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ONE-POT SYNTHESIS OF [1, 2, 3]TRIAZOLO [1, 5-*a*]PYRAZINE DERIVATIVES FROM YNONES AND AMINO AZIDE

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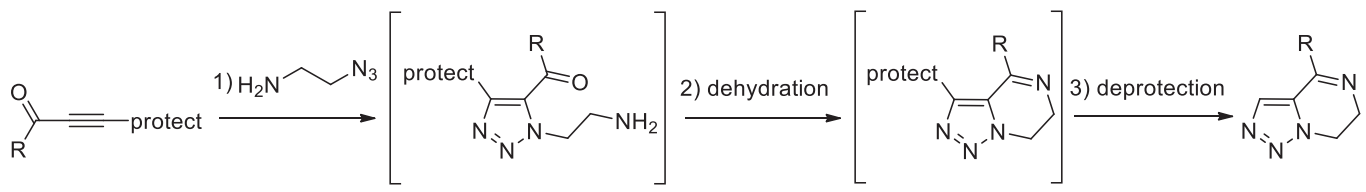
Abstract – A new procedure is described for the synthesis of [1,2,3]triazolo[1,5-*a*]pyrazine derivatives via a one-pot cycloaddition.

1,3-Dipolar cycloaddition is one of the widely used reactions in synthetic chemistry and has been extensively studied for heterocyclic formation. Numerous methods have been developed for the synthesis of 1,2,3-triazoles from azides and alkynes (Huisgen reaction). The most versatile 1,4-disubstituted 1,2,3-triazole synthetic method employs acetylene and azide with a copper catalyst, as developed by Sharpless et al. (copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) or click chemistry).[1] Few works have described the selective synthesis of 1,5-disubstituted triazoles.[2] Fokin and co-workers reported the ruthenium(II)-catalyzed [CpRu-Cl(PPh_3)$_2$], regioselective synthesis of 1,5-disubstituted 1,2,3-triazoles from azides and alkynes.[3] Coats and colleagues described click reactions using a silylacetylene derivative for the synthesis of 1,5-disubstituted products.[4] Recently, we reported the synthesis of novel 1,5-disubstituted 1,2,3-triazoles from a triazolium salt.[5] Herein, we describe the Huisgen-based, one-pot synthesis of [1,2,3]triazolo[1,5-*a*]pyrazine derivatives from ynones and amino azide via 1,5-disubstituted, 4-protected 1,2,3-triazoles (Scheme1).

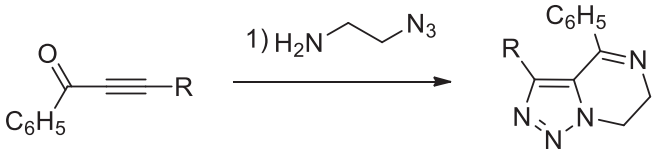
The use of imidazopyrazine derivatives as inhibitors and their syntheses have been studied extensively.[6] Based on these studies, triazolopyrazine derivatives are expected to be significant physiologically active compounds. However, the synthesis of [1,2,3]triazolo[1,5-*a*]pyrazine derivatives has not been reported.



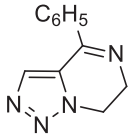
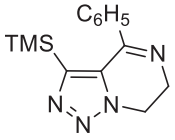
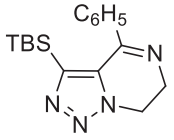
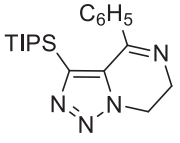
Scheme 1. New method for synthesis of [1,2,3]triazolo[1,5-*a*]pyrazine derivatives

We initially investigated the regioselective synthesis of 3-protected-4-phenyl-6,7-dihydro-[1,2,3]triazolo[1,5-*a*]pyrazine derivatives (**1**). The desired compound, 4-phenyl-6,7-dihydro-[1,2,3]triazolo[1,5-*a*]pyrazine (**1a**), was not obtained by reacting 1-phenylprop-2-yn-1-one with 2-azidoethanamine (Table 1, Entry 1). We developed cycloaddition reactions using silyl-protected ynone derivatives for the synthesis of 3-protected-4-phenyl-6,7-dihydro-[1,2,3]triazolo[1,5-*a*] pyazines. The reactions occurred favorably in all instances (Table 1, Entries 2 and 3). However, low reactivity was observed in cycloaddition using 1-phenyl-3-(triisopropylsilyl)prop-2-yn-1-one, most likely due to steric hindrance (Table 1, Entry 4).

Table 1. Synthesis of 3-protected-4-phenyl-6,7-dihydro-[1,2,3]triazolo[1,5-*a*]pyrazine derivatives



1

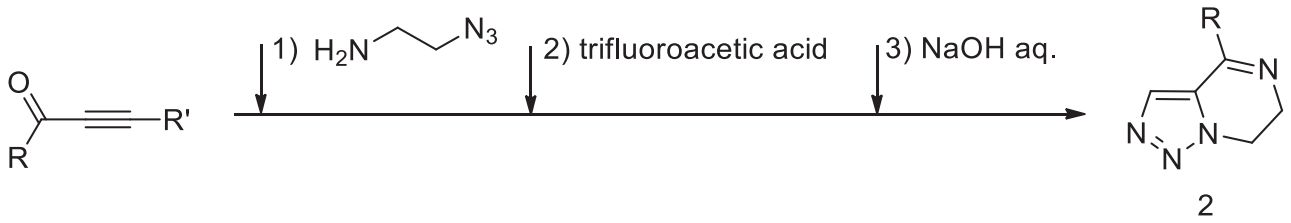
Entry	R [a]	Yield of 1 [b]
1	H	 1a n.d.
2	TMS	 1b quant.
3	TBS	 1c quant.
4	TIPS	 1d 79%

[a] TMS= trimethylsilyl, TBS= *tert*-butyldimethylsilyl, TIPS= triisopropylsilyl
[b] Yields of the isolated products.
Reagents and conditions: Ynones (0.5 mmol), 2-azidoethanamine (1.5 mmol), toluene (1 mL) 24 h, 120 °C.

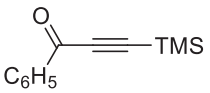
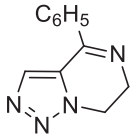
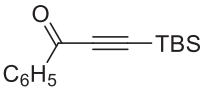
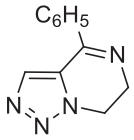
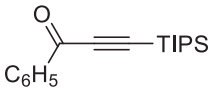
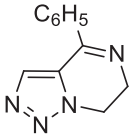
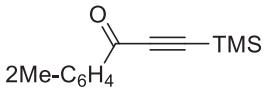
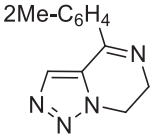
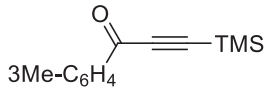
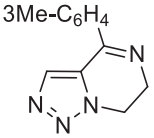
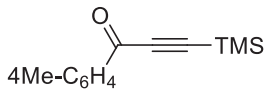
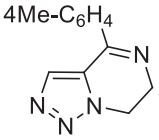
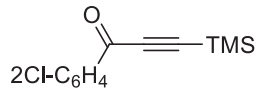
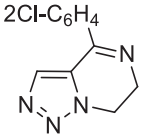
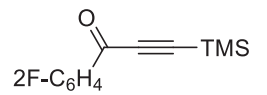
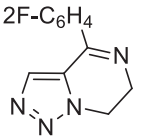
Next, we devised a method for selectively deprotecting silyl-protected compounds in the same vessel. We examined the deprotection of 3-protected-4-phenyl-6,7-dihydro-[1,2,3]triazolo[1,5-*a*]pyrazine derivatives using a number of developed deprotection methods. Trifluoroacetic acid efficiently cleaved the silyl group in our synthetic methodology. A mixture of 1-substituted-3-(trimethylsilyl)prop-2-yn-1-one (0.5 mmol), 2-azidoethanamine (1.5 mmol), and toluene (1 mL) was sealed in a glass vial and warmed to 120 °C overnight. Product formation was confirmed by thin-layer chromatography (TLC), and trifluoroacetic acid (1 mL) was added. The mixture was stirred at 120 °C for 5 h. Then, 1 M-NaOH (1 mL) was added to the reaction mixture. The mixture was stirred for 1 h at room temperature and then extracted with $CHCl_3$ and washed with water. The organic layer was dried and evaporated under vacuum, and the product was isolated by silica gel column chromatography to afford 4-substituted-6, 7-dihydro-[1,2,3]triazolo[1,5-*a*]pyrazine derivatives in excellent yields.

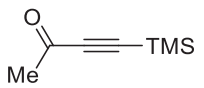
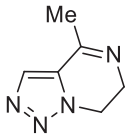
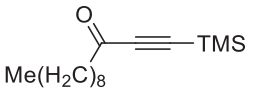
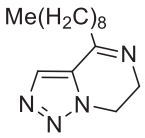
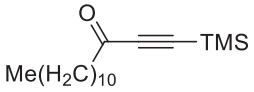
To investigate the substrate generality of this synthetic method, nine different [1,2,3]triazolo[1,5-*a*]pyrazine derivatives were synthesized using silyl-protected ynones and amino azide (Table 2). The silyl protecting group was substituted with trimethylsilyl (TMS), *tert*-butyldimethylsilyl (TBS), and triisopropylsilyl (TIPS) in Entries 1-3 in Table 2. 1-Phenyl-3-(trimethylsilyl)prop-2-yn-1-one and 3-(*tert*-butyldimethylsilyl)-1-phenylprop-2-yn-1-one were obtained quantitatively as the desired products (Table 2, Entries 1 and 2). However, low reactivity was observed in the reaction using 1-phenyl-3-(triisopropylsilyl)prop-2-yn-1-one (Table 2, Entry 3), analogous to that in Table 1. The synthesis of 4-aryl-6,7-dihydro-[1,2,3]triazolo[1,5-*a*]pyrazine generally proceeded well (Table 2, Entries 1-8). The synthesis of 4-alkyl-6,7-dihydro-[1,2,3]triazolo[1,5-*a*]pyrazine also generally proceeded well. (Table 2, Entries 9-11) Thus, the developed reaction occurred favorably in all instances.[7]

Table 2. One-pot synthesis of [1,2,3]triazolo[1,5-*a*]pyrazine derivatives



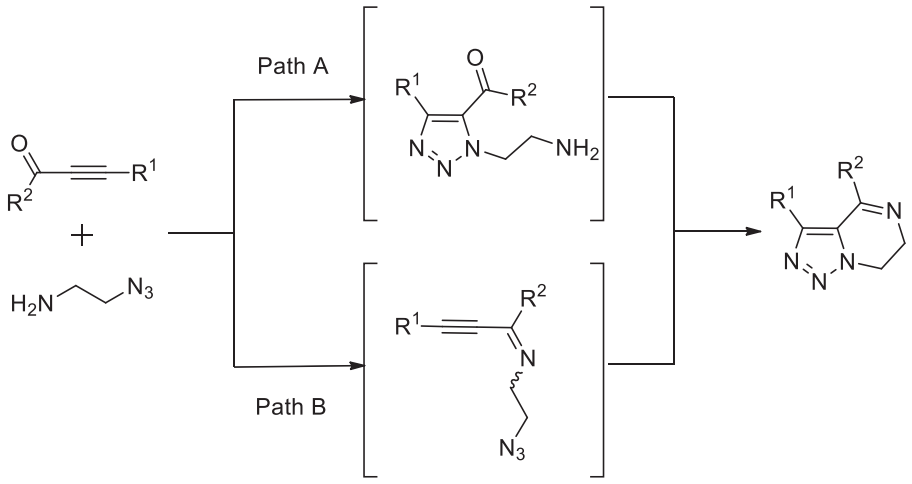
2

Entry	Ynone [a]	Product	Yield [b]
1			quant.
2			quant.
3			43%
4			81%
5			57%
6			96%
7			quant.
8			63%

9			quant.
10			45%
11			63%

[a]TMS= trimethylsilyl
[b] Yields of the isolated products.
Reagent and conditions; Silyl-protected ynones (0.5 mmol), 2-azidoethanamine (1.5 mmol), toluene (1 mL), 24 h, 120 °C. Trifluoroacetic acid (1 mL), 5 h, 120 °C. 1 M-NaOH (1 mL), 1 h, room temperature.

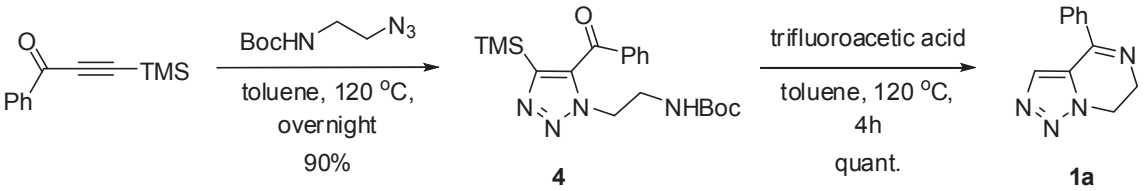
Finally, we investigated the reaction pathway of our synthetic methodology, that is, whether triazole formation (Path A) or imine formation (Path B) occur first.



Scheme 2. Proposed reaction pathway

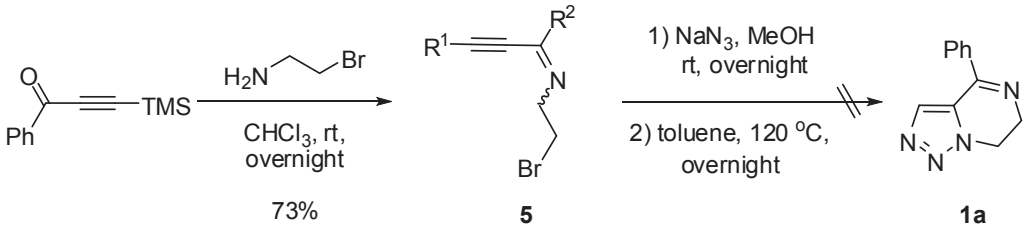
We prepared 1-phenyl-3-(trimethylsilyl)prop-2-yn-1-one (silyl-protected ynone) and *tert*-butyl (2-azidoethyl)carbamate (Boc-protected azide) to verify Path A. The silyl-protected ynone reacted with the Boc-protected azide to form the triazole intermediate in good yield (**4**). Subsequent deprotection of

triazole intermediate (**4**) afforded the [1,2,3]triazolo[1,5-*a*]pyrazine derivative (**1a**) in good yield (Scheme 3).



Scheme 3. Synthesis of 4-phenyl-6,7-dihydro-[1,2,3]triazolo[1,5-*a*]pyrazine from *tert*-butyl (2-azidoethyl)carbamate

We prepared 1-phenyl-3-(trimethylsilyl)prop-2-yn-1-one and 2-bromoethanamine to verify Path B. The silyl-protected ynone reacted with 2-bromoethanamine to form the imine intermediate (**5**) (E/Z isomer mixture). Subsequent azidation of the imine intermediate (**5**) afforded [1,2,3]triazolo[1,5-*a*]pyrazine derivative (**1a**) in only trace yields. We could not obtain the desired product in good yield (Scheme 4).



Scheme 4. Synthesis of 4-phenyl-6,7-dihydro-[1,2,3]triazolo[1,5-*a*]pyrazine from 2-bromoethanamine

Accordingly, the reaction pathway is suggested in Scheme 2 as Path A, in which the first stage is triazole formation and the second stage is imine formation.

In summary, we have demonstrated the one-pot synthesis of [1,2,3]triazolo[1,5-*a*]pyrazine derivatives from ynones and amino azide. Our synthetic method was effective in generating a variety of [1,2,3]triazolo[1,5-*a*]pyrazine derivatives, and we determined the reaction pathway for this synthetic methodology.

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7. General procedure for the synthesis of compounds **1a, 2a-h**; A solution of silyl protected ynones (0.5 mmol) in toluene (1 mL) was added 2-azidoethanamine (1.5 mmol). The mixture was stirred for 24 h at 120 °C in a sealed tube. Then the reaction mixture was confirmed using TLC and added trifluoroacetic acid (1 mL) and the mixture was stirred for 5 h at room temperature. Then to the reaction mixture was added 1M-NaOH aq (1 mL), and the whole was stirred 1 h at room temperature. The mixtuer was extracted with $CHCl_3$ and washed with water. Organic layer was dried and evaporated. The solvent was removed under vacuum and the product was isolated by silica gel column chromatography.

   Compound **1a**: Yellow oil; ^{1}H-NMR (500 MHz, $CDCl_3$): δ=4.24 (t, 2H, *J* =7.5), 4.56 (t, 2H, *J* =7.5), 7.54 (m, 3H), 7.82 (m, 2H), 7.87 (s, 1H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ=42.7, 48.2, 126.8,

127.5(2C), 128.9(2C), 131.3, 132.3, 136.0, 157.0. HRMS (APCI): *m/z* $[M+H]^+$ calcd for $C_{11}H_{10}N_4$: 199.0987; found; 199.0903.

Compound **2a**: Yellow oil. ^{1}H-NMR (500 MHz, $CDCl_3$): δ=2.32 (s, 3H), 4.30 (t, 2H, *J* =7.0Hz), 4.57 (t, 2H, *J* =7.0Hz), 7.26-7.38 (m, 4H), 7.54 (s, 1H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ=20.3, 42.6, 48.3, 126.0, 128.2, 129.3, 129.9, 131.0, 132.3, 135.7, 136.1, 152.7. HRMS (APCI): *m/z* $[M+H]^+$ calcd for $C_{12}H_{13}N_4$: 213.1140; found; 213.1073.

Compound **2b**: Orange oil. ^{1}H-NMR (500 MHz, $CDCl_3$): δ=2.43 (s, 3H), 4.23 (t, 2H, *J* =6.5Hz), 4.55 (t, 2H, *J* =6.5Hz), 7.37-7.65 (m, 4H), 7.87 (s, 1H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ=21.4, 42.7, 48.2, 124.7, 126.8, 128.0, 128.7, 132.1, 132.4, 135.9, 138.8, 157.1. HRMS (APCI): *m/z* $[M+H]^+$ calcd for $C_{12}H_{13}N_4$: 213.1140; found; 213.1060.

Compound **2c**: White solid, mp 92 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ=2.44 (s, 3H), 4.22 (t, 2H, *J* =6.5Hz), 4.55 (t, 2H, *J* =6.5Hz), 7.31 (d, 2H, *J* =8.0Hz), 7.72 (d, 2H, *J* =8.0Hz), 7.86 (s, 1H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ=21.4, 42.7, 48.0, 127.2, 129.2, 132.2, 133.2, 141.7, 156.7, 161.7. HRMS (APCI): *m/z* $[M+H]^+$ calcd for $C_{12}H_{13}N_4$: 213.1140; found; 213.1069.

Compound **2d**: Yellow oil. ^{1}H-NMR (500 MHz, $CDCl_3$): δ=4.39 (t, 2H, *J* =7.5), 4.59 (t, 2H, *J* =7.5), 7.39 (m, 2H), 7.44 (m, 2H), 7.57 (s, 1H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ=42.6, 48.6, 127.2, 129.9, 130.3, 131.3, 132.2, 132.2, 135.4, 156.5, 156.6. HRMS (APCI): *m/z* $[M+H]^+$ calcd for $C_{11}H_{10}ClN_4$: 233.0594; found; 233.0479.

Compound **2e**: Orange oil. ^{1}H-NMR (500 MHz, $CDCl_3$): δ=4.31 (t, 2H, *J* =7.5), 4.58 (t, 2H, *J* =7.5), 7.51 (m, 4H), 7.73 (s, 1H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ=41.5, 48.8, 115.4, 115.5, 126.4, 129.2, 131.2, 131.3, 131.5, 160.0, 160.6. HRMS (APCI): *m/z* $[M+H]^+$ calcd for $C_{11}H_{10}FN_4$: 217.0889; found; 217.0793.

Compound **2f**: White solid, mp 128 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ=2.40 (s, 3H), 4.05 (t, 2H, *J* =7.0), 4.43 (t, 2H, *J* =7.0), 7.83 (s, 1H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ=22.9, 42.4, 47.7, 128.0, 130.7, 155.8. HRMS (APCI): *m/z* $[M+H]^+$ calcd for $C_6H_9N_4$: 216.1140; found 213.1069.

Compound **2g**: Orange oil. ^{1}H-NMR (500 MHz, $CDCl_3$): δ=0.86-0.89 (m, 5H), 1.25-1.28 (m, 9H), 1.62-1.73 (m, 3H), 2.64-2.67 (m, 2H), 4.05 (t, 2H, *J* =7.0), 4.42 (t, 2H, *J* =7.0), 7.81 (s, 1H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ=14.1, 22.6, 26.4, 29.3, 29.4, 31.8, 36.5, 38.8, 38.9, 42.5, 50.9, 127.7, 130.5, 159.5. HRMS (APCI): *m/z* $[M+H]^+$ calcd for $C_{14}H_{25}N_4$: 249.2079; found 249.1961.

Compound **2h**: Orange oil. ^{1}H-NMR (500 MHz, $CDCl_3$): δ=0.84-0.0.86 (m, 8H), 1.23-1.66 (m, 13H), 2.63-2.64 (m, 2H), 4.04 (t, 2H, *J* =7.0), 4.38 (t, 2H, *J* =7.0), 7.79 (s, 1H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ=14.0, 22.5, 27.0, 29.2, 29.4, 29.5, 31.8, 34.1, 36.0, 36.8, 38.7, 42.5, 50.6, 127.6, 130.4, 159.4. HRMS (APCI): *m/z* $[M+H]^+$ calcd for $C_{16}H_{29}N_4$: 277.2392; found 277.2258.