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PAPER

Facile preparation of polycyclic halogen-substituted 1,2,3-triazoles by using intramolecular Huisgen cycloaddition†

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When 1-(ω-azidoalkyl)-2-(2,2-dihalovinyl)arenes were heated in DMF, the intramolecular Huisgen cycloaddition of an azido group with a 1,1-dihalovinyl group afforded 5-halo-1,2,3-triazole-fused tricyclic benzo compounds. Based on the remaining bromo groups, carbon elongation by the Mizoroki-Heck or Suzuki-Miyaura coupling reactions, followed by an intramolecular Friedel-Crafts reaction, afforded polycyclic compounds with fused triazole rings. Thereafter, the bromo groups were converted into 2-nitrophenyl groups via the Suzuki-Miyaura coupling reaction, which was followed by the Cadogan reaction; a fluorescent pentacyclic compound was obtained.

Introduction

1,2,3-Triazoles[1] have attracted considerable interest and are widely used in pharmaceutical development owing to their excellent biological activity, receptor-binding interactions, and metabolic stability.[2] Furthermore, 1,2,3-triazole derivatives are extensively used industrially as dyes, corrosion inhibitors, sensors, and light stabilizers.[3] In synthetic chemistry, 1,2,3-triazole derivatives are used as intermediates for the generation of α-iminocarbenes and are frequently used in various molecular transformation reactions.[4] In chemical biology, biomolecules have been chemically modified using 1,2,3-triazole derivatives; the click reaction between alkynes and azides is used for the modification and occurs even in water and under biocompatible conditions in the commonly named bioconjugate chemistry field.[5] Additionally, click chemistry is widely used to form 1,2,3-triazole rings in polymer synthesis and to develop new materials in materials science.[6] 1,2,3-

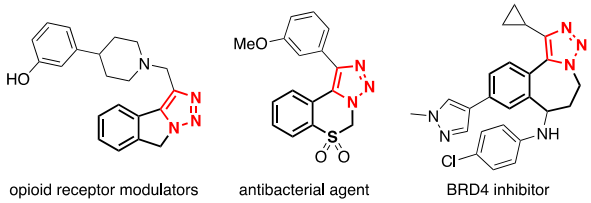
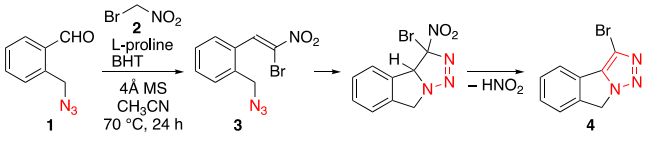


Fig. 1. Examples of fused 1,2,3-triazole derivatives exhibiting biological activities.

Triazole derivatives have a variety of applications, therefore, realizing efficient synthetic methods for 1,2,3-triazole derivatives have immense significance for synthetic organic chemists. Benzoazaheterocycles fused with 1,2,3-triazoles, specifically, serve as skeletons in various biologically active molecules, e.g., opioid receptor modulators, antibacterial agents, and BRD4 inhibitors (Fig. 1).[7] If the various tricyclic halogen-substituted 1,2,3-triazoles were readily afforded, it will be easy to convert to the bioactive compounds shown in Fig. 1.

Dehaen *et al* have reported the effective synthetic methods of functionalized tricyclic 1,2,3-triazoles from aldehydes and nitroalkanes by tandem intermolecular Knoevenagel condensation, Huisgen cycloaddition, and elimination of HNO_2.[8] Though tricyclic bromo-substituted 1,2,3-triazole **4** was also reported in their report, the yield of product **4** was low. This result was probably due to the inefficient synthesis of bromonitroalkene **3** from aldehyde **1** and less reactive bromonitromethane (**2**) *in situ* (Scheme 1).



Scheme 1. Preparation of tricyclic bromo-substituted 1,2,3-triazole **4** from aldehyde **1** and bromonitromethane (**2**) via bromonitroalkene **3** reported by Dehaen *et al*.

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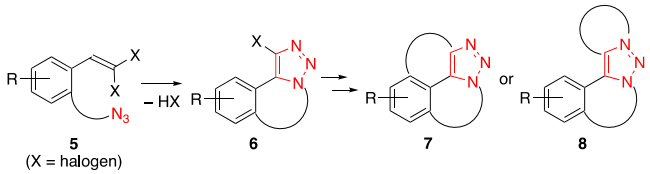
† Electronic supplementary information (ESI) available: Experimental procedures, and characterization of new compounds including NMR spectra. See DOI: 10.1039/d1ccxxxxxx



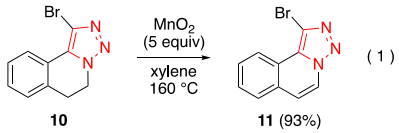
Scheme 2. Facile preparation of 5-halo-1,2,3-triazole-fused benzotricyclic compounds **6** from 1-(ω-azidoalkyl)-2-(2,2-dihalovinyl)arene **5** by intramolecular Huisgen cycloaddition. Extension to polycyclic triazole derivatives **7** or **8**.

Inspired by the finding of Dehaen *et al*, we planned a similar cyclization reaction using dihaloalkenes, which is easy and stable for synthetic preparation, instead of nitroalkenes.[9-10] Herein, we report that polycyclic halogen-substituted 1,2,3-triazole **6** was efficiently obtained by the intramolecular Huisgen cycloaddition of 1-(ω-azidoalkyl)-2-(2,2-dihalovinyl)arene **5**. Tricyclic 1,2,3-triazole **6** was also easily converted to polycyclic triazole derivatives **7** and **8** by carbon elongation of the remaining halogen groups of **6** (Scheme 1).

Results and discussion

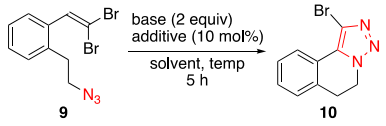
First, we investigated the optimal conditions required for the intramolecular cyclization of azide **9**[11]; the results are summarized in Table 1. Though the reaction was carried out by adding various bases to remove HBr generated in the reaction system, the corresponding bromo-substituted tricyclic triazole **10** was obtained in low yields (Table 1, entries 1–8).[12] Next, a transition metal catalyst effective for the Huisgen cyclization reaction was added, and heating at 100°C in toluene gave the corresponding cyclized product **10** in moderate yield (Table 1, entries 9–11). However, **10** was obtained in a similar yield when the toluene solution of **9** was heated in the absence of any transition metal catalyst (Table 1, entry 12). Further optimization of the reaction conditions afforded **10** in high yield; the optimized reaction was performed in DMF at 150 °C (Table 1, entry 16).[13] Treatment of **10** with manganese dioxide led to aromatic ring **11** without loss of the triazole ring (Eq. 1).[14]

Subsequently, various tricyclic triazole derivatives were synthesized under the optimized conditions listed in Table 1; the results are summarized in Table 2. The corresponding halogen-substituted triazole derivatives **20–21** were obtained easily, even when the halogen group on the vinyl group was a chloro or iodo group in addition to the bromo group (Table 2, entries 2–3). In case of bromofluoro olefin, the corresponding fluoro-substituted triazole **22** was afforded in a good yield with selective elimination of HBr (Table 2, entry 4). The substitution



(1)

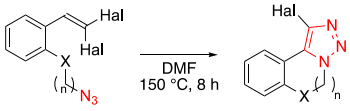
Table 1. Optimization of reaction condition.

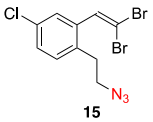
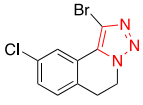
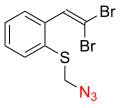
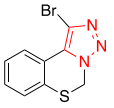
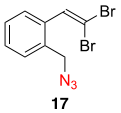
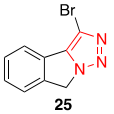
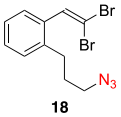
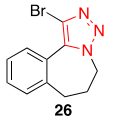
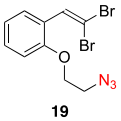
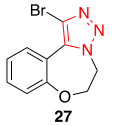


Entry	Solvent	Base	Additive	Temp. (°C)	Yield by ^{1}H NMR(%)[a]
1	toluene	L-proline	—	80	9
2	toluene	pyrrolidine	—	80	5
3	toluene	morpholine	—	80	6
4	toluene	piperidine	—	80	5
5	toluene	imidazole	—	80	2
6	toluene	$(i\text{-Pr})_2$NEt	—	80	5
7	toluene	Et_3N	—	80	6
8	CH_3CN	L-proline	—	80	4
9	toluene	—	CuI	100	34
10	toluene	—	$Ag(CF_3COO)$	100	45
11	toluene	—	$AuCl(PPh_3)$	100	37
12	toluene	—	—	100	44
13	1,4-dioxane	—	—	100	22
14	DMSO	—	—	100	68
15	DMF	—	—	100	69
16	DMF	—	—	150	(85)[b]

[a]Yields in parenthese is isolated yield. [b]Reaction period was 8 h.

Table 2. Syntheses of 5-halo-1,2,3-triazole-fused benzotricyclic compounds.



Entry	Substrate		Product		Isolated yield (%)
1	X, Y = Br	**9**	X = Br	**10**	85
2	= Cl	**12**	= Cl	**20**	98
3	= I	**13**	= I	**21**	80
4[a]	X = Br (or F) Y = F (or Br)	**14**	X = F	**22**	71
5		**15**		**23**	91
6		**16**		**24**	63
7		**17**		**25**	88
8[b]		**18**		**26**	75
9[b]		**19**		**27**	54

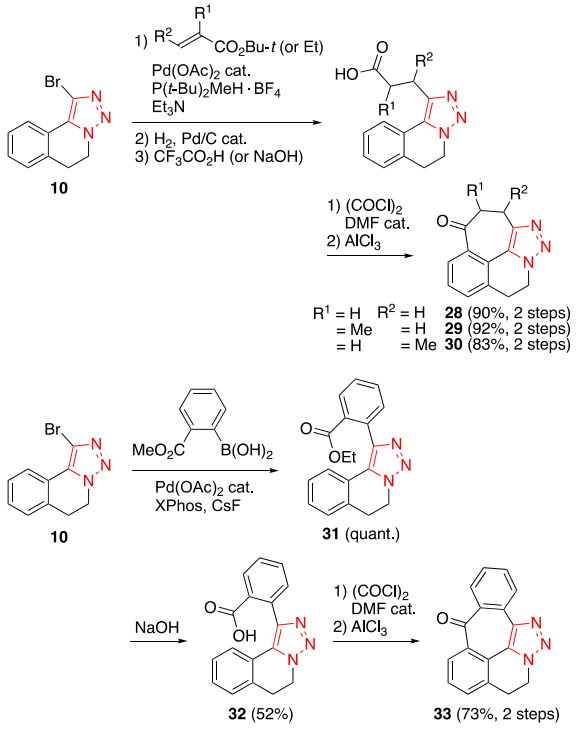
[a]Reaction period was 14 h. [b]Reaction period was 40 h.

of the halogen groups at positions adjacent to the 2-azidoethyl group afforded compound **23** in good yield (Table 2, entry 5). Furthermore, thioether derivative **24** was obtained from sulfur-containing azide **16** (Table 2, entry 8). The desired tricyclic compounds containing 5- and 7-membered rings, **25** and **26** were obtained in good yields (Table 2, entries 7–8)[15]; compounds **25** and **26** were obtained from the one carbon decreasing or increasing substrates **19** and **20**, respectively, against azide **9**. Azide **19** bearing a 1-azidoethoxy group afforded a 7-membered oxaazacycle **27** (Table 2, entry 9).

Next, the remaining bromo group of the tricyclic triazole derivative **10** was carbon-extended using the Mizoroki-Heck reaction. The Mizoroki-Heck reaction was followed by hydrogenation, conversion into acid chloride, and an intramolecular Friedel-Crafts cyclization to afford 1,2,3-triazole fused polycyclic compounds **28–30**.[16-18] Furthermore, pentacyclic compound **33** was obtained by an intramolecular Friedel-Crafts reaction after the derivation of carboxylic acid **32** using the Suzuki-Miyaura coupling reaction (Scheme 2).[19]

Fused-ring triazole derivatives have recently drawn attention owing to their fluorescent properties (Fig. 2).[20-24] Thus, it is imperative to construct new frameworks and develop efficient synthetic methods. In this study, the desired fused-ring triazole derivative **35** was obtained in high yield by the Suzuki-Miyaura coupling reaction of **10** with *o*-nitrophenylboronic acid to nitroarene **34**, followed by treatment with triphenylphosphine.[25-26] Although pentacyclic product **35** did not fluoresce much in the solid state, it exhibited strong fluorescence in various organic solvents (Scheme 3 and Table 3).

Scheme 2. Preparation of 1,2,3-triazole-fused polycyclic compounds using intramolecular Friedel-Crafts reaction.



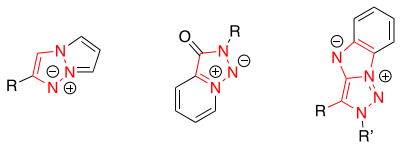
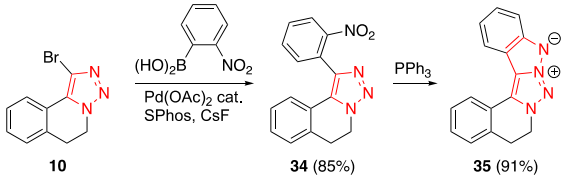


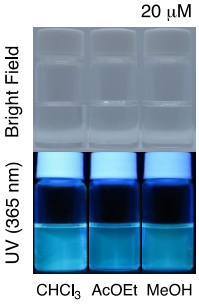
Fig. 2. Several fused 1,2,3-triazole derivatives with fluorescent properties.



Scheme 3. Preparation of 1,2,3-triazole-fused pentacyclic compound **38** by using Cadogan reaction.

Table 3. Fluorescent properties of compound **38**.

	Solution[a]			Solid
	$CHCl_3$	AcOEt	MeOH	
λ_{abs}/nm[b]	387.0	387.0	387.0	387.0
λ_{abs}/nm[b]	477.5	477.5	477.5	477.5
λ_{abs}/nm[b]	388.0	388.0	388.0	388.0
Φ%[b]	63.9	63.9	63.9	63.9



[a]20 μM soution in each solvent. [b]Excitation at the wavelength of absorption maxima in each solvent. [c]Measured at the fluorescence maximum wavelength in each solvent.

Conclusion

To summarize, the synthesis of halogen-substituted 1,2,3-triazoles from 1-(ω-azidoalkyl)-2-(2,2-dihalovinyl)arenes was accomplished via intramolecular Huisgen cycloaddition. Furthermore, the remaining halogen groups were carbon-enriched to afford 1,2,3-triazole-fused polycyclic compounds via intramolecular Friedel-Crafts or Cadogan reactions. Further investigations into the utility of these reactions are currently underway.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Experimental section

General. ^{1}H, ^{13}C NMR spectra were taken on an Agilent 400-MR and JEOL JNM-ECZL400S spectrometers at 400 and 100 MHz, respectively. ^{19}F NMR spectra were taken on a JEOL JNM-ECZL400S spectrometer at 282 MHz. $CDCl_3$ was used as the solvent. Chemical shifts are reported in parts per million shift (δ value) from Me_4Si (δ 0 ppm for ^{1}H) or based on the middle peak of the solvent ($CDCl_3$) (δ 77.00 ppm for ^{13}C), or based on C_6F_6 (δ −164.9 ppm for ^{19}F) as internal standards, respectively. Signal patterns are indicated as br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Coupling constants (J) are given in Hertz. Infrared (IR) spectra were recorded on a JASCO FT/IR-4100 spectrometer and are reported in wave numbers (cm^{-1}). High resolution mass spectra (HRMS) were obtained on Bruker micrOTOF Ⅱ by positive electrospray ionization (ESI) method calibrated with sodium formate and on a JEOL JMS-700 in electron impact ionization (EI) method calibrated with perfluorokerosene at the Suzukake-dai Material Analysis Center, Technical Department, Tokyo Institute of Technology. The ultraviolet−visible (UV−vis) spectra of the solutions were recorded on JASCO V760 spectrometers. The UV−vis spectra were recorded in the solid state utilizing JASCO V570 spectrometers, which were equipped with a calibrated integrating sphere system. The solid-state absorption spectra were obtained by measuring the diffuse reflectance spectra, followed by a Kubelka-Munk conversion. The fluorescence spectra and quantum yield of the solids were determined on a JASCO FP-8500 spectrofluorimeter that was equipped with a calibrated integrating sphere system.

Typical procedure for halogen-substituted tricyclic triazole derivatives from 1-(ω-azidoalkyl)-2-(2,2-dihalovinyl)arenes. 1-Bromo-5,6-dihydro-[1,2,3]triazolo[5,1-*a*]isoquinoline (10).

A mixture of 1-(azidomethyl)-2-(2,2-dibromovinyl)benzene (**9**) (1.31 g, 4.00 mmol) in DMF (20 mL) was stirred in an oil bath maintained at 150 °C for 8 h under argon. The reaction was terminated with the addition of water. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude solid, which was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (855 mg, 85%) as a white solid.

^{1}H NMR δ 3.26 (t, *J* = 7.2 Hz, 2H), 4.60 (t, *J* = 7.2 Hz, 2H), 7.34 (br dd, *J* = 1.6, 7.2 Hz, 1H), 7.38 (dt, *J* = 1.6, 7.2 Hz, 1H), 7.42 (dt, *J* = 1.6, 7.2 Hz, 1H), 8.20 (br dd, *J* = 1.6, 7.2 Hz, 1H). ^{13}C NMR δ 28.97, 49.37, 116.45, 123.42, 124.17, 127.75, 128.40, 129.72, 130.30, 132.20. IR (KBr) 3064, 3022, 2988, 2947, 2906, 1610, 1579, 1553, 1483, 1458, 1431, 1346, 1291, 1280, 1255, 1233, 1188, 1162, 1043, 998, 946, 915, 869, 768, 740, 716, 680 cm^{-1}. HRMS (ESI) Calcd for $C_{10}H_8{}^{79}BrN_3Na$ $[M+Na]^+$: 271.9794. Found: 271.9793. HRMS (ESI) Calcd for $C_{10}H_8{}^{81}BrN_3Na$ $[M+Na]^+$: 273.9774. Found: 273.9774. M.p. 88-89 °C.

Typical procedure for intramolecular Friedel-Crafts reaction. 3,4,9,10-Tetrahydro-5*H*-1,2,10a-triazanaphtho[2,1,8-*cde*]-azulen-5-one (28).

To a stirred solution of 3-(5,6-dihydro-[1,2,3]triazolo[5,1-*a*]isoquinolin-1-yl)propanoic acid (60.0 mg, 0.246 mmol) obtained above in CH_2Cl_2 (2 mL) were successively added DMF (1 drop) and oxalyl chloride (0.042 mL, 0.492 mmol) at room temperature. After the mixture was stirred for 1.5 h, the solvent and the excess oxalyl chloride were removed in vacuo to afford 3-(5,6-dihydro-[1,2,3]triazolo[5,1-*a*]isoquinolin-1-yl)propanoyl chloride as a crude oil, which was pure by ^{1}H NMR spectroscopy and directly used in the next step. To a solution of 3-(5,6-dihydro-[1,2,3]triazolo[5,1-*a*]isoquinolin-1-yl)propanoyl chloride obtained above in CH_2Cl_2 (2 mL) was added pulverized $AlCl_3$ (328 mg, 2.46 mmol) at –78 °C for 1 h under argon. After the mixture was stirred at room temperature for 12 h, the reaction was terminated by the addition of aqueous saturated NH_4Cl solution. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil which was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (50.3 mg, 90%, 2 steps) as a white solid.

^{1}H NMR δ 3.10 (dd, ***J*** = 5.2 7.6 Hz, 2H), 3.26 (dd, ***J*** = 5.2 7.6 Hz, 2H), 3.34 (t, ***J*** = 7.2 Hz, 2H), 4.62 (t, ***J*** = 7.2 Hz, 2H), 7.37 (t, ***J*** = 7.6 Hz, 1H), 7.47 (dd, ***J*** = 0.8, 7.6 Hz, 1H), 7.78 (dd, ***J*** = 0.8, 7.6 Hz, 1H). ^{13}C NMR δ 21.77, 28.84, 39.96, 44.61, 122.96, 128.41, 128.69, 129.72, 131.46, 132.23, 136.29, 144.26, 201.08. IR (KBr) 3073, 3040, 2935, 2896, 2847, 1669, 1591, 1439, 1328, 1281, 1091, 971, 807, 769, 480, 450 cm^{-1}. HRMS (ESI) Calcd for $C_{13}H_{11}N_3ONa$ $[M+Na]^+$: 248.0794. Found: 248.0794. M.p. 138-139 °C.

Typical procedure for Cadogan reaction. 5,6-Dihydroindazolo[2',3':3,4][1,2,3]triazolo[5,1-*a*]isoquinolin-9-ium-10-ide (35).

The mixture of 1-(2-nitrophenyl)-5,6-dihydro-[1,2,3]triazolo[5,1-a]isoquinoline (**34**) (50.0 mg, 0.170 mmol) obtained above and PPh_3 (133 mg, 0.51 mmol) in 1,2-dicholorobenzen (2 mL) was heated in an oil bath maintained at 200 °C for 20 h under argon. After being cooled to room temperature, the reaction mixture chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (40.3 mg, 91%) as a yellowish solid.

^{1}H NMR δ 3.42 (t, *J* = 7.2 Hz, 2H), 4.74 (t, *J* = 7.2 Hz, 2H), 7.17 (t, *J* = 8.0 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.44 (t, *J* = 8.0 Hz, 1H), 7.50 (t, *J* = 8.0 Hz, 1H), 7.55 (t, *J* = 8.0 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 8.01 (d, *J* = 8.0 Hz, 1H), 8.12 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR δ 28.34, 46.36, 109.90, 115.02, 118.02, 119.69, 124.04, 124.42, 124.79, 125.25, 127.04, 128.33, 128.69, 129.67, 131.27, 153.60. IR (KBr) 3050, 3027, 2998, 2951, 1508, 1488, 1466, 1442, 1383, 1344, 1255, 1194, 1177, 1136, 766, 744 cm^{-1}. HRMS (ESI) Calcd for $C_{16}H_{12}N_4Na$ $[M+Na]^+$: 283.0954. Found: 283.0950. M.p. > 200 °C.

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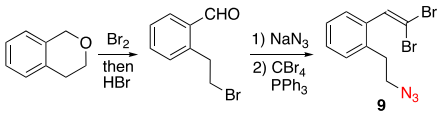

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