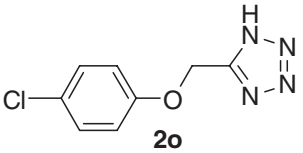
entry	Nitrile	Product[b]	time / h	Yield[c] / %
1	 **1a**	 **2a**	4	93
2	 **1b**	 **2b**	4	89
3	 **1c**	 **2c**	5	85
4	 **1d**	 **2d**	6	87
5	 **1e**	 **2e**	3.5	83
6	 **1f**	 **2f**	5.5	82
7	 **1g**	 **2g**	3	87
8	 **1h**	 **2h**	3.5	91

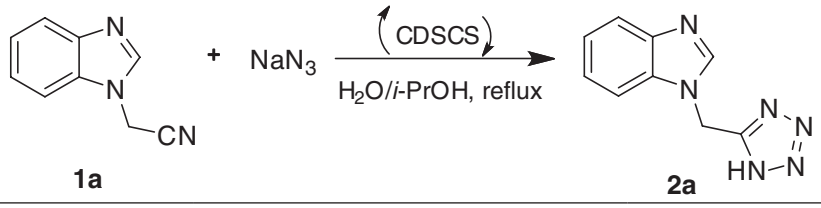
Table 3. Synthesis of 5-substituted-1*H*-tetrazole derivatives using CDSCS[a] (cont.)

9	 **1i**	 **2i**	4	90
10	 **1j**	 **2j**	7	86
11	 **1k**	 **2k**	4	89
12	 **1l**	 **2l**	5.5	92
13	 **1m**	 **2m**	6	91
14	 **1n**	 **2n**	6	89
15	 **1o**	 **2o**	6	90

[a]Reaction conditions: nitrile (0.01 mol), NaN_3 (0.015 mol), CDSCS (0.05 mol%), H_2O/*i*-PrOH (50 mL); [b]all products were characterized by ^1H and ^{13}C NMR, IR, CHN, and MS analysis; [c]isolated yield.

SILG/UV 254 silica-gel plates. The fresh CDSCS was prepared according to our previous reported procedure.[56,58] Column chromatography was performed on silica gel 60 (0.063-0.200 mm, 70-230 mesh; ASTM). Melting points were measured using Electrothermal IA 9000 melting point apparatus in open capillary tubes and are uncorrected. IR spectra were obtained using a Shimadzu FTIR-8300 spectrophotometer. ^1H and ^{13}C NMR spectrum was recorded on Brüker Avance-DPX-250/400 spectrometer operating at 250/62.5 and/or 400/100 MHz, respectively. Chemical shifts are given in δ relative to tetramethylsilane (TMS) as an internal standard, coupling constants *J* are given in Hz. Abbreviations used for ^1H NMR signals are: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad and etc. GC-MS was performed on a Shimadzu GCMS-QP1000-EX apparatus (*m/z*; rel. %). Elemental analyses were performed on a PerkinElmer 240-B micro-analyzer.

Table 4. The reusability of CDSCS in successive trails for synthesis of **2a**[a]



1a **2a**

entry[b]	time / h	Yield[c] / %
1	4	93
2	4	93
3	4.5	91
4	4.5	90
5	5	87

[a]Reaction conditions: nitrile (0.01 mol), NaN_3 (0.015 mol), recovered CDSCS, H_2O/*i*-PrOH (50 mL); [b]the entry number corresponds to the trial number; [c]isolated yield.

General procedure for synthesis of alkyl nitriles **1a-1o**

In a double-necked round bottom flask (100 mL) equipped with a condenser, it was added a mixture, consisting of nucleophile (including: *N*-heterocyclic compounds or phenolic derivatives) (0.01 mol), 2-chloroacetonitrile or 3-chloropropanenitrile (0.013 mol), Et_3N (0.01 mol), K_2CO_3 (0.01 mol), and a catalytic amount of TBAI (0.1 g) in anhydrous MeCN (40 mL). The mixture was refluxed until TLC monitoring indicates no further improvement in the reaction. The solvent was evaporated *in vacuo* and the remaining foam was dissolved in $CHCl_3$ (100 mL) and subsequently washed with water (2 × 100 mL). The organic layer was dried (Na_2SO_4) and evaporated. The crude product was purified by column chromatography on silica gel.

General procedure for synthesis of 5-substituted-1*H*-tetrazole **2a-2o**

In a double-necked round bottom flask (100 mL) equipped with a condenser, it was added a mixture, consisting of alkyl nitrile (0.01 mol), NaN_3 (0.015 mol), and CDSCS (0.3 g, 0.05 mol%) in H_2O/*i*-PrOH (1:1 v/v, 50 mL). The mixture was heated at reflux until TLC monitoring indicates no further improvement in the conversion (Table 3). The reaction mixture was then cooled to room temperature, vacuum-filtered using a sintered-glass funnel and the residue was washed with ethyl acetate (2 × 20 mL). The filtrate was treated with 5 N HCl to reach pH = 3 and it was allowed to stir for 30 minutes. Subsequently, the organic layer was separated, dried over anhydrous Na_2SO_4 and evaporated. The crude product was purified by recrystallization and/or column chromatography on silica gel eluted with proper solvents.

1-((1*H*-Tetrazol-5-yl)methyl)-1*H*-benzo[*d*]imidazole (**2a**)

Recrystallization (EtOAc) afforded a yellow solid; yield: 1.86 g (93%); mp 235-240 °C (dec.); IR (KBr) ν / cm^{-1} 3385, 3100, 2968, 2800, 1616, 1462, 1410; ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.28 (s, 1H, C(2)-H, benzimidazole), 7.64-7.61 (m, 2H, aryl), 7.22-7.13 (m, 2H, aryl), 5.55 (s, 2H, NCH_2), 2.51 (s, 1H, exchangeable with D_2O, NH, tetrazole); ^{13}C NMR (250 MHz, DMSO-d_6) δ 51.7, 116.6, 117.8, 122.2, 123.2, 133.6, 137.5, 145.6, 155.6; MS (EI): *m/z* (%) = 200 (14.5) [M^+]; anal. calcd. for $C_9H_8N_6$: C, 53.99; H, 4.03; N, 41.98; found: C, 54.06; H, 4.15; N, 41.92.

1-((1*H*-Tetrazol-5-yl)methyl)-2-methyl-1*H*-benzo[*d*]imidazole (**2b**)

Recrystallization (EtOAc) afforded a creamy solid; yield: 1.90 g (89%); mp > 300 °C (dec.); IR (KBr) ν / cm^{-1} 3384, 3100, 2982, 1619, 1580, 1480; ^{1}H NMR (250 MHz, DMSO-d_6) δ 7.57-7.46 (m, 2H, aryl), 7.16-7.08 (m, 2H, aryl), 5.46 (s, 2H, NCH_2), 4.55 (s, 1H, exchangeable with D_2O, NH, tetrazole), 2.67 (s, 3H, CH_3); ^{13}C NMR (250 MHz, DMSO-d_6) δ 17.9, 49.1, 115.5, 116.6, 121.5, 123.0, 134.7, 140.3, 151.2, 158.4; MS (EI): *m/z* (%) = 214 (11.4) [M^+]; anal. calcd. for $C_{10}H_{10}N_6$: C, 56.07; H, 4.71; N, 39.23; found: C, 56.19; H, 4.62; N, 39.35.

5-((2-Methyl-4-nitro-1*H*-imidazol-1-yl)methyl)-1*H*-tetrazole (**2c**)

Column chromatography (silica gel, EtOAc–MeOH, 1:1) afforded a brown solid; yield: 1.77 g (85%); mp 208-212 °C (dec.); IR (KBr) ν / cm^{-1} 3350, 3128, 2900, 1645, 1500, 1456, 1300; ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.30 (s, 1H, C(5)-H, imidazole), 5.40 (s, 2H, NCH_2), 4.40 (s, 1H, exchangeable with D_2O, NH, tetrazole), 2.43 (s, 3H, CH_3); ^{13}C NMR (250 MHz, DMSO-d_6) δ 15.7, 48.2, 121.1,

147.8, 153.0, 160.9; MS (EI): *m/z* (%) = 209 (8.1) [M$^+$]; anal. calcd. for $C_6H_7N_7O_2$: C, 34.45; H, 3.37; N, 46.88; found: C, 34.38; H, 3.42; N, 46.94.

5-((2-Phenyl-1*H*-imidazol-1-yl)methyl)-1*H*-tetrazole (**2d**)

Recrystallization (EtOAc) afforded a bright brown solid; yield: 1.96 g (87%); mp 216-220 °C (dec.); IR (KBr) ν / cm^{-1} 3280, 3150, 2937, 2850, 1653, 1476; ^{1}H NMR (250 MHz, DMSO-d_6) δ 7.94-7.91 (m, 2H, aryl), 7.58-7.46 (m, 3H, aryl), 7.20 (s, 1H, C(4)-H, imidazole), 6.95 (s, 1H, C(5)-H, imidazole), 5.28 (s, 2H, NCH_2), 2.50 (s, 1H, exchangeable with D_2O, NH, tetrazole); ^{13}C NMR (250 MHz, DMSO-d_6) δ 49.0, 121.0, 125.5, 127.0, 127.4, 129.6, 131.0, 152.1, 160.1; MS (EI): *m/z* (%) = 226 (17.3) [M$^+$]; anal. calcd. for $C_{11}H_{10}N_6$: C, 58.40; H, 4.46; N, 37.15; found: C, 58.31; H, 4.58; N, 37.02.

1-((1*H*-Tetrazol-5-yl)methyl)pyrimidine-2,4(1*H*,3*H*)-dione (**2e**)

Recrystallization (EtOAc) afforded a creamy solid; yield: 1.61 g (83%); mp 285-290 °C; IR (KBr) ν / cm^{-1} 3365, 3129, 2876, 1723, 1706, 1650, 1458; ^{1}H NMR (250 MHz, DMSO-d_6) δ 11.37 (s, 1H, exchangeable with D_2O, NH, uracil), 7.67 (d, 1H, *J* 7.5 Hz, C(6)-H, uracil), 5.70 (d, 1H, *J* 7.5 Hz, C(5)-H, uracil), 5.07 (s, 2H, NCH_2), 4.07 (s, 1H, exchangeable with D_2O, NH, tetrazole); ^{13}C NMR (250 MHz, DMSO-d_6) δ 47.3, 103.4, 142.1, 151.5, 156.4, 161.7; MS (EI): *m/z* (%) = 194 (10.8) [M$^+$]; anal. calcd. for $C_6H_6N_6O_2$: C, 37.12; H, 3.11; N, 43.29; found: C, 37.24; H, 3.26; N, 43.24.

9-((1*H*-Tetrazol-5-yl)methyl)-9*H*-purin-6-amine (**2f**)

Recrystallization (EtOAc) afforded a creamy solid; yield: 1.78 g (82%); mp > 300 °C (dec.); IR (KBr) ν / cm^{-1} 3328, 3100, 2853, 1676, 1520, 1471; ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.12 (s, 1H, C(8)-H, adenine), 8.05 (s, 1H, C(2)-H, adenine), 7.17 (s, 2H, exchangeable with D_2O, NH_2), 5.42 (s, 2H, NCH_2), 4.80 (s, 1H, exchangeable with D_2O, NH, tetrazole); ^{13}C NMR (250 MHz, DMSO-d_6) δ 54.3, 118.4, 139.9, 147.7, 151.5, 155.6, 162.8; MS (EI): *m/z* (%) = 217 (9.5) [M$^+$]; anal. calcd. for $C_7H_7N_9$: C, 38.71; H, 3.25; N, 58.04; found: C, 38.63; H, 3.18; N, 58.12.

2-((1*H*-Tetrazol-5-yl)methyl)benzo[*d*]isothiazol-3(2*H*)-one 1,1-dioxide (**2g**)

Recrystallization (EtOAc) afforded a pale-yellow solid; yield: 2.30 g (87%); mp 225-229 °C (dec.); IR (KBr) ν / cm^{-1} 3324, 3050, 2976, 1715, 1600, 1460, 1321, 761; ^{1}H NMR (250 MHz, DMSO-d_6) δ 7.84-7.45 (m, 4H, aryl), 4.44 (s, 2H, NCH_2), 2.51 (s, 1H, exchangeable with D_2O, NH, tetrazole); ^{13}C NMR (250 MHz, DMSO-d_6) δ 39.5, 126.3, 126.8, 127.3, 131.6, 132.0, 139.3, 156.6, 169.1; MS (EI): *m/z* (%) = 265 (19.7) [M$^+$]; anal. calcd. for $C_{10}H_8N_4O_3S$: C, 45.45; H, 3.05; N, 21.20; S, 12.13; found: C, 45.56; H, 3.11; N, 21.14; S, 12.25.

2-(2-(1*H*-Tetrazol-5-yl)ethyl)isoindoline-1,3-dione (**2h**)

Recrystallization (EtOAc) afforded a creamy solid; yield: 2.21 g (91%); mp > 300 °C (dec.); IR (KBr) ν / cm^{-1} 3374, 3063, 2950, 1772, 1620, 1510, 1458; ^{1}H NMR (250 MHz, DMSO-d_6) δ 7.28-7.09 (m, 4H, aryl), 4.34 (t, 2H, *J* 7.2 Hz, NCH_2), 3.46 (s, 1H, exchangeable with D_2O, NH, tetrazole), 3.08 (t, 2H, *J* 7.2 Hz, NCH_2CH_2); ^{13}C NMR (250 MHz, DMSO-d_6) δ 27.6, 42.6, 126.3, 131.6, 134.2, 159.4, 167.0; MS (EI): *m/z* (%) = 243 (13.9) [M$^+$]; anal. calcd. for $C_{11}H_9N_5O_2$: C, 54.32; H, 3.73; N, 28.79; found: C, 54.43; H, 3.82; N, 28.86.

7-(2-(1*H*-Tetrazol-5-yl)ethyl)-1,3-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione (**2i**)

Column chromatography (silica gel, MeOH) afforded a brown foam; yield: 2.48 g (90%); IR (KBr) ν / cm^{-1} 3300, 2985, 1716, 1702, 1693, 1658, 1379;^{1}H NMR(250 MHz, DMSO-d_6) δ 7.86 (s, 1H, C(8)-H, theophylline), 4.55 (t, 2H, *J* 5.7 Hz, NCH_2), 3.41 (t, 2H, *J* 5.7 Hz, NCH_2CH_2), 3.27 (s, 3H, N(1)-CH_3), 3.09 (s, 3H, N(3)-CH_3), 2.54 (s, 1H, exchangeable with D_2O, NH, tetrazole); ^{13}C NMR (250 MHz, DMSO-d_6) δ 20.1, 31.0, 32.3, 34.5, 106.3, 136.8, 145.9, 147.7, 154.5, 159.8; MS (EI): *m/z* (%) = 276 (20.7) [M$^+$]; anal. calcd. for $C_{10}H_{12}N_8O_2$: C, 43.48; H, 4.38; N, 40.56; found: C, 43.59; H, 4.27; N, 40.61.

5-(2-(2-Phenyl-1*H*-imidazol-1-yl)ethyl)-1*H*-tetrazole (**2j**)

Recrystallization (EtOAc) afforded a creamy solid; yield: 2.06 g (86%); mp 250-255 °C (dec.); IR (KBr) ν / cm^{-1} 3300, 3050, 2960, 1650, 1485; ^{1}H NMR (250 MHz, DMSO-d_6) δ 7.58-7.44 (m, 5H, aryl), 7.32 (s, 1H, C(4)-H), 6.95 (s, 1H, C(5)-H), 4.29 (t, 2H, *J* 7.5 Hz, NCH_2), 3.07 (t, 2H, *J* 7.5 Hz, NCH_2CH_2), 1.98 (s, 1H, exchangeable with D_2O, NH, tetrazole); ^{13}C NMR (250 MHz, DMSO-d_6) δ 30.0, 54.5, 120.8, 125.8, 126.3, 127.0, 127.2, 130.2, 149.7, 155.1; MS (EI): *m/z* (%) = 240 (15.8) [M$^+$]; anal. calcd. for $C_{12}H_{12}N_6$: C, 59.99; H, 5.03; N, 34.98; found: C, 60.07; H, 5.16; N, 34.87.

1-(2-(1*H*-Tetrazol-5-yl)ethyl)-1*H*-benzo[*d*]imidazole (**2k**)

Recrystallization (EtOAc) afforded a brown solid; yield: 1.90 g (89%); mp 300-304 °C (dec.); IR (KBr) ν / cm^{-1} 3326, 3100, 2926, 1653, 1501, 1470; ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.10 (s, 1H, C(2)-H, benzimidazole), 7.62-7.55 (m, 2H, aryl), 7.24-7.14 (m, 2H, aryl), 4.55 (t, 2H, *J* 6.5 Hz, NCH_2), 3.17 (t, 2H, *J* 6.5 Hz, NCH_2CH_2), 2.51 (s, 1H, exchangeable with D_2O, NH, tetrazole); ^{13}C NMR

(250 MHz, DMSO-d_6) δ 31.1, 60.5, 116.1, 117.3, 124.1, 125.2, 134.6, 138.7, 149.3, 161.7; MS (EI): *m/z* (%) = 214 (12.7) [M$^+$]; anal. calcd. for $C_{10}H_{10}N_6$: C, 55.94; H, 4.63; N, 39.14; found: C, 55.83; H, 4.75; N, 39.28.

1-(2-(1*H*-Tetrazol-5-yl)ethyl)-4-phenylpiperazine (**2l**)

Column chromatography (silica gel, EtOAc-*n*-hexane, 1:1) afforded a bright brown solid; yield: 2.37 g (92%); mp > 300 °C (dec.); IR (KBr) ν / cm^{-1} 3340, 3100, 2992, 1659, 1653, 1476; ^{1}H NMR (250 MHz, DMSO-d_6) δ 7.26-7.20 (m, 2H, aryl), 6.91-6.81 (m, 3H, aryl), 4.96 (s, 1H, exchangeable with D_2O, NH, tetrazole), 3.83 (t, 2H, *J* 6.5 Hz, CH_2), 3.09 (t, 2H, *J* 7.2 Hz, CH_2), 2.72-2.65 (m, 8H, 4 CH_2); ^{13}C NMR (250 MHz, DMSO-d_6) δ 28.2, 49.1, 52.2, 56.1, 114.3, 119.5, 130.5, 150.0, 160.2; MS (EI): *m/z* (%) = 258 (19.7) [M$^+$]; anal. calcd. for $C_{13}H_{18}N_6$: C, 60.44; H, 7.02; N, 32.53; found: C, 60.31; H, 7.08; N, 32.61.

5-((4-Ethylphenoxy)methyl)-1*H*-tetrazole (**2m**)

Recrystallization (EtOAc) afforded a creamy solid; yield: 1.85 g (91%); mp 83-85 °C; IR (KBr) ν / cm^{-1} 3300, 3040, 2957, 1654, 1458; ^{1}H NMR (250 MHz, DMSO-d_6) δ 7.18-7.06 (m, 2H, aryl), 6.97-6.93 (m, 1H, aryl), 6.86-6.77 (m, 1H, aryl), 5.42 (s, 2H, OCH_2), 4.36 (s, 1H, exchangeable with D_2O, NH, tetrazole), 2.57-2.45 (m, 2H, CH_2CH$_3$), 1.14 (t, 3H, *J* 7.5 Hz, CH_3); ^{13}C NMR (250 MHz, DMSO-d_6) δ 14.6, 32.3, 72.1, 115.9, 128.4, 132.4, 155.1, 159.7; MS (EI): *m/z* (%) = 204 (14.5) [M$^+$]; anal. calcd. for $C_{10}H_{12}N_4O$: C, 58.81; H, 5.92; N, 27.43; found: C, 58.89; H, 6.04; N, 27.51.

5-((3-Chloro-4-methylphenoxy)methyl)-1*H*-tetrazole (**2n**)

Recrystallization (EtOAc) afforded a white solid; yield: 1.99 g (89%); mp 145-147 °C; IR (KBr) ν / cm^{-1} 3250, 3028, 2947, 1657, 1451, 720; ^{1}H NMR (250 MHz, DMSO-d_6) δ 7.04 (d, 1H, *J* 8.0 Hz, aryl), 6.58 (d, 1H, *J* 8.0 Hz, aryl), 6.49 (s, 1H, aryl), 5.61 (s, 2H, OCH_2), 4.62 (s, 1H, exchangeable with D_2O, NH, tetrazole), 2.47 (s, 3H, CH_3); ^{13}C NMR (250 MHz, DMSO-d_6) δ 20.1, 70.8, 114.7, 116.4, 125.5, 129.0, 138.8, 155.9, 158.4; MS (EI): *m/z* (%) = 224 (19.1) [M$^+$]; anal. calcd. for $C_9H_9ClN_4O$: C, 48.12; H, 4.04; Cl, 15.78; N, 24.94; found: C, 48.05; H, 4.07; Cl, 15.71; N, 25.03.

5-((4-Chlorophenoxy)methyl)-1*H*-tetrazole (**2o**)

Recrystallization (EtOAc) afforded a bright brown solid; yield: 1.89 g (90%); mp 241-245 °C; IR (KBr) ν / cm^{-1} 3270, 3062, 2981, 1654, 1469, 715; ^{1}H NMR (250 MHz, DMSO-d_6) δ 7.13 (d, 2H, *J* 8.8 Hz, aryl), 6.91 (d, 2H, *J* 8.8 Hz, aryl), 5.05 (s, 2H, OCH_2), 4.39 (s, 1H, exchangeable with D_2O, NH, tetrazole); ^{13}C NMR (250 MHz, DMSO-d_6) δ 71.2, 116.3, 127.4, 129.7, 154.7, 159.0; MS (EI): *m/z* (%) = 210 (18.1) [M$^+$]; anal. calcd. for $C_8H_7ClN_4O$: C, 45.62; H, 3.35; Cl, 16.83; N, 26.60; found: C, 45.69; H, 3.43; Cl, 16.80; N, 26.67.

Supplementary Information

^{1}H and ^{13}C NMR spectra of synthesized tetrazoles are available free of charge at http://jbcs.sbq.org.br as PDF file.

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References

1. Butler, R. N. In *Comprehensive Heterocyclic Chemistry II*, vol. 4; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., eds.; Pergamon: Oxford, 1996, p. 897.
2. Ostrovskii, V. A.; Koldobskii, G. I.; Trifonov, R. E. In *Comprehensive Heterocyclic Chemistry III*, vol. 6; Katritzky, A. R.; Ramsden, C. A.; Scriven, E. F. V.; Taylor, R. J. K., eds.; Elsevier: Oxford, 2008, p. 257.
3. Jursic, B. S.; Leblanc, B. W.; *J. Heterocycl. Chem.* **1998**, *35*, 405 and references cited therein.
4. Koldobskii, G. I.; Ostrovskii, V. A.; Popavskii, V. S.; *Khim. Geterotsikl. Soedin.* **1981**, *10*, 1299.
5. Zhao-Xu, C.; Heming, X.; *Int. J. Quantum Chem.* **2000**, *79*, 350.
6. Kharaghiosoff, K.; Klapotke, T. M.; Mayer, P.; Piotrowski, H.; Polborn, K.; Willer, R. L.; Weigand, J. J.; *J. Org. Chem.* **2006**, *71*, 1295.
7. Hammerl, A.; Hiskey, M. A.; Holl, G.; Klapoetke, T. M.; Polborn, K.; Stierstorfer, J.; Weigand, J. J.; *Chem. Mater.* **2005**, *17*, 3784.
8. Downard, A. J.; Steel, P. J.; Steenwijk, J.; *Aust. J. Chem.* **1995**, *48*, 1625.
9. Mukhopadhyay, S.; Lasri, J.; Guedes da Silva, M. F. C.; Januário Charmier, M. A.; Pombeiro, A. J. L.; *Polyhedron* **2008**, *27*, 2883.
10. McManus, J. M.; Herbst, R. M.; *J. Org. Chem.* **1959**, *24*, 1464.
11. Li, J.; Ren, T.; Liu, H.; Wang, D.; Liu, W.; *Wear* **2000**, *246*, 130.
12. Herr, R. J.; *Bioorg. Med. Chem.* **2002**, *10*, 3379.
13. Meanwell, N. A.; *J. Med. Chem.* **2011**, *54*, 2529.
14. Pegklidou, K.; Koukoulitsa, C.; Nicolaou, I.; Demopoulos, V. J.; *Bioorg. Med. Chem.* **2010**, *18*, 2107.
15. Holland, G. F.; Pereira, J. N.; *J. Med. Chem.* **1967**, *10*, 149.
16. Marvi, O.; Alizadeh, A.; Zarrabi, S.; *Bull. Korean Chem. Soc.* **2011**, *32*, 4001.
17. Aureggi, V.; Sedelmeier, G.; *Angew. Chem., Int. Ed.* **2007**, *46*, 8440.

18. Alonen, A.; Finel, M.; Kostiainen, R.; *Biochem. Pharmacol.* **2008**, *76*, 763.
19. Alonen, A.; Jansson, J.; Kallonen, S.; Kiriazis, A.; Aitio, O.; Finel, M.; Kostiainen, R.; *Bioorg. Chem.* **2008**, *36*, 148.
20. Bräuner-Osborne, H.; Egebjerg, J.; Nielsen, E. O.; Madsen, U.; Krogsgaard-Larsen, P.; *J. Med. Chem.* **2000**, *43*, 2609.
21. Lusina, M.; Cindrić, T.; Tamaić, J.; Peko, M.; Pozaić, L.; Musulin, N.; *Int. J. Pharm.* **2005**, *291*, 127.
22. Narasaiaha, T.; Subba Raoa, D.; Rasheeda, S.; Madhavaa, G.; Srinivasulua, D.; Brahma Naidub, P.; Naga Rajua, C.; *Der Pharm. Lett.* **2012**, *4*, 854.
23. Andrus, A.; Partridge, B.; Heck, J. V.; Christensen, B. G.; *Tetrahedron Lett.* **1984**, *25*, 911.
24. Dhayanithhi, V.; Syed, S. S.; Kumaran, K.; Sankar, K. R. J.; Ragavan, R. V.; Goud, P. S. K.; Kumari, N. S.; Pati, H. N.; *J. Serb. Chem. Soc.* **2011**, *76*, 165.
25. Rajasekaran, A.; Sankaranarayanan, M.; Rajagopal, K. A.; *Arch. Pharm. Res.* **2006**, *29*, 535.
26. Upadhayaya, R. S.; Jain, S.; Sinha, N.; Kishore, N.; Chandra, R.; Arora, S. K.; *Eur. J. Med. Chem.* **2004**, *39*, 579.
27. Mohite, P. B.; Pandhare, R. B.; Khanage, S. G.; Bhaskar,V. H.; *J. Pharm. Res.* **2010**, *3*, 43.
28. Maxwell, J. R.; Wasdahl, D. A.; Wolfson, A. C.; Stenberg, V. I.; *J. Med. Chem.* **1984**, *27*, 1565.
29. Adamec, J.; Waisser, K.; Kunes, J.; Kaustova, J.; *Arch. Pharm.* **2005**, *338*, 385.
30. De Souza, A. O.; Pedrosa, M. T.; Alderete, J. B.; Cruz, A. F.; Prado, M. A.; Alves, R. B.; Silva, C. L.; *Pharmazie* **2005**, *60*, 396.
31. Akimoto, H.; Ootsu, K.; Itoh, F.; *Eur. Patent EP 530,537* **1993** *(CA 119:226417).*
32. Peet, N. P.; Baugh, L. E.; Sunder, S.; Lewis, J. E.; Matthews, E. H.; Olberding, E. L.; Shah, D. N.; *J. Med. Chem.* **1986**, *29*, 2403.
33. Ellis, G. P.; Shaw, D.; *J. Med. Chem.* **1972**, *15*, 865.
34. Nohara, A.; Kuriki, H.; Saijo, T.; Sugihara, H.; Kanno, M.; Sanno, Y.; *J. Med. Chem.* **1977**, *20*, 141.
35. Vieira, E.; Huwyler, S.; Jolidon, S.; Knoflach, F.; Mutel, V.; Wichmann, J.; *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4628.
36. Gagnon, A.; Landry, S.; Coulombe, R.; Jakalian, A.; Guse, I.; Thavonekham, B.; Bonneau, P. R.; Yoakim, C.; Simoneau, B.; *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1199.
37. Katritzky, A. R.; Cai, C.; Meher, N. K.; *Synthesis* **2007**, 1204 and all references cited therein.
38. Patil, U. B.; Kumthekar, K. R.; Nagarkar, J. M.; *Tetrahedron Lett.* **2012**, *53*, 3706.
39. Demko, Z. P.; Sharpless, K. B;. *J. Org. Chem.* **2001**, *66*, 7945.
40. Himo, F.; Demko, Z. P.; Noodleman, L.; Sharpless, K. B.; *J. Am. Chem. Soc.* **2003**, *125*, 9983.
41. Roh, J.; Vávrová, K.; Hrabálek, A.; *Eur. J. Org. Chem.* **2012**, 6101.
42. Voitekhovich, S. V.; Ivashkevich, O. A.; Gaponik, P. N.; *Russ. J. Org. Chem.* **2013**, *49*, 635.
43. Sreedhar, B.; Kumar, A. S.; Yada, D.; *Tetrahedron Lett.* **2011**, *52*, 3565.
44. Nasrollahzadeh, M.; Bayat, Y.; Habibi, D.; Moshaee, S.; *Tetrahedron Lett.* **2009**, *50*, 4435.
45. Du, Z.; Si, C.; Li, Y.; Wang, Y.; Lu, J.; *Int. J. Mol. Sci.* **2012**, *13*, 4696.
46. Esmaeilpour, M.; Javidi, J.; Nowroozi Dodeji, F.; Mokhtari Abarghoui, M.; *J. Mol. Catal. A: Chem.* **2014**, *393*, 18.
47. Najafi Chermahini, A.; Teimouri, A.; Momenbeik, F.; Zarei, A.; Dalirnasab, Z.; Ghaedi, A.; Roosta, M.; *J. Heterocycl. Chem.* **2010**, *47*, 913.
48. Teimouri, A.; Najafi Chermahini, A.; *Polyhedron* **2011**, *30*, 2606.
49. Nasrollahzadeh, M.; Habibi, D.; Shahkarami, Z.; Bayat, Y.; *Tetrahedron* **2009**, *65*, 10715.
50. Sharghi, H.; Ebrahimpourmoghaddam, S.; Doroodmand, M. M.; *J. Organomet. Chem.* **2013**, *738*, 41.
51. Dehghani, F.; Sardarian, A. R.; Esmaeilpour, M.; *J. Organomet. Chem.* **2013**, *743*, 87.
52. Kantam, M. L.; Shiva Kumar, K. B.; Phani Raja, K. J.; *J. Mol. Catal. A: Chem.* **2006**, *247*, 186.
53. Lakshmi Kantam, M.; Balasubrahmanyam, V.; Shiva Kumar, K. B.; *Synth. Commun.* **2006**, *36*, 1809.
54. He, J.; Li, B.; Chen, F.; Xu, Z.; Yin, G.; *J. Mol. Catal. A: Chem.* **2009**, *304*, 135.
55. Lang, L.; Zhou, H.; Xue, M.; Wang, X.; Xu, Z.; *Mater. Lett.* **2013**, *106*, 443.
56. Soltani Rad, M. N.; Behrouz, S.; Doroodmand, M. M.; Movahediyan, A.; *Tetrahedron* **2012**, *68*, 7812.
57. Soltani Rad, M. N.; Behrouz, S.; Faghihi, M. A.; *J. Iran Chem. Soc.* **2014**, *11*, 361.
58. Soltani Rad, M. N.; Behrouz, S.; Doroodmand, M. M.; Moghtaderi, N.; *Synthesis* **2011**, 3915.
59. Reichardt, C.; *Solvents and Solvent Effects in Organic Chemistry*; VCH Verlagsgesellschaft mbH: Weinheim, 1988.

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