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Facile Synthesis of 4,5-Disubstituted 2*H*-1,2,3-Triazoles by Catalyst-free Cycloaddition between Substituted Vinyl Sulfones and Sodium Azide under Ambient Conditions†

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A highly efficient method for readily preparing 4,5-disubstituted 2*H*-1,2,3-triazoles was found. Under ambient conditions, a catalyst free cycloaddition between substituted vinyl sulfones and sodium azide could be completed in a very short time. In this cycloaddition process, sulfonyl group acts as a leaving group, while its ester group was retained.

Keywords vinyl sulfone, sodium azide, cycloaddition, 1,2,3-triazole, catalyst free

Introduction

1,2,3-Triazoles are an important type of heterocyclic compounds due to their broad spectrum biological activities. They are widely employed in pharmaceutical and agrochemical fields. Other industrial application related to 1,2,3-triazole compounds have also been developed, such as dyes, corrosive inhibitors and photostabilizers.[1] The conventional route to 1,2,3-triazoles is the Huisgen 1,3-dipolar cycloaddition of alkynes with organic azides. Since Sharpless[2] developed Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC) to achieve 1,2,3-triazoles with great efficiency and selectivity, this reaction has become one of the most effective methods for preparing variety of 1,2,3-triazoles containing compounds, and it has been widely applied as a powerful tool in related research fields, such as bioconjugation, material science and drug discovery, and their related applications have been reviewed.[3] Except Cu(I) catalyst, other organic and inorganic catalyst are also used to promote this reaction.[4] On the other hand, for biological study requirement, transient metal free 1,3-dipolar cycloaddition between azides and strained alkynes such as cyclooctynes to form 1,2,3-triazoles at lower temperature without using any toxic catalyst was reported.[5] However, multiple steps reactions are usually required to prepare such kind of strained alkynes. In most of above mentioned cases, only organic azides could be used as substrates in this reaction, and inexpensive inorganic azides are not good substrate. Thus 1,2,3-triazoles, which also have a wide range of uses due to organic synthesis and its biological activities,[6] could not be prepared directly by catalytic cycloaddition. Recently, a few of methods for the synthesis of 1,2,3-triazoles are reported, including Pd catalyzed cycloaddition between sodium azide and alkynes with an electron withdrawing substituent, the reaction of sodium azide with nitroalkenes, the rearrangement of propargyl azides and other strategies which requires deprotection steps and the employment of more elaborated azides.[7] It is noticeable that most of these processes have drawbacks, such as high temperature, time consuming, low yield and requirement of transient metal-phosphine complex as catalyst.

Recently, we prepared a type of substituted vinyl sulfones through the Ti(O*i*-Pr)$_4$ mediated Knoevenagel condensation between benzothiazol-2-yl sulfones **1** (BT sulfone, Julia reagent) and aldehydes with good yield and exclusively *E* isomers.[8] With the substituted vinyl sulfone, we explored sodium azide as a nucleophile reagent to react with these substituted vinyl sulfones in DMSO for the preparation of sulfonyl azides by a 1,4-Michael addition. However, no sulfonyl azides are formed, instead, disubstituted *2H*-1,2,3-triazoles **2** are obtained with excellent yield at room temperature within a few minutes (Scheme 1). This is an unexpected result, and it should be an alternative access for readily and efficiently obtaining 2*H*-1,2,3-triazoles. For the reaction of allenyl esters with sodium azide, only azide addition product was obtained, and no cycloaddition product was observed.[9] Herein, we would like to describe our findings on this new and interesting reaction.

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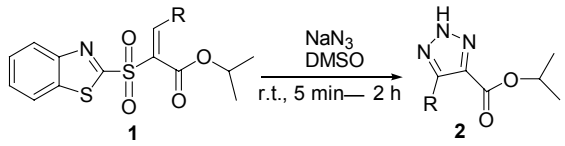
Scheme 1 Cycloaddition between substituted vinyl sulfones and sodium azide to afford 4,5-disubstituted 2*H*-1,2,3-triazoles



Results and Discussion

This is an efficient and rapid access for easily preparing 4,5-disubstituted 1,2,3-triazoles without using any catalyst, in which commercial solvents such as DMSO, DMF, ethanol and methanol could be used directly without any preliminary purification (Table 1). Further more, reaction time is also very short and no critical reaction condition is required. In most of these cases, reaction could be completed in 2 h. However, when other solvents, such as water, chloroform and dichloromethane (Table 1), were utilized in this reaction, no reaction was observed, which may be attributed to insolubility of vinyl sulfones in water and sodium azide in chloroform and dichloromethane respectively. Then the reaction was carried out in DMSO. Under the same reaction conditions, the scope of this reaction was tested: all these substituted vinyl sulfones could react readily with sodium azide to afford 4,5-disubstituted 2*H*-1,2,3-triazoles with good to excellent yields (Table 2).

Table 1 Solvent effect on the reaction of substituted vinyl sulfones with sodium azide

R	Solvent	Reaction time	Conversion[a]/%
phenyl (**a**)	DMSO	5 min	100
phenyl (**a**)	DMF	5 min	100
phenyl (**a**)	H_2O	overnight	NR
phenyl (**a**)	MeOH	4.5 h	100
phenyl (**a**)	EtOH	2 h	100
phenyl (**a**)	$CHCl_3$	overnight	NR
phenyl (**a**)	CH_2Cl_2	overnight	NR

[a] Reaction conditions: sulfone (39 mg, 0.1 mmol), NaN_3 (7 mg, 0.105 mmol) in 1 mL solvent, and the reaction was detected by TLC or GC, NR (no reaction).

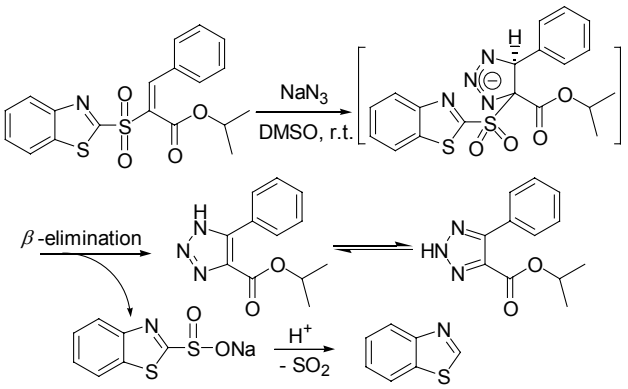
The possible reaction pathway could be proposed as follows (Scheme 2): a [3+2] cycloaddition between vinyl sulfone and azide anion forms a 1,2,3-triazole intermediate substituted by sulfonyl, ester and phenyl groups, which would then undergo a *β*-elimination to afford 4,5-substituted 2*H*-1,2,3-triazole, and the by-product may be water soluble sodium benzo[*d*]thiazole-2-sulfinate. This was confirmed by a reaction in NMR tube (^{1}H NMR, DMSO-d_6), a group of peaks related to 2-substituted benzo[*d*]thiazole protons appeared after addition of sodium azide to vinyl sulfone in DMSO-d_6, while the olefine proton in substrate disappeared.

Table 2 Reaction of substituted vinyl sulfones with sodium azide

Entry	R	Solvent	Reaction time	Yield[a]/%
1	phenyl (**a**)	DMSO	5 min	98
2	2,4-dimethoxyl phenyl (**b**)	DMSO	2 h	95
3	2,3-dimethoxyl phenyl (**c**)	DMSO	20 min	97
4	4-chloro phenyl (**d**)	DMSO	5 min	98
5	2,4-dichloro phenyl (**e**)	DMSO	10 min	94
6	4-methoxy phenyl (**f**)	DMSO	5 min	96
7	4-bromo phenyl (**g**)	DMSO	10 min	95
8	2-furyl (**h**)	DMSO	1.5 h	95
9	4-methyl phenyl (**i**)	DMSO	5 min	98
10	1-naphthyl (**j**)	DMSO	5 min	98
11	4-fluoro phenyl (**k**)	DMSO	5 min	96
12	3-bromo phenyl (**l**)	DMSO	2 h	90
13	2-naphthyl (**m**)	DMSO	5 min	95
14	2-methyl phenyl (**n**)	DMSO	10 min	95
15	heptyl (**o**)	DMSO	40 min	96

[a] Reaction conditions: sulfone (0.3 mmol), NaN_3 (21 mg, 0.32 mmol) in 3 mL DMSO, isolated yield.

Scheme 2 Possible reaction pathway to form 2*H*-1,2,3-triazole by a cycloaddition between substituted vinyl sulfones and sodium azide



After the reaction was quenched by water, only 4,5-substituted 1,2,3-triazole was extracted out. Further more, when the aqueous layer was acidified with aqueous HCl and extracted with ethyl acetate, benzo[*d*]thiazole could be detected by GC-Mass. In this case, sulfonyl group acts as a leaving group, while its ester group is retained.

However, under this reaction condition, organic azide does not react with these substituted vinyl sulfones at all, which may be attributed to that the vinyl sulfone acts as an electronic acceptor while the sodium azide as an electronic donor in the reaction. The azide

anion in sodium azide obviously possesses the stronger nucleophilic property than that of organic azide, thus azide anion may react with vinyl sulfone by an addition process firstly, then cyclization and elimination to achieve corresponding 1,2,3-triazole subsequently. While organic azide could not react with vinyl sulfone firstly due to its weak nucleophilic attach ability.

Conclusions

In summary, a novel access for readily and efficiently preparation of 4,5-disubstituted 2*H*-1,2,3-triazoles was found. Without using any catalyst, disubstituted vinyl sulfones could react with sodium azide quickly under ambient conditions.

Experimental

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AV400. Chemical shifts (δ) are referenced to the solvent residual peak: proton (chloroform δ 7.26), carbon (chloroform δ 77.0) and TMS peak as an internal standard. High resolution mass spectra (HRMS) were performed using a Bruker Daltronics MicroTof. TLC analyses were performed on commercial aluminum sheets bearing 0.25 mm layer of silica gel. 200—300 mesh silica gel was used for column chromatography. All chemicals were of reagent grade quality obtained from commercial sources and used without further purification unless otherwise noted.

General procedure for the synthesis of 4,5-disubstituted 2*H*-1,2,3-triazoles 2

Substituted vinyl sulfone **1** (0.30 mmol) and NaN_3 (21 mg, 0.32 mmol, 1.06 equiv.) were added into DMSO (3 mL) in turn, and the mixture was stirred at room temperature. The reaction was detected by TLC. After substituted vinyl sulfone **1** was consumed out, 15 mL of H_2O was added and extracted with EtOAc (15 mL×3). The combined organic layer was dried over anhydrous Na_2SO_4. Removal of all solvent left a residue which was passed through a flash silica gel column [*V*(petroleum ether)∶*V*(EtOAc)=4∶1, as eluent] to afford product 4,5-substituted 1*H*-1,2,3-triazoles **2**.

Isopropyl 5-phenyl-2*H*-1,2,3-triazole-4-carboxylate (**2a**): Prepared from **1a** (116 mg, 0.3 mmol) and NaN_3 (0.32 mmol, 21 mg). White solid; yield 68 mg, 98%; m.p. 68—69 ℃; *V*(petroleum ether)∶*V*(ethyl acetate)=2∶1, R_f=0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.84—7.82 (m, 2H), 7.46 (t, *J*=3.2 Hz, 3H), 5.26—5.32 (m, 1H), 1.33 (d, *J*=6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.7, 129.6, 129.3, 128.3, 69.7, 21.7; HRMS (ESI) calcd for $C_{12}H_{13}N_3O_2$ $[M]^+$ 231.1008, found 231.1007.

Isopropyl 5-(2,4-dimethoxyphenyl)-2*H*-1,2,3-triazole-4-carboxylate (**2b**): Prepared from **1b** (134 mg, 0.3 mmol) and NaN_3 (0.32 mmol, 21 mg). Pale yellow solid; yield 83 mg, 95%; m.p. 151—152 ℃; *V*(petroleum ether)∶*V*(ethyl acetate)=1∶1, R_f=0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 13.12 (s, 1H), 7.96—7.94 (m, 1H), 6.63 (dd, *J*=2.4, 8.8 Hz, 1H), 6.56—6.64 (m, 2H), 5.25—5.32 (m, 1H), 3.88 (s, 6H), 1.37 (d, *J*=6.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.4, 161.4, 157.9, 132.8, 104.8, 98.6, 68.9, 55.7, 55.5, 21.8; HRMS (ESI) calcd for $C_{14}H_{17}N_3O_4$ $[M+Na]^+$ 314.1117, found 314.1133.

Isopropyl 5-(2,3-dimethoxyphenyl)-2*H*-1,2,3-triazole-4-carboxylate (**2c**): Prepared from **1c** (134 mg, 0.3 mmol) and NaN_3 (0.32 mmol, 21 mg). Colourless oil; yield 85 mg, 97%; *V*(petroleum ether)∶*V*(ethyl acetate)=1∶1, R_f=0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36 (s, 1H), 7.17 (t, *J*=8.0 Hz, 1H), 7.04 (d, *J*=8.4 Hz, 1H), 5.24—5.30 (m, 1H), 3.92 (s, 3 H), 3.70 (s, 3H), 1.33 (d, *J*=6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.9, 152.6, 146.7, 124.2, 123.1, 114.0, 69.2, 61.2, 55.9, 21.7; HRMS (ESI) calcd for $C_{14}H_{17}N_3O_4$ $[M+Na]^+$ 314.1117, found 314.1135.

Isopropyl 5-(4-chlorophenyl)-2*H*-1,2,3-triazole-4-carboxylate (**2d**): Prepared from **1d** (126 mg, 0.3 mmol) and NaN_3 (0.32 mmol, 21 mg). White solid; yield 78 mg, 98%; m.p. 132—133 ℃; *V*(petroleum ether)∶*V*(ethyl acetate)=2∶1, R_f=0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.83 (d, *J*=8.4 Hz, 2H), 7.44 (d, *J*=8.4 Hz, 2H), 5.28—5.34 (m, 1H), 1.36 (d, *J*=6.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.9, 136.0, 130.9, 128.7, 70.0, 21.5; TOF-MS calcd for $C_{12}H_{12}ClN_3O_2$ $[M]^+$ 265.06168, found 265.0616.

Isopropyl 5-(2,4-dichlorophenyl)-2*H*-1,2,3-triazole-4-carboxylate (**2e**): Prepared from **1e** (137 mg, 0.3 mmol) and NaN_3 (0.32 mmol, 21 mg). White solid; yield 84 mg, 94%; m.p. 104—105 ℃; *V*(petroleum ether)∶*V*(ethyl acetate)=2∶1, R_f=0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.53 (d, *J*=2.0 Hz, 1H), 7.42—7.34 (m, 2H), 5.19—5.25 (m, 1H), 1.24 (d, *J*=6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.4, 136.1, 135.0, 132.4, 129.4, 127.0, 69.7, 21.1; HRMS (ESI) calcd for $C_{12}H_{11}Cl_2N_3O_2$ $[M+Na]^+$ 322.0126, found 322.0144.

Isopropyl 5-(4-methoxyphenyl)-2*H*-1,2,3-triazole-4-carboxylate (**2f**): Prepared from **1f** (125 mg, 0.3 mmol) and NaN_3 (0.315 mmol, 20.5 mg). White solid; yield 76 mg, 96%; m.p. 81—82 ℃; *V*(petroleum ether)∶*V*(ethyl acetate)=2∶1, R_f=0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.80 (d, *J*=8.8 Hz, 2H), 6.97 (d, *J*=8.8 Hz, 2H), 5.25—5.32 (m, 1H), 3.86 (s, 3H), 1.34 (d, *J*=6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.7, 130.7, 113.7, 69.5, 55.3, 21.7; HRMS (ESI) calcd for $C_{13}H_{15}N_3O_3$ $[M+Na]^+$ 284.1011, found 284.1041.

Isopropyl 5-(4-bromophenyl)-2*H*-1,2,3-triazole-4-carboxylate (**2g**): Prepared from **1g** (140 mg, 0.3 mmol) and NaN_3 (0.32 mmol, 21 mg). White solid; yield 88 mg, 95%; m.p. 121—122 ℃; *V*(petroleum ether)∶*V*(ethyl acetate)=2∶1, R_f=0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.76 (d, *J*=8.4 Hz, 2H), 7.60 (d, *J*=8.4 Hz, 2H), 5.28—5.34 (m, 1H), 1.37 (d, *J*=6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 131.5, 130.9, 124.0, 70.0, 40.4, 21.7; HRMS (ESI) calcd for $C_{12}H_{12}BrN_3O_2$ $[M+Na]^+$ 332.0011, found 332.0042.

Isopropyl 5-(furan-2-yl)-2*H*-1,2,3-triazole-4-carboxylate (**2h**): Prepared from **1h** (113 mg, 0.3 mmol) and NaN_3 (0.32 mmol, 21 mg). Yellow oil; yield 63 mg, 95%; *V*(petroleum ether)∶*V*(ethyl acetate)=2∶1, R_f=0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.61 (s, 1H), 7.56 (s, 1H), 6.58 (m, 1H), 5.33—5.39 (m, 1H), 1.41 (d, J=6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.4, 144.0, 114.5, 112.1, 69.6, 21.8; HRMS (ESI) calcd for $C_{10}H_{11}N_3O_3$ [M+Na]$^+$ 244.0698, found 244.0717.

Isopropyl 5-*p*-tolyl-2*H*-1,2,3-triazole-4-carboxylate (**2i**): Prepared from **1i** (121 mg, 0.3 mmol) and NaN_3 (0.32 mmol, 21 mg). White solid; yield 72 mg, 98%; m.p. 70—71 ℃; *V*(petroleum ether)∶*V*(ethyl acetate)=2∶1, R_f=0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.72 (d, J=8.0 Hz, 2H), 7.26 (d, J=8.0 Hz, 2H), 5.26—5.32 (m, 1H), 2.41 (s, 3H), 1.34 (d, J=6.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.8, 139.8, 129.2, 129.0, 69.5, 21.7, 21.4; HRMS (ESI) calcd for $C_{13}H_{15}N_3O_2$ [M+Na]$^+$ 268.1062, found 268.1078.

Isopropyl 5-(naphthalen-1-yl)-2*H*-1,2,3-triazole-4-carboxylate (**2j**): Prepared from **1j** (131 mg, 0.3 mmol) and NaN_3 (0.32 mmol, 21 mg). Colourless oil; yield 83 mg, 98%; *V*(petroleum ether)∶*V*(ethyl acetate)=2∶1, R_f=0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.59—7.89 (m, 2H), 7.60—7.43 (m, 5H), 4.97—5.03 (m, 1H), 0.94 (d, J=6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.5, 133.3, 131.9, 129.8, 128.4, 128.3, 126.5, 126.1, 125.3, 124.8, 69.2, 21.2; HRMS (ESI) calcd for $C_{16}H_{15}N_3O_2$ [M+ Na]$^+$ 304.1062, found 304.1076.

Isopropyl 5-(4-fluorophenyl)-2*H*-1,2,3-triazole-4-carboxylate (**2k**): Prepared from **1k** (122 mg, 0.3 mmol) and NaN_3 (0.32 mmol, 21 mg). White solid; yield 72 mg, 96%; m.p. 128—129 ℃; *V*(petroleum ether)∶*V*(ethyl acetate)=2∶1, R_f=0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.88—7.85 (m, 2H), 7.17—7.13 (m, 2H), 5.27—5.34 (m, 1H), 1.35 (d, J=6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.7, 162.3, 160.6, 131.4, 131.3, 115.5, 115.2, 69.9, 21.7; HRMS (ESI) calcd for $C_{12}H_{12}FN_3O_2$ [M+Na]$^+$ 272.0811, found 272.0829.

Isopropyl 5-(3-bromophenyl)-2*H*-1,2,3-triazole-4-carboxylate (**2l**): Prepared from **1l** (140 mg, 0.3 mmol) and NaN_3 (0.32 mmol, 21 mg). White solid; yield 83 mg, 90%; m.p. 124—125 ℃ ; *V*(petroleum ether)∶*V*(ethyl acetate)=2∶1, R_f=0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.05 (s, 1H), 7.83 (d, J=7.6 Hz, 1H), 7.59 (d, J=8.0 Hz, 1H), 7.35 (t, J=8.0 Hz, 1H), 5.31—5.37 (m, 1H), 1.38 (d, J=6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.5, 132.4, 130.6, 129.8, 128.0, 122.1, 70.2, 21.7; HRMS (ESI) calcd for $C_{12}H_{12}BrN_3O_2$ [M + Na]$^+$ 332.0011, found 331.0958.

Isopropyl 5-(naphthalen-2-yl)-2*H*-1,2,3-triazole-4-carboxylate (**2m**): Prepared from **1m** (131 mg, 0.3 mmol) and NaN_3 (0.32 mmol, 21 mg). Yellow oil; yield 80 mg, 95%; *V*(petroleum ether)∶*V*(ethyl acetate)=2∶1, R_f=0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.37 (s, 1H), 7.90—7.86 (m, 4H), 7.55—7.54 (m, 2H), 5.29—5.35 (m, 1H), 1.34 (d, J=6.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.7, 133.6, 132.8, 129.2, 128.5, 127.8, 127.7, 127.0, 126.5, 69.7, 21.7; HRMS (ESI) calcd for $C_{16}H_{15}N_3O_2$ [M + Na]$^+$ 304.1062, found 304.1078.

Isopropyl 5-*o*-tolyl-2*H*-1,2,3-triazole-4-carboxylate (**2n**): Prepared from **1n** (121 mg, 0.3 mmol) and NaN_3 (0.32 mmol, 21 mg). White solid; yield 70 mg, 95%; m.p. 88—89 ℃; *V*(petroleum ether)∶*V*(ethyl acetate)=2∶1, R_f=0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38—7.34 (m, 1H), 7.29—7.22 (m, 3H), 5.13—5.19 (m, 1H), 2.16 (s, 3H), 1.20 (d, J=6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.5, 137.4, 130.2, 130.1, 129.5, 125.4, 69.2, 21.6, 19.9; HRMS (ESI) calcd for $C_{13}H_{15}N_3O_2$ [M+ Na]$^+$ 268.1062, found 268.1076.

Isopropyl 5-heptyl-2*H*-1,2,3-triazole-4-carboxylate (**2o**): Prepared from **1o** (123 mg, 0.3 mmol) and NaN_3 (0.32 mmol, 21 mg). Yellow oil; yield 73 mg, 96%; *V*(petroleum ether)∶*V*(ethyl acetate)=2∶1, R_f=0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.33 (m, 1H), 3.03 (t, J=7.6 Hz, 2H), 1.70—1.73 (m, 2H), 1.40 (d, J=6.4 Hz, 6H), 1.23—1.37 (m, 8H), 0.89 (t, J=6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.2, 69.0, 31.7, 29.3, 29.0, 29.0, 22.6, 21.9, 14.1; HRMS (ESI) calcd for $C_{13}H_{23}N_3O_2$ [M+ Na]$^+$ 276.1688, found 276.1720.

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