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Safe and highly efficient syntheses of triazole drugs using Cu_2O nanoparticle in aqueous solutions

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ABSTRACT

Triazole moiety is frequently employed in drug discovery and optimization. However, most syntheses of triazole drugs involve isolation of highly explosive azides. Herein we report safe and high efficient syntheses of triazole drugs in aqueous/organic solvent systems with Cu_2O nanoparticle (Cu_2O-NP) as the catalyst of azide–alkyne cycloaddition (CuAAC). Since Cu_2O-NP can be efficiently dispensed in aqueous and some organic solvents, the azide solutions from the previous preparation could be used directly in the next CuAAC stage without isolation. Therefore, this synthetic strategy is safe, convenient, and high yielding for the syntheses of triazole drugs.

Introduction

Triazole moiety can be frequently found in clinical drugs or drug candidates, probably due to its capability to form hydrogen bonds with the active site,[1] and triazoles were recently reported to be isosteres of amides,[2–4] olefins,[5] and other heterocycles.[6]

The generation of triazoles in drugs was usually through the copper-catalyzed azide–alkyne cycloaddition (CuAAC).[7,8] The catalyst systems that were employed in this type of ring formation includes: $CuSO_4$/NaAsc,[8c] CuI/DIEA,[9] $Cu(CH_3CN)_4PF_6$,[10] and CuBr/1,8-diaza-bicyclo [5.4.0]undec-7-ene (DBU)[11] and nearly all these catalyst systems were used either in organic solvents or aqueous solution. Chen and Kong recently reported the application of Cu_2O-NP as CuAAC catalyst under physiological conditions or in organic solvents such as CH_3CN and EtOH. This Cu_2O-NP catalyst demonstrated less cytotoxicity and superior efficiency than traditional systems,[12] and it was used as catalyst in the large ring formation of triazole-Epothilones.[13] Thus, we report a safe and highly efficient synthesis of triazole drugs using Cu_2O-NP catalyst in aqueous/organic solvents for the key azide–alkyne cycloaddition stage, and the synthesis of rufinamide is the first example we investigated.

Results and discussion

Rufinamide is a drug with anticonvulsant activity, and it is used for treating some kinds of epilepsies, especially Lennox–Gastaut syndrome.[14] Rufinamide contains structure of triazoles, and several syntheses of rufinamide have been reported. All of these syntheses began with 2,6-difluorobenzyl halide **1**, followed by treatment with sodium azide to obtain 2,6-difluorobenzyl azide **3**, and then compound **3** undergoes a 1,3-dipolar cycloaddition with different dipolarophiles to provide the precursors of rufinamide **5** or rufinamide **6** (Scheme 1).[15–19]

The azide **3** in these syntheses was isolated by concentration or even purified by vacuum distillation at high temperature.[16–19] These procedures are not safe for the highly explosive properties of azide compounds. Therefore, we modified Attolino's method[20] for the synthesis of rufinamide. First of all, we applied H_2O/CH_3CN solvent system with tetrabutylammonium chloride as phase transfer additive (Scheme 2).

The reaction mixture after the azide substitution was used directly in the next Cu_2O-NP catalyzed cycloaddition stage (Scheme 3), since the H_2O/CH_3CN solvent system in the first stage is compatible with Cu_2O-NP catalyst.

Finally, concentrated ammonia was added to the cycloaddition reaction mixture to convert compound **5** into rufinamide directly. Filtration followed by washing with water and CH_3OH provided rufinamide in high purity (>99.0% by HPLC). In summary, rufinamide can be prepared by safe and efficient synthesis with simple

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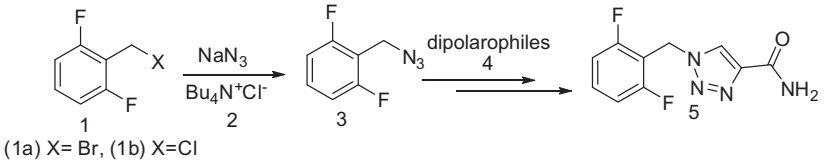
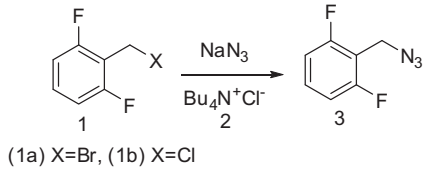
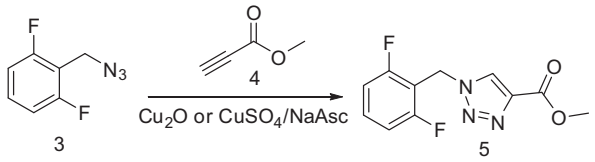


Scheme 1. General formula of synthesis of rufinamide.



Scheme 2. The preparation of 2,6-difluorobenzyl azide[a]. [a]The reaction condition with 2,6-difluorobenzyl bromide or chloride was optimized to: H_2O/CH_3CN = 3:16 (V/V), concentration: 0.18 mol/L, azide: 3 equiv, tetrabutylammionium chloride 0.2 equiv temperature: 18–30 °C, reaction time: 2 h.



Scheme 3. CuAAC reaction catalyzed with Cu_2O-NP.

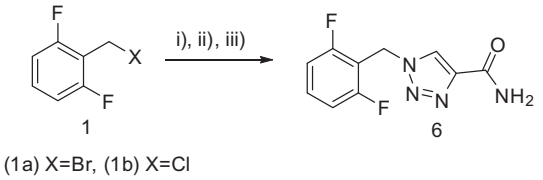
purification at the end of the preparation, and the overall time to complete the synthesis and purification was reduced to about 10 h.

Therefore, a series of experiments were conducted to systematically investigate this synthesis of rufinamide (Table 1).

No products were observed when there was no catalyst (entry 1) or Cu_2O powder (200 meshes) was applied as the catalyst (entry 2). Compound 2,6-difluorobenzyl bromide **1a** was applied as the starting material at first, and the yields of rufinamide were 21%, 49%, 60%, 36.7%, and 32.6% when the amounts of Cu_2O-NP were 0.6%, 3.0%, 6.0%, 9.0%, and 12.0%, respectively (entries 3–7). Replace compound **1a** with 2,6-difluorobenzyl chloride **1b**, and the reactions were run with 1.0%, 2.0%, 3.0%, 4.0%, 5.0% 6.0%, 9.0%, and 12.0% of Cu_2O-NP respectively (entries 8–15), and then higher yields of rufinamide were obtained at different catalyst loadings. These data indicated that 3–6% is the best range of the ratio of catalyst. Thus, the optimal ratio of Cu_2O-NP was set to 6%, and 2,6-difluorobenzyl chloride was set as the starting material. This reaction with the optimal condition was conducted in a gram scale (entries 16 and 17), 69.0% and 71.6% yield of rufinamide was obtained, respectively. Compared with the yield of this reaction with $CuSO_4$/NaAsc as the catalyst system (17.3% in entry 18), the higher yield with Cu_2O-NP (66.6% in entry 13) suggests that the Cu_2O-NP is a superior catalyst system than $CuSO_4$/NaAsc. The possible reason is that Cu_2O-NP catalyst can be dispensed in both organic solvent (CH_3CN) and water, while the application of $CuSO_4$/NaAsc system requires solvent system with higher ratio of water. Moreover, note that traditional methods of rufinamide applied high temperature or distillation of explosive azide, while our syntheses of rufinamide were carried on with water as one of the solvents in all stages of reactions at room temperature, and the target product rufinamide was obtained in high yield and purity after simple filtration. Finally, the gram scale syntheses indicate that this procedure has high potential to be applied for industrial production of rufinamide.

The second example is triazole analogues of imatinib, which was synthesized by Arioli et al.[3] Starting with compound **7**, oxidation followed by $CuSO_4$/NaAsc catalyzed cycloaddition provides triazoles imatinib analogue **9a** in overall yield of 61.5%. Herein we utilized synthetic strategy with Cu_2O-NP catalyst, and to our delight, the target molecule **9a** was obtained in higher yield of 81.0% (Table 2, entry 1). Moreover, other analogues **9a**, **9b**, **9c,** and **9d** were also obtained in satisfactory yields (Table 2, entries 2–5).

Table 1
The reaction conditions for preparation of rufinamide



Entry	Crude material	Catalyst	mol %	Isolated yield [%]
1[a]	**1a**	None	0	0
2[a]	**1a**	Cu_2O	6.0	0
3[a]	**1a**	Cu_2O-NP	0.6	21.0
4[a]	**1a**	Cu_2O-NP	3.0	49.0
5[a]	**1a**	Cu_2O-NP	6.0	60.0
6[a]	**1a**	Cu_2O-NP	9.0	36.7
7[a]	**1a**	Cu_2O-NP	12.0	32.6
8[b]	**1b**	Cu_2O-NP	1.0	22.1
9[b]	**1b**	Cu_2O-NP	2.0	54.8
10[a]	**1b**	Cu_2O-NP	3.0	63.4
11[b]	**1b**	Cu_2O-NP	4.0	65.6
12[b]	**1b**	Cu_2O-NP	5.0	63.4
13[a]	**1b**	Cu_2O-NP	6.0	66.6
14[a]	**1b**	Cu_2O-NP	9.0	55.9
15[a]	**1b**	Cu_2O-NP	12.0	46.6
16[c]	**1b**	Cu_2O-NP	3.0	69.0
17[d]	**1b**	Cu_2O-NP	6.0	71.6
18[a]	**1b**	$CuSO_4$/NaAsc	6.0	17.3
19[a]	**1b**	Cu2O-NP	5.0	59.8

(i) NaN_3, tetrabutylammonium chloride, (ii) methyl propiolate, Cu_2O-NP, (iii) $NH_3 \cdot H_2O$.

[a] Entries 1–7, 10, 13–15, and 18–19 were conducted with azide (1.45 mmol) and alkyne (1.5 mmol) in CH_3CN (8 mL) and H_2O (1.5 mL), reaction time is 8 h, and the solvent of last step is methanol.

[b] Entries 8–9 and 11–12 were conducted with azide (1.45 mmol) and alkyne (1.5 mmol) in CH_3CN (8 mL) and H_2O (1.5 mL), reaction time is 8 h, and the solvent of last step is CH_3CN.

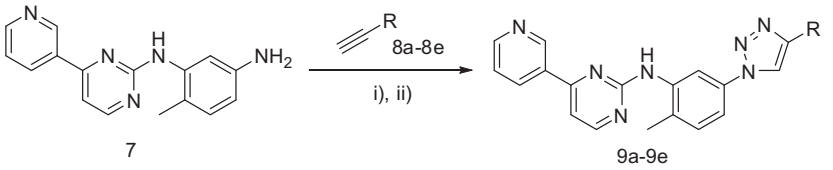
[c] Entry 16 was conducted with azide (5.0 g, 30.86 mmol) and alkyne (2.8 mL, 31.3 mmol) in CH_3CN (80 mL) and H_2O (20 mL), reaction time is 8 h, and the solvent of last step is CH_3CN.

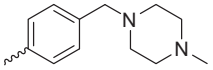
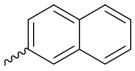
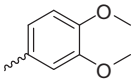
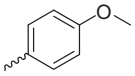
[d] Entry 17 was conducted with azide (5.0 g, 30.86 mmol) and alkyne (2.8 mL, 31.3 mmol) in CH_3CN (80 mL) and H_2O (20 mL), reaction time is 8 h, and the solvent of last step is methanol.

Conclusion

Cu_2O-NP can be efficiently dispensed in water and in organic solvent such as CH_3CN and EtOH, and then Cu_2O-NP is highly compatible with some organic solvents and water.[10] Therefore, the synthetic strategy with the application of Cu_2O-NP to avoid the

Table 2
The reaction conditions for preparation of analogue of imatinib



Entry[a]	Compound	R	Isolated yield [%]
1	**9a**		81.0
2	**9b**		56.2
3	**9c**		49.6
4	**9d**		62.7
5	**9e**		42.4

(i) $NaNO_2$, HCl, H_2O, NaN_3, (ii) Cu_2O-NP.
[a] All reactions were conducted with azide (0.514 mmol) and alkyne (0.467 mmol) in ethanol/H_2O solution (15 mL, ethanol/water = 4:1), reaction time is 8 h.

isolation of highly explosive azide is feasible, and then the azide solutions from the previous preparation were used directly in the next CuAAC stage. The examples of safe and highly efficient syntheses of rufinamide and triazole analogues of imatinib demonstrated several advantages over the conventional step-wise syntheses of triazole drugs with Cu_2O/NaAsc: safe, higher yielding, and time efficient. And the gram scale synthesis of rufinamide with Cu_2O-NP suggests that this strategy has high potential to be used for the industrial production of triazole drugs.

Experimental procedures

All reagents were of analytical grade and were dried and purified if necessary. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 spectrometer. Chemical shifts are reported in parts per million (ppm) relative to either a tetramethylsilane internal standard or solvent signals. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, br. = broad, m = multiplet), coupling constants, and integration. The melting point of rufinamide was detected by a microscopic melting point meter. The method of preparation of Cu_2O-NP is same as lit. 12.

Typical procedure for the synthesis of rufinamide with concentration after 'click reaction'

Synthesis of compound ***6****: A* 250 mL two-necked round bottom flask was charged with sodium azide (6.10 g, 93.8 mmol), compound **2** (1.90 g, 6.84 mmol), and water (20 mL). After the solid was completely dissolved, compound **1a** (5.0 g, 31.37 mmol) and CH_3CN (80 mL) were added. The mixture was stirred at room temperature for 3 h, and then the CH_3CN layer was separated. To the CH_3CN solution were added Cu_2O-NP (0.42 g) and compound **4** (2.80 mL, 31.3 mmol), and the reaction mixture was stirred for 8 h at room temperature under protection of inert gas. The mixture was filtered and the filtrate was concentrated, and was charged with methanol (40 mL) and 35% ammonia in water (100 mL). The mixture was heated to 65 °C and refluxed for 4 h, cooled to room temperature, and filtered. The resulting solid was washed with water and methanol to obtain rufinamide (5.25 g, 71.6%) as colorless crystalline product. Mp: 242–244 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.549 (s, 1H), 7.842 (br s, 1H), 7.566–7.470 (m, 2H), 7.215–7.174 (m, 2H), 5.723 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.5, 161.7, 160.0, 143.3, 132.3, 127.4, 112.4, 111.5, 41.66. MS (ESI$^+$): 239.06.

Typical procedure for the synthesis of rufinamide without concentration after 'click reaction'

Synthesis of compound ***6****: A* 250 mL two-necked round bottom flask was charged with sodium azide (6.10 g, 93.8 mmol), compound **2** (1.90 g, 6.84 mmol), and water (20 mL). After the solid was completely dissolved, compound **1b** (5.0 g, 30.86 mmol) and CH_3CN (80 mL) were added. The mixture was stirred at room temperature for 3 h, and then the CH_3CN layer was separated. To the CH_3CN solution were added Cu_2O-NP (0.21 g) and compound **4** (2.80 mL, 31.3 mmol), and the reaction mixture was stirred for 8 h at room temperature under protection of inert gas. The mixture was filtered and the filtrate was charged with 35% ammonia in water (100 mL). The mixture was heated to 65 °C and refluxed for 4 h, cooled to room temperature, and filtered. The resulting solid was washed with water and methanol to obtain rufinamide (5.10 g, 69.0%) as colorless crystalline product. Mp: 242–244 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.549 (s, 1H), 7.842 (br s, 1H), 7.566–7.470 (m, 2H), 7.215–7.174 (m, 2H), 5.723 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.5, 161.7, 160.0, 143.3, 132.3, 127.4, 112.4, 111.5, 41.66. MS (ESI$^+$): 239.06.

Typical procedure for the synthesis of analogue of imatinib

Synthesis of compound ***9a–9e****: A* two-necked round-bottom flask, was charged with compound **7** (0.142 g, 0.514 mmol), $NaNO_2$ (0.071 g, 1.028 mmol), and water (15 mL), and aqueous HCl

(1.514 mmol) was added dropwise at 0 °C, and the reaction mixture was stirred for 1 h. A solution of NaN_3 (0.037 g, 0.565 mmol) in water (5 mL) was added dropwise into the reaction mixture slowly, and then the reaction mixture was stirred at the same temperature for 2 h. The reaction was quenched and aqueous layer was extracted by ethyl acetate (3 × 10 mL). The organic layer was separated, concentrated to 10 mL, and was put into solution of **8(a–e)** (0.467 mmol) and Cu_2O-NP (6.0 mol %) in ethanol/H_2O solution (15 mL, ethanol/water = 4:1). When the reaction was completed, the ethanol was evaporated in reaction system and Cu_2O-NP was removed by filtration. The aqueous layer was extracted with ethyl acetate (3 × 10 mL), and the combined organic layers were dried by anhydrous sodium sulfate, filtered, and were concentrated to afford the crude product. The resulting residue was purified by silica gel column chromatography to obtain compound **9**(**a**–**e**) as solid.

*Compound **9a**:* Yield: 81.0%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.319 (s, 1H), 9.505 (s, 1H), 8.771 (s, 1H), 8.591 (d, J = 5.2 Hz, 1H), 8.540 (d, J = 8.2 Hz, 1H), 8.226 (s, 1H), 7.902 (d, J = 8 Hz, 2H), 7.515 (m, 1H), 7.433–7.453 (m, 3H), 7.385 (d, J = 8 Hz, 1H), 7.285–7.300 (m, 2H), 3.592 (s, 2H), 2.578 (br s, 8H), 2.474 (s, 3H), 2.364 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 160.0, 159.0, 151.5, 148.3, 147.9, 138.6, 138.4, 135.4, 134.6, 132.2, 131.1, 129.6, 129.1, 127.1, 125.6, 123.7, 117.3, 113.8, 111.9, 108.6, 62.7, 55.1, 53.0, 46.0, 17.7. MS (ESI$^+$): 518.29.

*Compound **9b**:* Yield: 56.2%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.417 (s, 1H), 9.337 (s, 1H), 9.188 (s, 1H), 8.710 (d, J = 4.0 Hz, 1H), 8.605 (d, J = 4.0 Hz, 1H), 8.525 (s, 1H), 8.512 (s, 1H), 8.475–8.470 (d, J = 2.0 Hz, 1H), 8.113–7.947 (m, 4H), 7.686–7.661 (m, 1H), 7.574–7.498 (m, 5H), 2.389 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 161.2, 160.1, 152.0, 148.7, 147.7, 139.6, 135.2, 134.9, 133.6, 133.2, 132.6, 132.3, 131.9, 129.1, 128.5, 128.4, 128.2, 127.2, 126.8, 124.3, 124.2, 124.2, 120.3, 116.0, 115.6, 108.8, 18.3. MS (ESI$^+$): 456.32.

*Compound **9c**:* Yield: 49.6%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.310 (br s, 1H), 9.010 (s, 1H), 8.751 (d, J = 4.0 Hz, 1H), 8.571 (d, J = 5.2 Hz, 1H), 8.517 (d, J = 8.0 Hz, 1H), 8.166 (s, 1H), 7.582 (d, J = 1.6 Hz, 1H), 7.489 (t, J = 4.0 Hz, 1H), 7.439–7.348 (m, 3H), 7.222 (s, 1H), 6.954 (d, J = 8.0 Hz, 1H), 4.006 (s, 3H), 3.949 (s, 3H), 2.451 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 160.2, 159.2, 151.7, 149.4, 149.3, 148.4, 148.2, 138.7, 135.7, 134.8, 132.5, 131.3, 127.1, 123.9, 123.4, 118.4, 116.9, 114.3, 112.3, 111.4, 109.1, 108.9, 56.1, 55.9, 17.8. MS (ESI$^+$): 466.34.

*Compound **9d**:* Yield: 62.7%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.301 (s, 1H), 9.017 (d, J = 1.6 Hz, 1H), 8.756 (d, J = 1.6 Hz, 1H), 8.569–8.513 (m, 1H), 8.136 (s, 1H), 7.865(d, J = 8.8 Hz, 2H), 7.510–7.479 (m, 1H), 7.425–7.400 (m, 1H), 7.343 (d, J = 8.0 Hz, 1H), 7.260 (d, J = 5.2 Hz, 1H), 7.229 (s, 1H), 7.002 (d, J = 8.8 Hz, 2H), 3.874 (s, 3H), 2.438 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 160.1, 159.7, 159.2, 151.6, 148.4, 148.1, 138.7, 135.8, 134.9, 132.5, 131.3, 127.2, 127.0, 123.9, 123.1, 116.7, 114.3, 114.2, 112.2, 108.9, 55.4, 17.8. MS (ESI$^+$): 436.35.

*Compound **9e**:* Yield: 42.4%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.324 (s, 1H), 8.958 (d, J = 2.0 Hz, 1H), 8.706 (s, 1H), 8.499 (d, J = 5.2 Hz, 1H), 8.353 (d, J = 8.0 Hz, 1H), 7.998 (s, 1H), 7.482 (s, 1H), 7.400–7.375 (m, 1H), 7.265 (d, J = 8.0 Hz, 1H), 7.199–7.186 (d, J = 5.2 Hz, 1H), 4.041 (t, J = 5.4 Hz, 2H), 3.087 (t, J = 5.6 Hz, 2H), 2.404 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 159.9, 159.3, 151.3, 148.1, 146.7, 138.5, 135.8, 134.9, 131.3, 126.1, 124.0, 123.9, 119.9, 114.2, 111.4, 108.8, 60.7, 29.0, 17.7. MS (ESI$^+$): 374.41.

Acknowledgments

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Supplementary data

Supplementary data (NMR spectra of compounds **6**, **9a–9e** and photo of crystals of compound **6**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.04.067.

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