An Efficient Access to 4-Alkylidene-5,6-dihydro-4*H*-pyrrolo[1,2-*c*][1,2,3]triazoles

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Abstract: From alkylidenecyclopropanes (MCPs), 4-alkylidene-5,6-dihydro-4*H*-pyrrolo-[1,2-*c*][1,2,3]triazoles **6** were prepared in moderate yields through diiodogenation, Cu(I)-catalyzed 1,3-dipolar cycloaddition and subsequent intramolecular Heck reaction.

Key words: 1,2,3-trizaole, alkylidenecyclopropanes (MCPs), 1,3-dipolar cycloaddition, Heck reaction

Pyrrolotriazoles are an important class of heterocycles due to their applications as bioactive compounds and synthetic intermediates in organic synthesis.[1] However, there are only limited reports about their synthesis with substituent groups and they involve thermal intramolecular cycloaddition.[2,3] Thus, there is a need to develop new methodology for the efficient synthesis of these compounds with different substituent groups.

Recently, Cu(I)-catalyzed one-pot synthesis of 1,4-disubstituted 1,2,3-triazoles derived from organic azides generated in situ from halides and inorganic azides with alkynes has enjoyed considerable use since its discovery.[4] During our study of methylenecyclopropanes (MCPs),[5] we found that CuX_2-mediated dihalogenation of MCPs **1** offered a stereoselective synthesis of (*Z*)-2,4-dihalobutenes.[6] These dihalobutenes, containing a homoallylic halogen and a vinyl halogen, may react with various reagents and can be used as building blocks for further organic transformations.[6,7] Retrosynthetically, pyrrolotriazoles could be prepared by scission of the C–C bond of the pyrrole to the triazole containing a vinyl iodide. This triazole could be obtained by a dipolar cycloaddition of the pendant azide, which in turn could be synthesized from (*Z*)-2,4-dihalobutenes (Figure 1).

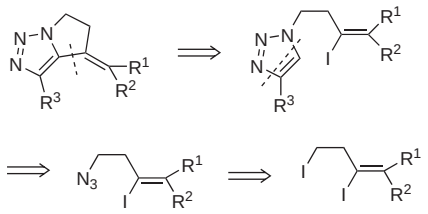
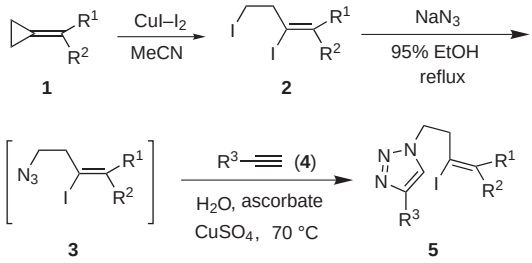


Figure 1

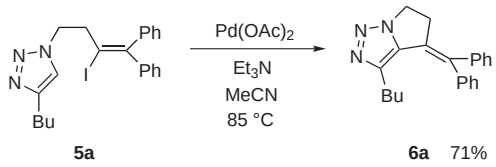
According to the above synthetic route, herein we wish to report an efficient synthesis of 4-alkylidene-5,6-dihydro-4*H*-pyrrolo[1,2-*c*][1,2,3]triazoles **6** through the Cu(I)-catalyzed regioselective 1,3-dipolar cycloaddition followed by an intramolecular Heck reaction from (*Z*)-2,4-dihalobutenes in moderate yields.

The various (*Z*)-2,4-diiodobutenes **2** could be conveniently prepared by CuX_2-mediated dihalogenation of MCPs **1**.[6] By refluxing (*Z*)-2,4-diiodobutenes with NaN_3 and subsequent Cu(I)-catalyzed regioselective 1,3-dipolar cycloaddition,[4] 3-iodo-3-butenyl-1*H*-[1,2,3]triazoles **5** were obtained at moderate yields in one pot (Scheme 1).[8,9] The results are summarized in Table 1.



Scheme 1

Next, we carried out the Heck-type[10] reactions of 1,4-disubstituted 1,2,3-triazoles **5a**–**l**. Initially, we tested the reaction of 4-butyl-1-(3-iodo-4,4-diphenyl-but-3-enyl)-1*H*-[1,2,3]triazole (**5a**) with 10 mol% of $Pd(OAc)_2$ and 2 equivalents of Et_3N at 85 °C in acetonitrile. After work-up and isolation, the product **6a** was obtained in 71% yield (Scheme 2).



Scheme 2

The structure was assigned on the basis of its ^1H NMR, ^{13}C NMR, and IR spectra, MS data and microanalyses. Further screening demonstrated that DMF as the solvent, $NaHCO_3$ as the base were more suitable for this reaction

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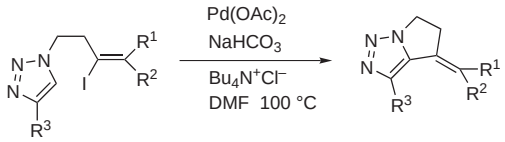
Table 1 Synthesis of 3-Iodo-3-butenyl-1*H*-[1,2,3]triazole **5**[a]

Entry	R^1/R^2 (**2**)	R^3 (**4**)	Time (h)	Yield (%)[a]
1	Ph/Ph (**2a**)	Bu (**4a**)	18	**5a** (65)
2	**2a**	C_5H_{11} (**4b**)	17	**5b** (62)
3	**2a**	$MeOCH_2$ (**4c**)	18	**5c** (51)
4	**2a**	Ph (**4d**)	15	**5d** (70)
5	*p*-ClC_6H_4/*p*-ClC_6H_4 (**2b**)	**4a**	20	**5e** (63)
6	**2b**	**4b**	20	**5f** (60)
7	*p*-FC_6H_4/*p*-FC_6H_4 (**2c**)	**4a**	19	**5g** (57)
8	**2c**	**4b**	19	**5h** (62)
9	Me/Ph (**2d**)	**4b**	17	**5i** (61)
10	H/*p*-ClC_6H_4 (**2e**)	**4a**	15	**5j** (59)
11	**2e**	**4b**	16	**5k** (60)
12	**2e**	**4d**	15	**5l** (62)

[a] Overall yield based on **2**.

Table 2 Synthesis of 4-Alkylidene-5,6-dihydro-4*H*-pyrrolo[1,2-*c*][1,2,3]triazoles **6**[a]

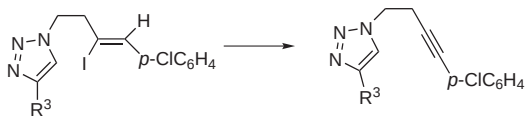


Entry	$R^1/R^2/R^3$	Time (h)	Yield (%)[a]
1	Ph/Ph/Bu (**5a**)	20	**6a** (82)
2	Ph /Ph/C_5H_{11} (**5b**)	20	**6b** (85)
3	Ph /Ph/$MeOCH_2$ (**5c**)	19	**6c** (52)
4	*p*-ClC_6H_4/*p*-ClC_6H_4/Bu (**5e**)	21	**6e** (82)
5	*p*-ClC_6H_4/*p*-ClC_6H_4/C_5H_{11} (**5f**)	22	**6f** (58)
6	*p*-FC_6H_4/*p*-FC_6H_4/Bu (**5g**)	23	**6g** (68)
7	*p*-FC_6H_4/*p*-FC_6H_4/C_5H_{11} (**5h**)	22	**6h** (70)
8	Me/Ph/C_5H_{11} (**5i**)	20	**6i** (71)

[a] Overall yields based on **5**.

and the yield of **6a** could increase to 82% (Table 2, entry 1). With this result in hand, we then carried out the reactions of various 1,4-disubstituted 1,2,3-triazoles **5** in the presence of 10 mol% $Pd(OAc)_2$ under the optimized conditions.[11] The results were summarized in Table 2. Using this method, we obtained the new pyrrolotriazole ring system incorporating an exocyclic double bond and the configuration of the double bond was retained through the Heck reaction. However, when substrates containing a vinyl hydrogen were employed (**5j**–**l**), only the elimination products (**7a**–**c**) were obtained (Scheme 3). This showed that the intramolecular elimination reaction occurred more readily than the Heck reaction and could be used to access triazoles incorporating a homopropargyl substituent.

In summary, we have developed an efficient method for the preparation of 4-alkylidene-5,6-dihydro-4*H*-pyrrolo-[1,2-*c*][1,2,3]triazoles and 1*H*-[1,2,3]triazoles incorporating a homopropargyl group in moderate yields. It is expected that this kind of pyrrolotriazole derivatives could be used as bioactive compounds and synthetic intermediates.[1] Further application of this synthetic methodology is being investigated in our laboratory.



R^3 = Bu (**5j**) — **7a** 82%
C_5H_{11} (**5k**) — **7b** 80%
Ph (**5l**) — **7c** 85%

Scheme 3

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(8) **Typical Procedure for the Synthesis of 5.**
To a stirred 95% EtOH (2 mL) solution of NaN_3 (0.6 mmol), **2** (0.5 mmol) was added and the reaction mixture was stirred under reflux until the reaction was complete, as monitored by TLC. Then, H_2O (4 mL), ascorbic acid (0.1 g, 0.56 mmol), NaOH (0.022 g, 0.56 mmol), $CuSO_4$ (0.01 g, 0.04 mmol), and alkyne **4** (0.6 mmol) were added and heated together at 70 °C until the reaction was complete (monitored by TLC). Afterwards, the mixture was cooled to r.t. and H_2O (15 mL) was added. The aqueous layer was extracted with EtOAc (3 × 15 mL). The organic layer was dried over anhyd $MgSO_4$. After evaporation, the residue was subjected to preparative TLC (eluent: PE–EtOAc, 1:6 to 1:3) to afford 1,4-disub-stituted 1,2,3-triazoles **5**.

Selected Spectral Data for 5a.

Solid, mp 70–72 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95 (t, 3 H, *J* = 7.33 Hz), 1.39–1.44 (m, 2 H), 1.64–1.71 (m, 2 H), 2.74 (t, 2 H, *J* = 7.66 Hz), 3.08 (t, 2 H, *J* = 6.41 Hz), 4.58 (t, 2 H, *J* = 6.41 Hz), 6.75 (dd, 2 H, *J* = 1.75, 7.79 Hz), 7.10–7.32 (m, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.17, 148.27, 146.08, 139.29, 128.50, 128.24, 127.91, 127.60, 127.56, 121.04, 102.68, 49.67, 42.45, 31.77, 25.32, 22.35, 13.85. IR: 2955, 2926, 1437, 1043, 701 cm^{-1}.

(9) The temperature (70 °C) is required for the triazole synthesis step in our reaction by trial and error. At higher temperature 1,5-regioisomers can be formed and at lower temperature the reaction was not complete after several hours.

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(11) **Typical Procedure for the Synthesis of 6.**
Compound **5** (0.25 mmol), $Pd(OAc)_2$ (0.025 mmol), tetrabutylammonium chloride (TBAC, 0.25 mmol), $NaHCO_3$ (0.5 mmol), and *N*,*N*-dimethylformamide (DMF, 1 mL) were added into a Schlenk tube at r.t. The reaction mixture was stirred at 100 °C until the reaction was complete, as monitored by TLC. Then the reaction mixture was cooled and H_2O (15 mL) was added. The aqueous layer was extracted with EtOAc (3 × 15 mL). The organic layer was dried over anhyd $MgSO_4$. After evaporation, the residue was subjected to preparative TLC (eluent: PE–EtOAc, 1:6 to 1:3) to afford 4-alkylidene-5,6-dihydro-4*H*-pyrrolo-[1,2-*c*][1,2,3]-triazoles **6**.

Selected Data.

Compound **6a**: solid, mp 124–126 °C. IR: 2948, 2924, 1440, 764, 703 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.74 (t, 3 H, *J* = 7.26 Hz), 0.92–1.00 (m, 2 H), 1.20–1.28 (m, 2 H), 1.49 (t, 2 H, *J* = 7.45 Hz), 3.51 (t, 2 H, *J* = 6.89 Hz), 4.36 (t, 2 H, *J* = 6.89 Hz), 7.18–7.38 (m, 10 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.97, 141.94, 141.30, 138.43, 137.67, 129.92, 129.18, 128.72, 128.21, 127.86, 127.70, 123.51, 45.24, 37.50, 31.62, 25.35, 22.28, 13.76. MS (EI, 70 eV): *m*/*z* (%) = 329 (19) [M^+]. Anal. Calcd for $C_{22}H_{23}N_3$: C, 80.21; H, 7.04; N, 12.76. Found: C, 80.00; H, 7.16; N, 12.83.

Compound **7a**: solid, mp 126–128 °C. IR: 2926, 1486, 1086, 828 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91 (t, 3 H, *J* = 7.33 Hz), 1.34–1.40 (m, 2 H), 1.61–1.68 (m, 2 H), 2.73 (t, 2 H, *J* = 7.58 Hz), 2.99 (t, 2 H, *J* = 6.71 Hz), 4.54 (t, 2 H, *J* = 6.71 Hz), 7.27 (s, 4 H), 7.40 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.35, 134.24, 132.75, 128.61, 121.27, 120.96, 86.01, 82.23, 48.65, 31.55, 25.28, 22.22, 21.63, 13.78. MS (EI, 70 eV): *m*/*z* (%) = 287 (29.08) [M^+]. Anal. Calcd for $C_{16}H_{18}ClN_3$: C, 66.78; H, 6.30; N, 14.60. Found: C, 66.90; H, 6.21; N, 14.65.