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Regiospecific synthesis of 2-allylated-5-substituted tetrazoles via palladium-catalyzed reaction of nitriles, trimethylsilyl azide, and allyl acetates†

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Abstract

A variety of 2-allylated-5-substituted tetrazoles were prepared in excellent yields through the reaction of alkyl- and arylidenemalononitriles, allyl acetates and trimethylsilyl azide in the presence of a palladium catalyst.

Keywords: tetrazole; palladium catalyst; nitrile; trimethylsilyl azide; allyl acetate.

There are a large number of tetrazole compounds reported to have biological activity.[1] To construct these important tetrazole derivatives, the alkylation reactions of tetrazole anions are often used. However, due to the ambient nature of the anions **1a↔1b**, the alkylations give mixtures of *N*(1)- and *N*(2)-alkylation isomers.[2] For example, the reaction of 5-substituted tetrazoles with either alkyl halides[3] or dialkyl sulfates[4] in the presence of a base, or with diazomethane[5] gave a mixture of 1,5- and 2,5-disubstituted tetrazoles and the ratio of the regioisomers was effected by the electronic and steric effect of the substituent. Even by blocking the *N*(2)-position with tri-*n*-butyltin prior to the alkylation, the 2,5-isomer was still formed in about a 10% average yield.[6] Nelson et al.[7] obtained the 1,5-isomer exclusively by blocking the 2-position with cobalt complexes. Kondo et al.[8] prepared 2,5-diarylsubstituted tetrazoles from phenylsulfonylhydrazones and arene diazonium salts. We now report the regiospecific synthesis of 2-allylated-5-substituted tetrazoles **4** through the palladium-catalyzed reaction of alkyl- and arylidenemalononitriles **2**, allylic acetates **3** and $TMSN_3$.

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† Dedicated to Professor Richard Neidlein on the occasion of his 70th birthday in recognition of his outstanding contributions to the areas of organic chemistry.

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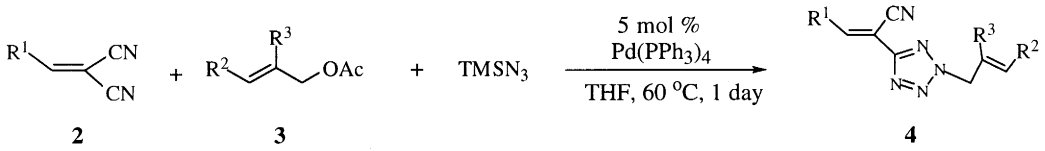
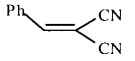
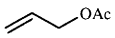
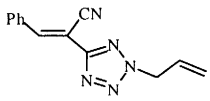
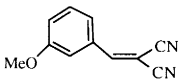
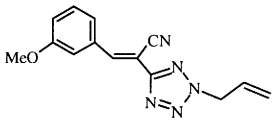
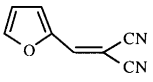
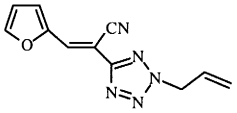
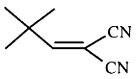
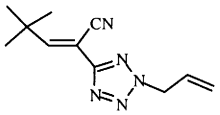
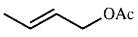
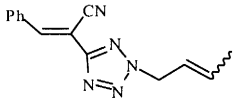
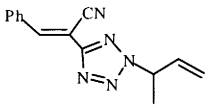
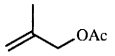
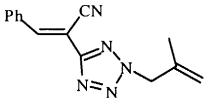
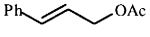
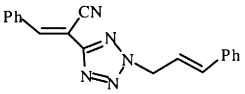
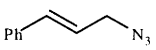
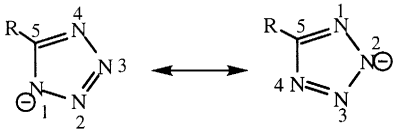
Table 1
Palladium-catalyzed 2-allylated-5-substituted tetrazole synthesis[a]



2 **3** **4**

Entry	Nitrile		Acetate	Product		Yield (%)[b]
1		**2a**	 **3a**		**4a**	93
2		**2b**	**3a**		**4b**	97
3		**2c**	**3a**		**4c**	81
4		**2d**	**3a**		**4d**	79
5[c]	**2a**		 **3b**		**4e**	39
					**4f**	60
6[c]	**2a**		 **3c**		**4g**	99
7[c]	**2a**		 **3d**		**4h**	69
					**4i**	21

[a]Unless otherwise noted, all reactions were conducted with **2** (0.5 mmol), **3** (1.0 mmol) and $TMSN_3$ (0.6 mmol) in the presence of 5 mol % $Pd(PPh_3)_4$ in 3 mL THF at 60°C for 1 day. [b]Isolated yield. [c]The reaction was carried out using 2 equiv. of $TMSN_3$ at 100°C for 1 day.



1a **1b**

As shown in Table 1, the reaction of benzylidenemalononitrile **2a** with trimethylsilyl azide and allyl acetate in the presence of 5 mol% of $Pd(PPh_3)_4$ in THF at 60°C for 24 h gave regiospecifically 2-allyl-5-((*E*)-1-cyano-2-phenylethenyl)tetrazole **4a** in 93% isolated yield (entry 1). The malononitriles **2b** and **2c** gave the corresponding tetrazoles **4b** and **4c** in 91 and 81% yield, respectively (entries 2 and 3). Similarly, 1,1-dicyano-3,3-dimethyl-1-butene **2d** produced the corresponding tetrazole **4d** in 79% yield (entry 4). The reaction of **2a** with crotyl acetate **3b** at 100°C for 1 day gave a 39:60 mixture of the regioisomers **4e** and **4f** (entry 5). However, the reaction of **2a** with methallyl acetate **3c** produced single product **4g** in 99% yield. The reaction of **2a** with cinnamyl acetate **3d** gave the corresponding tetrazole **4h** in 69% yield along with 21% of cinnamyl azide **4i**. The structures of **4a**–**h** were confirmed by ^{1}H NMR, ^{13}C NMR and mass spectrometry and no regioisomeric 1,5-substituted tetrazole derivatives were produced.[9] In addition to those spectroscopic structural determinations, the 2,5-substituted structure of **4a** was unambiguously determined by X-ray crystal structural analysis (Fig. 1).[10] The ORTEP drawing of **4a** illustrates that the tetrazole ring (C1–N4), phenyl ring (C4–C7), and ethylene (C2–C3) are co-planar.

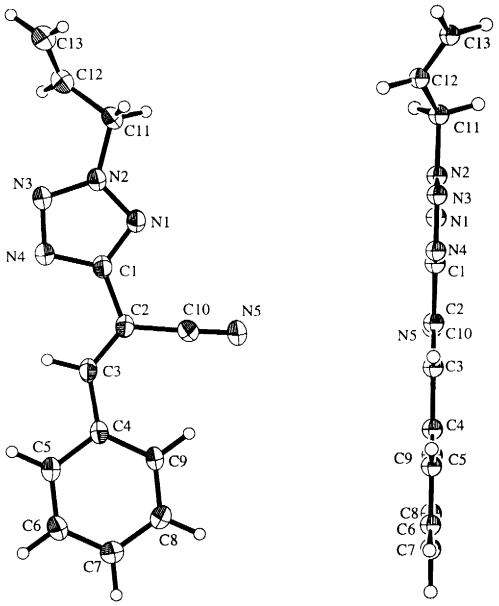


Fig. 1. The ORTEP drawing of **4a**

A mixture of **2a**, **3a**, and $TMSN_3$ in the absence of Pd catalyst were heated at 100°C for 1 day, but the starting materials were recovered. Accordingly, the presence of the Pd catalyst is essential for the present regiospecific tetrazole formation. No reaction took place using nitriles, such as dimethylmalononitrile, benzonitrile, and tetracyanoethylene; the starting materials were recovered. Although the precise mechanism for this unprecedented reaction is not yet known, we are in a position to carry out a regiospecific and convenient one-pot synthesis of 2-allylated-5-substituted tetrazoles from the corresponding alkyl- and arylidenemalononitriles, allyl acetates and trimethylsilyl azide in the presence of tetrakis(triphenylphosphine)palladium catalyst.

General experimental procedure: To a solution of **2a** (0.077 g, 0.5 mmol) and $Pd(PPh_3)_4$ (0.029 g, 0.025 mmol) in THF (3 mL) were added **3a** (0.109 mL, 1.0 mmol) and trimethylsilyl azide (0.079 mL, 0.6 mmol) at room temperature. The resulting mixture was stirred at 60°C for 1 day. The reaction progress was monitored by TLC and GC. When the reaction was complete, the solvent was evaporated and the residue was subjected to silica gel column chromatography using *n*-hexane:ethyl acetate (20:1) as eluent. The tetrazole **4a** was obtained in 93% yield (0.110 g).

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9. Selected data for compound **4a**: ^{1}H NMR ($CDCl_3$) δ 8.34 (s, 1H), 8.01–7.99 (m 2H), 7.53–7.51 (m, 3H), 6.19–6.05 (m, 1H), 5.47–5.41 (m, 2H), 5.29–5.26 (dd, *J*=1.1, 6.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 161.6, 147.2, 132.3, 132.0, 130.0, 129.3, 129.1, 121.4, 115.5, 93.5, 55.7; HRMS calcd for $C_{13}H_{11}N_5$: 237.1014; found: 237.1015. Anal. calcd for $C_{13}H_{11}N_5$: C, 65.81; H, 4.67; N, 29.52; found: C, 66.08; H, 4.93; N, 29.28.
10. Crystal data for compound **4a**: $C_{13}H_{11}N_5$ *M*-237.26, 0.20×0.35×0.40 mm, monoclinic, space group $P2_1/a$ (#14), *a*=7.641(1), *b*=15.317(2), *c*=10.6268(8) Å, β=103.778(9)°, *V*=1208.0(2) Å^3, *Z*=4, D_c=1.304 g cm^{-3}, μ(Mo-Kα)=0.84 cm^{-1}, *T*=286 K, $2\theta_{max}$=52.0°, 2445 reflections measured, 2276 unique (R_{ini}=0.014). The refinement (163 variables) based on full-matrix least-squares with *R*=0.061, R_w=0.070, and *GOF*=3.51 using 1247 unique reflections ($I > 3.00\sigma(I)$).