An Efficient Synthesis of 2-Diazo-2-(trimethylsilyl)ethanols and Their Application to Pyrazole Synthesis

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Abstract: Reaction of diazo(trimethylsilyl)methylmagnesium bromide with aldehydes or ketones gave 2-diazo-2-(trimethylsilyl)ethanols, which were applied to the synthesis of di- and trisubstituted pyrazoles via [3+2] cycloaddition reaction with ethyl propiolate or dimethyl acetylenedicarboxylate.

Key words: diazoalcohol, 2-diazo-2-(trimethylsilyl)ethanols, diazo(trimethylsilyl)methylmagnesium bromide, pyrazoles, trimethylsilyldiazomethane

a-Trimethylsilylated diazo compounds are very useful and attractive building blocks in organic synthesis. For example, trimethylsilyldiazoacetates have been reported to be applicable to the aldol reaction with aldehydes,¹ the synthesis of α -trimethylsilyl- α -amino acids² and α -trimethylsilyltetrahydrofurans,³ and so on.⁴ Furthermore, α trimethylsilyldiazoketones and 1-diazo-1-(trimethylsilyl)alkanes, involving trimethylsilyldiazomethane (TMSCHN₂), have also been used for various synthetic processes.⁵⁻⁷ However, concerning 2-diazo-2-(trimethylsilyl)ethanols, there is only one report; in it, Schöllkopf et al. described that 2-diazo-2-(trimethylsilyl)ethanols could be synthesized by the reaction of carbonyl compounds with lithium trimethylsilyldiazomethane [TMSC(Li)N₂] in moderate yield and the resulting 2-diazo-2-(trimethylsilyl)ethanols afforded trimethylsilyloxiranes with spontaneous expulsion of N_2 at room temperature (Scheme 1).⁸ To date, the synthetic application of 2-diazo-2-(trimethylsilyl)ethanols is almost unexplored.

Recently, we reported the one-pot synthesis of cis- β -trimethylsilyl- α , β -epoxy esters from α -keto esters using the magnesium bromide salt of TMSCHN₂ [TMSC(Mg-Br)N₂].⁹ In this study, we found that the reaction of TMSC(MgBr)N₂ with ethyl 4-phenyl-2-oxobutanoate at -78 °C efficiently gave the corresponding trimethylsilylated diazoalcohol in high yield as an isolable product while the reaction with TMSC(Li)N₂ gave a complex mixture (Scheme 2). From these results, we envisaged that TMSC(MgBr)N₂ would also react with simple aldehydes and ketones to give the corresponding 2-diazo-2-(trimethylsilyl)ethanols. This paper describes our results on the synthesis of 2-diazo-2-(trimethylsilyl)ethanols using TMSC(MgBr)N₂ and their application to the pyrazole synthesis¹⁰ by [3+2]-cycloaddition reaction with ethyl propiolate or dimethyl acetylenedicarboxylate (DMAD).

First, we examined the reaction conditions using TMSC(Li)N₂ or TMSC(MgBr)N₂, 4-chlorobenzaldehyde and DMAD as a model system (Table 1). According to Schöllkopf's method,⁸ the 2-diazo-2-(trimethylsilyl)ethanol (2a) (58% yield) was prepared from the aldehyde 1a and subsequent [3+2] cycloaddition of 2a with DMAD was carried out, but the yield of desired trisubstituted pyrazole 3a was very low (20% yield from 1a) (Table 1, entry 1). This low yield was presumably due to the decomposition of 2a by a trace amount of remaining AcOH used as a quencher.¹¹ When H₂O or aqueous saturated NH₄Cl was used as a quencher instead of AcOH, the reaction gave a complex mixture and 2a was not obtained (Table 1, entries 2 and 3). However, as expected, replacement of TMSC(Li)N₂ by TMSC(MgBr)N₂ caused a dramatic improvement in both reactions, and 2a and 3a were obtained in high yields (Table 1, entry 4).



Scheme 1 An example of 2-diazo-2-(trimethylsilyl)ethanols



Scheme 2 Reaction of $TMSC(M)N_2$ (M = Li or MgBr) with ethyl 4-phenyl-2-oxobutanoate

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CI CHO 1a	i) TMSC(M)N ₂ (1.2 equiv), THF -78 °C, 1.5 h ii) quencher	OH TMS DMAD (2.0 equiv) THF reflux, 1 d		Me
Entry	TMSC(M)N ₂	Quencher	Yield (%) of 2a ^a	Yield (%) of 3a ^b
1	TMSC(Li)N ₂	AcOH (1.2 equiv)	58	20
2	TMSC(Li)N ₂	H ₂ O	_c	_
3	TMSC(Li)N ₂	aq sat. NH ₄ Cl	_c	_
4	TMSC(MgBr)N ₂	H ₂ O	quant	80

^a The purity was confirmed by ¹H NMR measurement.

^b Isolated yield from **1a**.

^c The reaction gave a complex mixture.

 Table 2
 2-Diazo-2-trimethylsilylethanols 2
 Prepared

R ¹ COR ²	i) TMSC(MgBr)N ₂ (1.2 equiv), THF –78 °C, 1.5 h ii) H ₂ O	$R^{1} \qquad R^{2} \qquad N_{2}$	MS	
Entry	Substrate		Product	Yield (%) ^a
	\mathbf{R}^1	\mathbb{R}^2		
1	4-ClC ₆ H ₄	Н	2a	quant
2	Ph	Н	2b	quant
3	4-MeOC ₆ H ₄	Н	2c	quant
4	<i>t</i> -Bu	Н	2d	93
5	Ph	Me	2e	94
6	PhCH ₂ CH ₂	Me	2f	quant

^a The purity was confirmed by ¹H NMR measurement.

Next, under optimized conditions, generality for the synthesis of 2-diazo-2-(trimethylsilyl)ethanols was examined (Table 2). Various aldehydes 1b-d including aromatic and aliphatic ones smoothly reacted with TMSC(Mg- $Br)N_2$ to give the corresponding 2-diazo-2-(trimethylsilyl)ethanols 2b-d in nearly quantitative yields, respectively (Table 2, entries 2-4). Ketones such as acetophenone (1e) and 4-phenylbutan-2-one (1f) also underwent the reaction to afford 2e and 2f in high yields (Table 2, entries 5 and 6). Finally, the pyrazole synthesis using 2 was examined and the results were summarized in Table 3. Analogous to 2a, the diazoalcohol 2f derived from the ketone 1f reacted with DMAD to give the trisubstituted pyrazole 3f in high yield (83%) (Table 3, entries 1 and 2). Ethyl propiolate could also be used as a dipolarophile. Thus, the reaction of 2a with ethyl propiolate smoothly proceeded to give the 3,5-disubstituted pyrazole 4a in high yield with high regioselectivity and its regioisomer was not produced in detectable amounts (Table 3, entry 3).¹² It has already been reported that the reaction of TMSCHN₂ with methyl but-2-ynoate furnished a mixture of regioisomers.¹³ The observed high regioselectivity in the synthesis of 4a is presumably due to the steric repulsion between the (4-chlorophenyl)(hydroxy)methyl and TMS groups of 2a, and the ethoxycarbonyl group of a dipolarophile. Other 2-diazo-2-(trimethylsilyl)ethanols 2b-f regioselectively afforded the corresponding pyrazoles **4b–f** in good to high yields in two steps (entries 4– 8 in Table 3).¹²

In conclusion, we have found that $TMSC(MgBr)N_2$ is a quite useful reagent for the synthesis of 2diazo-2-(trimethylsilyl)ethanols from aldehydes and ketones. Moreover, the present method described above makes possible the synthesis of polysubstituted pyrazoles from aldehydes or ketones in two steps and will provide an added flexibility in the pyrazole synthesis.

All melting points were measured on a Yanagimoto micro melting points apparatus and are uncorrected. IR spectra were recorded on a Shimadzu FTIR-8400S spectrophotometer. ¹H and ¹³C NMR spectra were recorded on a Jeol JNM-EX-270 spectrometer (¹H, 270 MHz; ¹³C, 67.8 MHz). MS spectra (bp = base peak) were recorded on a Jeol JMS-SX-102A spectrometer. A solution of MgBr₂ in Et₂O-toluene (1:1) was prepared from MgBr₂ etherate (Aldrich) dried well under reduced pressure at 100 °C, and freshly distilled Et₂O (from Na/benzophenone ketyl) and toluene (from CaH₂). Carbonyl compounds 1a-f were distilled prior to use. THF was distilled from Na/benzophenone ketyl prior to use.

Dimethyl 3-[(4-Chlorophenyl)(trimethylsilyloxy)methyl]-1Hpyrazole-4,5-dicarboxylate (3a) Using TMSC(Li)N₂

Under argon, n-BuLi (1.65 M in hexane solution, 0.73 mL, 1.20 mmol) was added to a solution of TMSCHN₂ (1.73 M in hexane solution, 0.70 mL, 1.20 mmol) in THF (4 mL) at -78 °C and the mixture was stirred at -78 °C for 20 min. A solution of 4chlorobenzaldehyde (1a; 141 mg, 1.00 mmol) in THF (1 mL) was added to the above mixture at -78 °C and the mixture was further stirred at -78 °C for 1.5 h. After addition of a solution of AcOH (69 μ L, 1.20 mmol) in THF (1 mL) and dilution with H₂O at -78 °C, the mixture was extracted with EtOAc (3×30 mL). The organic ex-





Entry	Substrate		Alkyne	Product	Yield (%) ^a
	\mathbb{R}^1	R ²			
1	4-ClC ₆ H ₄	Н	$R^3 = R^4 = CO_2Me$	3a	80
2	PhCH ₂ CH ₂	Me	$R^3 = R^4 = CO_2 Me$	3f	83
3	$4-ClC_6H_4$	Н	$R^3 = H, R^4 = CO_2Et$	4a	81
4	Ph	Н	$R^3 = H, R^4 = CO_2Et$	4b	65
5	4-MeOC ₆ H ₄	Н	$R^3 = H, R^4 = CO_2Et$	4c	78
6	<i>t</i> -Bu	Н	$R^3 = H, R^4 = CO_2Et$	4d	66
7	Ph	Me	$R^3 = H, R^4 = CO_2Et$	4e	77
8	PhCH ₂ CH ₂	Me	$R^3 = H, R^4 = CO_2Et$	4f	92

^a Isolated yield from 1.

tracts were washed successively with $H_2O(10 \text{ mL})$, aq sat. NaHCO₃ (10 mL), $H_2O(10 \text{ mL})$, and brine (10 mL), and dried (Na₂SO₄). The concentration of the solvent in vacuo gave **2a** (148 mg, 58%), which was dissolved in THF (5 mL), and dimethyl acetylenedicarboxylate (0.24 mL, 2.00 mmol) was added. After refluxing for 1 day, the mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane–EtOAc, 3:1) to give **3a** (79 mg, 20% from **1a**). For analytical and spectral data: see below.

Pyrroles 3 and 4 Using TMSC(MgBr)N₂; Dimethyl 3-[(4-Chlorophenyl)(trimethylsilyloxy)methyl]-1*H*-pyrazole-4,5-dicarboxylate (3a);

Typical Procedure

Under argon, n-BuLi (1.57 M in hexane solution, 0.37 mL, 0.58 mmol) was added to a solution of TMSCHN2 (1.80 M in hexane solution, 0.32 mL, 0.58 mmol) in THF (3.5 mL) at -78 °C and the mixture was stirred at -78 °C for 20 min. After the addition of MgBr₂ [1.43 M in toluene-Et₂O (1:1) solution, 0.41 mL, 0.58 mmol], the mixture was further stirred at -78 °C for 10 min. A solution of 4-chlorobenzaldehyde (1a; 68 mg, 0.49 mmol) in THF (0.5 mL) was added to the above mixture at -78 °C and the mixture was further stirred at -78 °C for 1.5 h. After the addition of H₂O at -78 °C, the mixture was extracted with EtOAc (3 × 30 mL). The organic extracts were washed with H₂O (10 mL) and brine (10 mL), and dried (Na₂SO₄). The concentration of the solvent in vacuo gave 2a (124 mg, quant), which was dissolved in THF (2 mL), and dimethyl acetylenedicarboxylate (0.114 mL, 0.93 mmol) was added. After refluxing for 1 day, the mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane-EtOAc, 4:1) to give **3a** (153 mg, 80% from **1a**).

1-(4-Chlorophenyl)-2-diazo-2-(trimethylsilyl)ethanol (2a) Yield: >99%; yellow oil.

IR (neat): 3408, 2046 cm⁻¹.

¹H NMR (DMSO- d_6): $\delta = 0.11$ (9 H, s), 5.23 (1 H, d, J = 4.6 Hz), 5.88 (1 H, d, J = 4.6 Hz), 7.33–7.41 (4 H, m).

MS (EI): $m/z = 228 (M^+ - N_2), 226 (M^+ - N_2), 73 (bp).$

HRMS (EI): m/z calcd for $C_{11}H_{15}^{35}$ ClOSi (M⁺ – N₂): 226.0586; found: 226.0581; m/z calcd for $C_{11}H_{15}^{37}$ ClOSi (M⁺ – N₂): 228.0568; found: 228.0551.

2-Diazo-1-phenyl-2-(trimethylsilyl)ethanol (2b)

Yield: >99%; orange oil. IR (neat): 3398, 2044 cm⁻¹.

¹H NMR (CD₂Cl₂): δ = 0.17 (9 H, s), 2.07 (1 H, s), 5.30 (1 H, s), 7.30–7.37 (5 H, m).

MS (EI): $m/z = 220 (M^+)$, 192 (M⁺ – N₂), 73 (bp).

HRMS (EI): m/z calcd for $C_{11}H_{16}OSi$ (M⁺ – N₂): 192.0988; found: 192.0971.

2-Diazo-1-(4-methoxyphenyl)-2-(trimethylsilyl)ethanol (2c) Yield: >99%; yellow oil.

IR (neat): 3481, 2042 cm⁻¹.

¹H NMR (CD₂Cl₂): δ = 0.18 (9 H, s), 1.55 (1 H, s), 3.80 (3 H, s), 5.30 (1 H, s), 6.87–6.91 (2 H, m), 7.28–7.32 (2 H, m).

MS (EI): $m/z = 222 (M^+ - N_2)$, 121 (bp).

HRMS (EI): m/z calcd for $C_{12}H_{18}O_2Si$ (M⁺ – N₂): 222.1058; found: 222.1076.

1-Diazo-3,3-dimethyl-1-(trimethylsilyl)butan-2-ol (2d) Yield: 93%; yellow oil.

IR (neat): 3454, 2042 cm⁻¹.

¹H NMR (CD₂Cl₂): $\delta = 0.18$ (9 H, s), 0.98 (9 H, s), 1.68 (1 H, s). MS (EI): m/z = 127 (M⁺ – TMS), 73 (bp).

1-Diazo-2-phenyl-1-(trimethylsilyl)propan-2-ol (2e) Yield: 94%; yellow oil.

IR (neat): 3446, 2039 cm⁻¹.

¹H NMR (CD₂Cl₂): δ = 0.07 (9 H, s), 1.73 (3 H, s), 2.04 (1 H, s), 7.25–7.37 (5 H, m).

MS (EI): m/z = 234 (M⁺), 206 (M⁺ – N₂), 73 (bp).

HRMS (EI): m/z calcd for $C_{12}H_{18}OSi (M^+ - N_2)$: 206.1127; found: 206.1127.

1-Diazo-2-methyl-4-phenyl-1-(trimethylsilyl)butan-2-ol (2f) Yield: >99%; yellow oil.

IR (neat): 3435, 2039 cm⁻¹.

¹H NMR (CD₂Cl₂): δ = 0.25 (9 H, s), 1.47 (3 H, s), 1.62 (1 H, s), 1.91–1.98 (2 H, m), 2.69–2.77 (2 H, m), 7.18–7.28 (5 H, m).

MS (EI): $m/z = 234 (M^+ - N_2)$, 73 (bp).

HRMS (EI): m/z calcd for $C_{14}H_{22}OSi (M^+ - N_2)$: 234.1420; found: 234.1440.

Dimethyl 3-[(4-Chlorophenyl)(trimethylsilyloxy)methyl]-1*H*pyrazole-4,5-dicarboxylate (3a)

Yield: 80%; pale yellow oil.

IR (neat): 3284, 1738, 1728 cm⁻¹.

¹H NMR (CDCl₃): δ = 0.08 (9 H, s), 3.78 (3 H, s), 3.92 (3 H, s), 6.58 (1 H, s), 7.28 (4 H, m), 11.21 (1 H, br).

¹³C NMR (CDCl₃): δ = -0.1, 51.8, 52.6, 58.6, 109.8, 118.2, 127.9, 128.5, 133.9, 139.3, 150.1, 162.1, 162.5.

MS (EI): *m*/*z* = 398 (M⁺), 396 (M⁺), 364 (bp).

HRMS (EI): m/z calcd for $C_{17}H_{21}^{35}CIN_2O_5Si$ (M⁺): 396.0879; found: 396.0893; m/z calcd for $C_{17}H_{21}^{37}CIN_2O_5Si$ (M⁺): 398.0879; found: 398.0895.

Dimethyl 3-[4-Phenyl-2-(trimethylsilyloxy)butan-2-yl]-1*H*pyrazole-4,5-dicarboxylate (3f)

Yield: 83%; pale yellow oil.

IR (neat): 3326, 1738, 1730 cm⁻¹.

 1H NMR (CDCl₃): δ = 0.26 (9 H, s), 1.75 (3 H, s), 2.02–2.27 (2 H, m), 2.45–2.63 (2 H, m), 3.85 (3 H, s), 3.93 (3 H, s), 7.06–7.26 (5 H, m), 10.8 (1 H, br).

¹³C NMR (CDCl₃): δ = 2.5, 28.9, 30.5, 43.9, 52.2, 52.5, 109.9, 125.7, 128.1, 128.2, 141.3, 151.5, 162.1, 163.9.

MS (EI): $m/z = 389 (M^+ - Me)$, 282 (bp).

HRMS (EI): m/z calcd for $C_{19}H_{25}N_2O_5Si$ (M⁺ – Me): 389.1529; found: 389.1533.

Ethyl 3-[(4-Chlorophenyl)(trimethylsilyloxy)methyl]-1*H*-pyrazole-5-carboxylate (4a)

Yield: 81%; yellow oil.

IR (neat): 3287, 1728 cm⁻¹.

¹H NMR (CDCl₃): $\delta = 0.11$ (9 H, s), 1.37 (3 H, t, J = 7.1 Hz), 4.36 (2 H, q, J = 7.1 Hz), 5.86 (1 H, s), 6.61 (1 H, s), 7.28 (4 H, m), 10.40 (1 H, br).

¹³C NMR (CDCl₃): δ = 0.1, 14.3, 61.2, 69.9, 106.0, 127.4, 127.4, 128.5, 128.5, 133.3, 141.0, 160.6.

MS (EI): m/z = 354 (M⁺), 352 (M⁺), 291 (bp).

HRMS (EI): m/z calcd for $C_{16}H_{21}^{35}ClN_2O_3Si$ (M⁺): 352.1010; found: 352.1009; m/z calcd for $C_{17}H_{21}^{37}ClN_2O_3Si$ (M⁺): 354.0981; found: 354.1001.

Ethyl 3-[Phenyl(trimethylsilyloxy)methyl]-1*H*-pyrazole-5-carboxylate (4b)

Yield: 65%; pale yellow oil.

IR (neat): 3277, 1725 cm⁻¹.

¹H NMR (CDCl₃): δ = 0.10 (9 H, s), 1.36 (3 H, t, *J* = 7.1 Hz), 4.35 (2 H, q, *J* = 7.1 Hz), 5.89 (1 H, s), 6.61 (1 H, s), 7.27–7.35 (5 H, m), 10.52 (1 H, br).

¹³C NMR (CDCl₃): δ = 0.1, 14.3, 61.1, 70.4, 105.9, 126.1, 127.7, 128.3, 142.2, 161.0.

MS (EI): m/z = 318 (M⁺), 303 (M⁺ – Me), 257 (bp).

HRMS (EI): m/z calcd for $C_{16}H_{22}N_2O_3Si$ (M⁺): 318.1400; found: 318.1366.

Ethyl 3-[(4-Methoxyphenyl)(trimethylsilyloxy)methyl]-1*H*-pyrazole-5-carboxylate (4c)

Yield: 78%; pale yellow oil.

IR (neat): 3281, 1717 cm⁻¹.

¹H NMR (CDCl₃): δ = 0.09 (9 H, s), 1.36 (3 H, t, *J* = 7.1 Hz), 3.79 (3 H, s), 4.35 (2 H, q, *J* = 7.1 Hz), 5.88 (1 H, s), 6.61 (1 H, s), 6.86 (2 H, d, *J* = 8.4 Hz), 7.28 (2 H, d, *J* = 8.4 Hz), 11.05 (1 H, br).

¹³C NMR (CDCl₃): δ = 0.1, 14.3, 55.2, 61.0, 70.0, 105.7, 113.7, 127.5, 134.4, 140.2, 151.7, 159.0, 161.1.

MS (EI): m/z = 348 (M⁺), 333 (M⁺ – Me), 287 (bp).

HRMS (EI): m/z calcd for $C_{17}H_{24}N_2O_4Si$ (M⁺): 348.1505; found: 348.1505.

Ethyl 3-[2,2-Dimethyl-1-(trimethylsilyloxy)propyl]-1*H*-pyr-azole-5-carboxylate (4d)

Yield: 66%; colorless crystals (hexane–EtOAc); mp 133–134 °C. IR (neat): 3177, 1730 cm⁻¹.

¹H NMR (CDCl₃): δ = 0.03 (9 H, s), 0.88 (9 H, s), 1.38 (3 H, t, *J* = 7.1 Hz), 4.43 (2 H, q, *J* = 7.1 Hz), 6.65 (1 H, s), 10.70 (1 H, br). ¹³C NMR (CDCl₃) δ = -0.2, 14.4, 25.6, 35.9, 61.0, 75.6, 106.3, 144.2, 145.3, 161.8.

MS (EI): m/z = 298 (M⁺), 283 (M⁺ – Me), 241 (bp).

Anal. Calcd for $C_{14}H_{26}N_2O_3Si$: C, 56.34; H, 8.78; N, 9.39. Found: C, 56.32; H, 8.90; N, 9.43.

Ethyl 3-[1-Phenyl-1-(trimethylsilyloxy)ethyl]-1*H*-pyrazole-5-carboxylate (4e)

Yield: 77%; pale yellow oil.

IR (neat): 3274, 1724 cm⁻¹.

¹H NMR (CDCl₃): δ = 0.06 (9 H, s), 1.38 (3 H, t, *J* = 7.1 Hz), 1.99 (3 H, s), 4.37 (2 H, q, *J* = 7.1 Hz), 6.68 (1 H, s), 7.22–7.31 (3 H, m), 7.36–7.39 (2 H, m), 10.97 (1 H, br).

¹³C NMR (CDCl₃): δ = 1.9, 14.3, 30.2, 61.1, 74.7, 105.8, 125.1, 127.1, 128.0, 140.8, 146.7, 154.3, 161.4.

MS (EI): $m/z = 317 (M^+ - Me, bp)$.

HRMS (EI): m/z calcd for $C_{16}H_{21}N_2O_3Si$ (M⁺ – Me): 317.1324; found: 317.1322.

Ethyl 3-[4-Phenyl-2-(trimethylsilyloxy)butan-2-yl]-1*H*-pyrazole-5-carboxylate (4f) Yield: 92%; pale yellow oil.

IR (neat): 3291, 1728 cm⁻¹.

¹H NMR (CDCl₃): δ = 0.17 (9 H, s), 1.41 (3 H, t, *J* = 7.1 Hz), 1.69 (3 H, s), 2.09 (2 H, t, *J* = 8.7 Hz), 2.32–2.37 (1 H, m), 2.57–2.68 (1 H, m), 4.40 (2 H, q, *J* = 7.1 Hz), 6.66 (1 H, s), 7.07–7.26 (5 H, m).

¹³C NMR (CDCl₃): δ = 2.4, 14.4, 22.7, 30.5, 46.6, 61.1, 74.4, 104.2, 125.7, 128.1, 128.2, 141.6, 142.0, 153.4, 161.7.

MS (EI): m/z = 345 (M⁺ – Me), 317 (bp).

HRMS (EI): m/z calcd for $C_{18}H_{25}N_2O_3Si$ (M⁺ – Me): 345.1643; found: 345.1635.

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- (7) Reactions using 1-diazo-1-trimethylsilylalkanes except for TMSCHN₂: (a) Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* 1986, 27, 2005. (b) Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* 1988, 29, 6295. (c) Aoyama, T.; Shioiri, T. *Chem. Pharm. Bull.* 1989, 37, 2261. (d) Han, S.; Kass, S. R. J. Chem. Soc., Perkin Trans. 1 1999, 1553.
- (8) Schöllkopf, U.; Scholz, H.-U. Synthesis 1976, 271.
- (9) Hari, Y.; Tsuchida, S.; Aoyama, T. *Tetrahedron Lett.* **2006**, *47*, 1977.
- (10) For a review: Elguero, J. Comprehensive Heterocyclic Chemistry II, Vol. 3; Shinkai, I., Ed.; Elsevier: Oxford, 1996, 1–75.
- (11) When, during the workup of **2a**, the organic extracts were not washed with aq sat. NaHCO₃, no final product **3a** was obtained after the reaction with DMAD.
- (12) The position of the ethoxycarbonyl group in **4** was determined by NOE measurement (Figure 1). For example:



Figure 1 NOE data for 4

(13) Chan, K. S.; Wulff, W. D. J. Am. Chem. Soc. 1986, 108, 5229.