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Reactions of 2-[Lithio(trimethylsilyl)methyl]-2*H*-tetrazoles: Synthesis of 2-[1-(Trimethylsilyl)alkyl]-2*H*-tetrazoles and (2*H*-Tetrazol-2-yl)acetates

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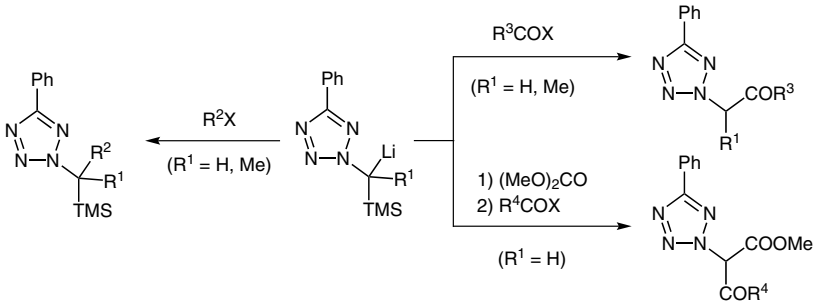

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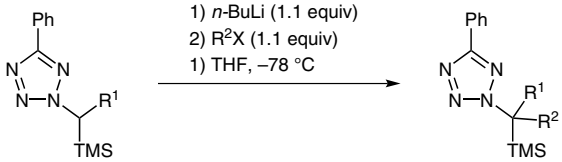
Abstract The reaction of 2-[(trimethylsilyl)methyl]-2*H*-tetrazoles with various alkyl halides and carbonates using *n*-butyllithium or lithium diisopropylamide (LDA) gave 2-[1-(trimethylsilyl)alkyl]-2*H*-tetrazoles and (2*H*-tetrazol-2-yl)acetates as useful synthons of modified tetrazoles.

Key words tetrazoles, synthetic methods, lithiation, synthons

Tetrazoles are heterocyclic compounds used in agrochemicals, materials science, and biochemistry.[1] In addition, some tetrazole derivatives, such as losartan,[2] candesartan,[2c,d] zolarsartan,[2c,d] and varsartan,[2b] play an important role in medicinal chemistry as blockers of the angiotensin II receptor. Other tetrazole derivatives are used as chemotherapeutic agents against certain types of cancer[3] and in the treatment of AIDS.[4] Recently, 2-substituted 2*H*-tetrazoles have been shown to exhibit remarkable biological properties, including hepatitis C serine protease inhibition,[5] metabotropic glutamate receptor antagonism,[6] inhibition of stearoyl-coenzyme A δ-9 desaturase,[7] G-protein coupled receptor agonism,[8] squalene synthase inhibition,[9] and antimicrobial and anticonvulsant activities.[10] These properties directed our research toward the development of a synthetic method for creating functionalized tetrazole derivatives. We recently reported the regioselective 2-arylation of 5-substituted tetrazoles in the preparation of 2-aryl-2*H*-tetrazoles.[11] This report details the functionalization of 2-alkyl-2*H*-tetrazoles by alkylation of the α-carbon on the 2-alkyl group as a useful preparation of 2-functional tetrazoles. To our knowledge, only the analogous reactions with aldehydes and ketones have been reported.[12] We focused on commercially available 2-[(trimethylsilyl)methyl]-2*H*-tetrazole, which was expected to have a higher acidity than the non-TMS-substituted derivative,[13] and found that the reaction of 2-[(trimethylsilyl)methyl]-2*H*-tetrazole with various alkyl halides and carbonates afforded 2-substituted tetrazoles.

We first examined the lithiation of 5-phenyl-2-[(trimethylsilyl)methyl]-2*H*-tetrazole (**1**) followed by alkylation with alkyl halides. The lithiation of **1** with *n*-BuLi was conducted in THF at –78 °C. Subsequent reaction with iodomethane successfully afforded 5-phenyl-2-[1-(trimethylsilyl)ethyl]-2*H*-tetrazole (**2a**) with 90% yield (Table 1, entry 1). 2-[1-(Trimethylsilyl)butyl]-2*H*-tetrazole (**2b**) and 2-[1-(trimethylsilyl)methyl]-2-phenylethyl-2*H*-tetrazole (**2c**) were also obtained in high yields (87–94%; entries 2 and 3). Similarly, 2-[1-methyl-1-(trimethylsilyl)ethyl]-2*H*-tetrazole (**2d**) and 2-[1-methyl-1-(trimethylsilyl)butyl]-2*H*-tetrazole (**2e**) were obtained in good yields (70–72%; entries 4 and 5). The TMS group could be removed by treatment in MeOH under basic conditions.

Table 1 Reaction of 2-[2-(Trimethylsilyl)alkyl]-2*H*-tetrazoles with Alkyl Halide

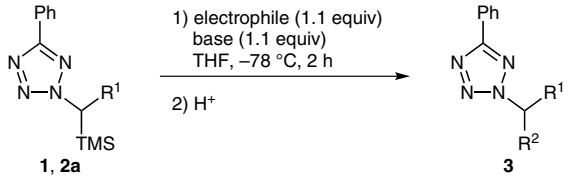


Entry	**1**, **2a**	R^1	R^2X	Time (h)	**2**	Yield (%)[a]
1	**1**	H	MeI	2	**2a**	90
2	**1**	H	*n*-PrI	4	**2b**	87
3	**1**	H	BnBr	2	**2c**	94
4	**2a**	Me	MeI	2	**2d**	70
5	**2a**	Me	*n*-PrI	4	**2e**	72

[a] Isolated yield.

The introduction of a carbonyl function group into a 2-[(trimethylsilyl)methyl]-2*H*-tetrazole derivative was also evaluated. Reactions of 2-[1-(trimethylsilyl)ethyl]-2*H*-tetrazole (**2a**) with several acylating reagents did not yield satisfactory results. Dimethyl carbonate, however, was a successful acylating reagent and yielded methyl 2-(5-phenyl-2*H*-tetrazol-2-yl)propionate (**3a**) with 77% yield (Table 2, entry 1). The analogous reaction with 2-[(trimethylsilyl)methyl]-2*H*-tetrazole (**1**) gave the desired product (**3b**)[14] with only a 34% yield and **1** was recovered with 45% yield (entry 2). Although the reaction of **1** using 1.1 equiv of lithium *N*,*N*-diisopropyl amide (LDA) resulted in 47% yield and the recovery of **1** with 34% yield (entry 3), the use of 2.1 equiv of LDA led to complete reaction, and **3b** was obtained with 88% yield (entry 4). *S*,*S*′-Dimethyl dithiocarbonate was also effective and provided thioester **3c** with 79% yield (entry 5). The reaction of **1** with *N*,*N*-dimethylbenzamide gave ketone **3d**[15] with 64% yield (entry 6), but the same reaction with *N*,*N*-dimethylacetamide gave poor results due to the acidic α-proton of *N*,*N*-dimethylacetamide. No reaction was observed with acetic anhydride (entry 8).

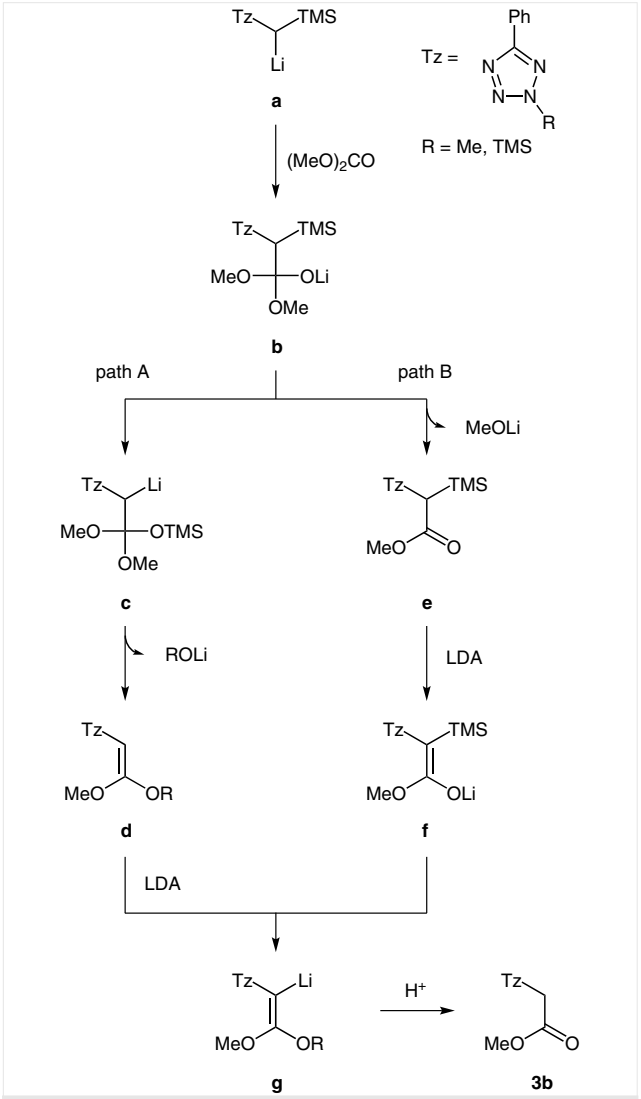
Table 2 Reaction of 2-[1-(Trimethyl)alkyl]-2*H*-tetrazoles with Carbonates



Entry	**1**, **2a**	R^1	Electrophile	Base (equiv)	R^2	**3**	Yield (%)[a]
1	**2a**	Me	$(MeO)_2CO$	*n*-BuLi (1.1)	CO_2Me	**3a**	77
2	**1**	H	$(MeO)_2CO$	*n*-BuLi (1.1)	CO_2Me	**3b**	34[b]
3	**1**	H	$(MeO)_2CO$	LDA (1.1)	CO_2Me	**3b**	47[c]
4	**1**	H	$(MeO)_2CO$	LDA (2.1)	CO_2Me	**3b**	88
5	**1**	H	$(MeS)_2CO$	LDA (2.1)	COSMe	**3c**	79
6	**1**	H	$PhCONMe_2$	LDA (2.1)	COPh	**3d**	64
7	**1**	H	$AcNMe_2$	LDA (2.1)	COMe	**3e**	14[d]
8	**1**	H	Ac_2O	LDA (2.1)	COMe	**3e**	n.r.[e]

[a] Isolated yield.
[b] Starting material was recovered with 45% yield.
[c] Starting material was recovered with 34% yield.
[d] Starting material was recovered with 47% yield.
[e] No reaction.

Two different paths for this series of reactions may be hypothesized (Scheme 1). One is a Peterson type reaction (path A). The reaction of 2-(lithiomethyl)tetrazole (**a**), which is generated from 2-[(trimethylsilyl)methyl]tetrazole (**1**) and LDA, with dimethyl carbonate gives the adduct **b**, which immediately undergoes a Brook rearrangement to yield the intermediate **c**. ROLi (R = Me or TMS) is eliminated from intermediate **c** to form ketene acetal **d**, which reacts again with LDA to give a lithiated ketene acetal **g**.



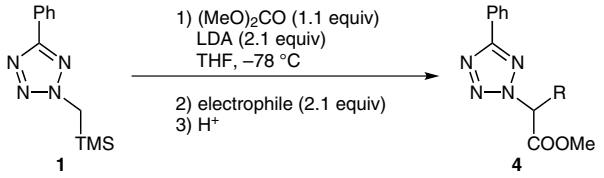
Scheme 1 Proposed mechanisms of esterification

The second proposed pathway proceeds via the ester (path B). Adduct **b** eliminates MeOLi to form ester **e** and a further reaction with LDA affords ketene acetal **f**. Finally, a Brook rearrangement of **f** leads to **g**. Because the acidity of both intermediates **d** and **e** is stronger than that of **1**, starting material remained with the use of 1.1 equiv of LDA.

A multicomponent reaction was evaluated to confirm the possible reaction mechanisms described above (Table 3). The reaction of lithiated ketene acetal, generated from 2-[(trimethylsilyl)methyl]-2*H*-tetrazole (**1**) and dimethyl carbonate, was treated with $ClCO_2Me$ at 10 °C to give dimethyl malonate (**4a**) with 51% yield. Methyl benzyl malonate (**4b**) and methyl *tert*-butyl malonate (**4c**) were also obtained

yields of 46–74% by reactions with $ClCO_2Bn$ and $(Boc)_2O$, respectively. Reaction with Ac_2O also provided the acetylated product **4d** with 75% yield (entry 4).

Table 3 Multicomponent Reaction of 2-[1-(Trimethyl)methyl]-2*H*-tetrazole



Entry	Electrophile	Temp (°C)	Time (h)	R	Yield (%)[a]	
1	$ClCO_2Me$	10	14	CO_2Me	**4a**	51
2	$ClCO_2Bn$	10	14	CO_2Bn	**4b**	46
3	$(Boc)_2O$	10	14	CO_2t-Bu	**4c**	74
4	Ac_2O	r.t.	2	=C(OH)Me	**4d**	75

[a] Isolated yield.

In conclusion, this study demonstrates the reactivity of 2-[lithio(trimethylsilyl)methyl]-2*H*-tetrazoles and the synthesis of 2-[1-(trimethylsilyl)alkyl]-2*H*-tetrazoles or (2*H*-tetrazol-2-yl)acetates, which may be used as synthons of modified tetrazoles.[16–18]

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1378933.

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(16) **Reaction of 2-[2-(Trimethylsilyl)alkyl]-2*H*-tetrazoles with Alkyl Halides; Typical Procedure for 5-Phenyl-2-[1-(trimethylsilyl)ethyl]-2*H*-tetrazole (2a):**
A solution of **1** (0.50 mmol) in anhydrous THF (1 mL) was cooled to –78 °C under an argon atmosphere. *n*-BuLi (1.6 M in *n*-hexane, 0.55 mmol) was added to the suspension dropwise over 30 min, and the mixture was stirred further for 1 h. Iodomethane (0.55 mmol) was added to the mixture, which was stirred at –78 °C for 2 h. After quenching with HCl, the reaction mixture was extracted with EtOAc. The organic layer was washed with H_2O, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to afford **2a** (90%) as a colorless oil.
^1H NMR ($CDCl_3$): δ = 0.15 [s, 9 H, $(CH_3)_3Si$], 1.71 (d, *J* = 7.6 Hz, 3 H, CH_3), 4.52 (q, *J* = 5.6 Hz, 1 H, CH), 7.42–7.53 (m, 3 H, ArH), 8.12–8.20 (m, 2 H, ArH); ^{13}C NMR ($CDCl_3$): δ = –3.50, 16.23, 51.86, 126.73, 127.90, 128.82, 130.00, 164.49; HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{19}N_4Si$: 247.1379; found: 247.1353.

(17) **Preparation of Acetates and Ketones; Typical Procedure for Methyl (5-Phenyl-2*H*-tetrazol-2-yl)acetate (3b):** A mixture of **1** (0.50 mmol) and dimethyl carbonate (0.55 mmol) in anhydrous THF (1 mL) was cooled to –78 °C under an argon atmosphere. LDA (1.1 M in *n*-hexane–THF, 1.05 mmol) was added to the suspension dropwise over 60 min. After stirring for 2 h at –78 °C, HCl (1.0 M, 3 mL) was added to the mixture. The mixture was allowed to reach r.t., and stirred for 30 min. The reaction mixture was extracted with EtOAc and the organic layer was

washed with H_2O, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to afford **3b** (88%) as a white solid.
Mp 97–98 °C (*n*-hexane–$CHCl_3$) (Lit.[14] 93–94 °C); IR (ATR): 1756 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 3.83 (s, 3 H, $COOCH_3$), 5.48 (s, 2 H, CH_2), 7.47–7.53 (m, 3 H, ArH), 8.13–8.20 (m, 2 H, ArH); ^{13}C NMR ($CDCl_3$): δ = 53.23, 53.31, 127.01, 127.04, 128.93, 130.56, 165.53, 165.71; HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{11}N_4O_2$: 219.0882; found: 219.0872.

(18) **Multicomponent Reaction of 2-[1-(Trimethylsilyl)methyl]-2*H*-tetrazole; Typical Procedure for Dimethyl 2-(5-Phenyl-2*H*-tetrazol-2-yl)malonate (4a):** A mixture of **1** (0.50 mmol) and dimethyl carbonate (0.55 mmol) in anhydrous THF (1 mL) was cooled to –78 °C under an argon atmosphere. LDA (1.1 M in *n*-hexane–THF, 1.05 mmol) was added to the suspension dropwise over 30 min. After stirring for 30 min, methyl chloroformate (1.05 mmol) was added to the mixture. The mixture allowed to reach 10 °C slowly, and stirred overnight. After quenching with HCl, the reaction mixture was extracted with EtOAc and the organic layer was washed with H_2O, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to afford **4a** (51%) as a colorless oil.
IR (ATR): 1752 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 3.91 (s, 6 H, $COOCH_3$), 6.37 (s, 1 H, CH), 7.47–7.51 (m, 3 H, ArH), 8.16–8.22 (m, 2 H, ArH); ^{13}C NMR ($CDCl_3$): δ = 54.13, 66.61, 126.73, 127.14, 128.87, 130.70, 162.51, 165.69; HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{13}N_4O_2$: 277.0937; found: 277.0927.