Synthesis of 2-Pyrazoline-5-Carboxylic Acid Derivatives Using Trimethylsilyldiazomethane

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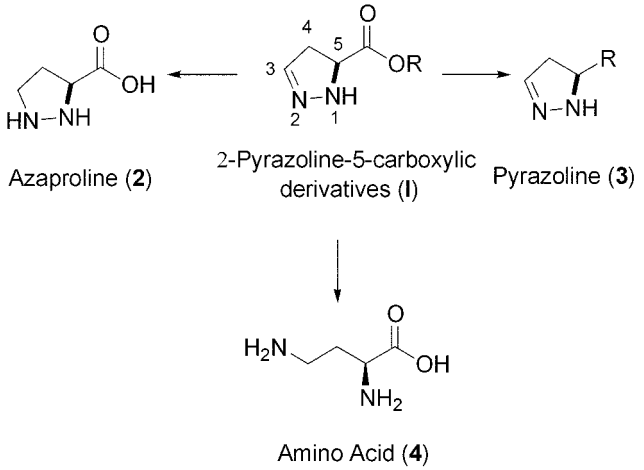
Received November 5, 2004

Key Words : 2-Pyrazoline-5-carboxylic acid derivatives, [2+3] Cycloaddition, Trimethylsilyldiazomethane

1,3-Dipolar cycloaddition reaction of α,β-unsaturated esters, amides or nitriles with diazomethane or trimethylsilyldiazomethane can be one of the powerful methods for the synthesis of pyrazoline building blocks, particularly, 2-pyrazoline-5-carboxylic ester (**1**), amide or nitrile which can be used as chiral precursors in the preparation of several unnatural amino acids (**2** and **4**)[1-4] and as building blocks, pyrazoline derivative (**3**), for the asymmetric synthesis.

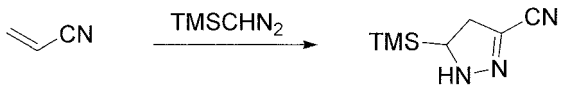


Scheme 1

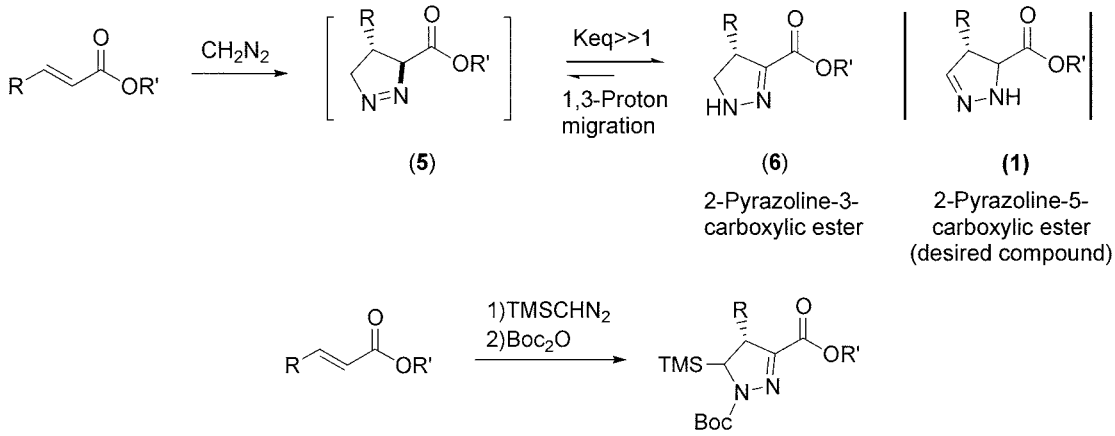
But, prior studies[3-5] on the cycloadditions of α,β-unsaturated ester with diazoalkanes or trimethylsilyldiazomethane had indicated that the pyrazoline (**5**) initially formed in such cycloadditions readily isomerized (1,3-proton migration) to the corresponding conjugated 2-pyrazoline-3-carboxylic ester (**6**), not to the desired 2-pyrazoline-5-carboxylic ester (**1**) (Scheme 2).

Also, reaction of α,β-unsaturated nitrile with trimethylsilyldiazomethane gave the same result (Scheme 3)[6] and so far no single example has been reported for the cycloaddition of diazomethane or trimehtylsilyldiazomethane with α,β-unsaturated amide for the synthesis of 2-pyrazoline-5-carboxamide.

These reports prompted us to attempt synthesis of 2-pyrazoline-5-carboxylic ester, amide and nitrile through controlling the reaction before 1,3-proton migration. Therefore, under several conditions, we investigated cycloaddition reaction of α,β-unsaturated ester, amide and nitrile with trimethylsilyldiazomethane.

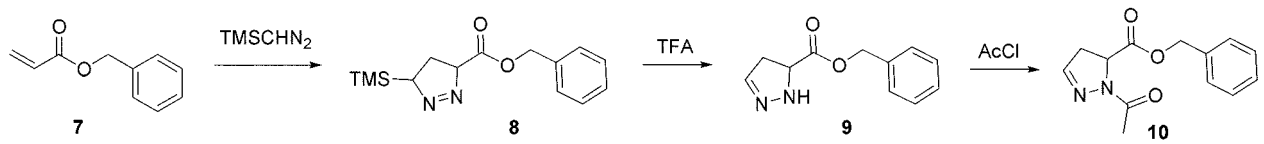


Scheme 3



Scheme 2

Table 1. Reaction of benzyl acrylate with trimethylsilyldiazomethane



Entry	Benzyl acrylate (eq.)	$TMSCHN_2$ (eq.)	Temp.	Rxn time	TFA (eq.)	Overall Yield (%)[a]
1	1	3	0 °C	3 h	3	88
2	1	3	room temp.	3 h	3	85
3	1	3	80 °C	3 h	3	29
4	1	2	room temp.	3 h	3	85
5	1	1.5	room temp.	3 h	3	85
6	1	1	room temp.	3 h	3	78

[a]Isolated yield

As a model test, we tried the reaction of benzyl acrylate and trimethylsilyldiazomethane, and a final compound was isolated after *N*-protection with acetyl group. The results were summarized in Table 1.

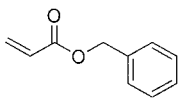
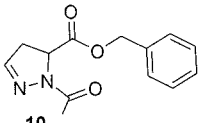
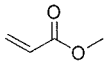
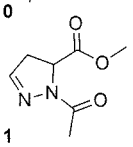
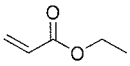
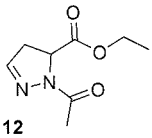
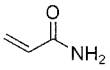
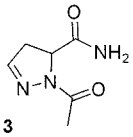
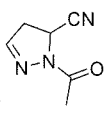
As we hoped, the reactions performed at 0 °C or room temperature provided the desired benzyl 2-pyrazoline-5-carboxylate (**10**) in 88% and 85% yields, respectively. (entries 1 and 2) It is noteworthy that benzyl 2-pyrazoline-5-carboxylate (**10**) was directly synthesized from benzyl acrylate and trimethylsilyldiazomethane without 1,3-migration. Whereas, the yield was decreased to 29% when the reaction was run at 80 °C. This result suggested that initially formed 1-pyrazoline was converted to 2-pyrazoline-3-carboxylic ester and by-products at high temperature. Use of 1.5 eq or 1.2 eq of trimethylsilyldiazomethane also gave satisfactory results. Based on these preliminary results, the application of this procedure to α,β-unsaturated esters, amide or nitrile was investigated.

As shown in Table 2, benzyl, methyl and ethyl acrylate afforded the corresponding 2-pyrazoline-5-carboxylic esters in moderate to good yields (entries 7-9, 80-91%). Acrylamide cyclized to give 2-pyrazoline-5-amide in 60% yield. (entry 10) Also, acrylonitrile was smoothly converted to the corresponding 2-pyrazoline-5-nitrile. (entry 11)

Next stage was the adoption of chirality at 5-position of 2-pyrazoline-5-ester. There have been reports by two groups that chiral alkene (alkenoyl oxazolidinone[7] or ankenoyl sultam[4]) was treated with trimethylsilyldiazomethane to yield chiral 5-substituted pyrazoline, but they used an expensive camphorsultam[4] or commercially unavailable ligand (DBFOX/Ph).[7] Therefore, we investigated the reaction of chiral α,β-unsaturated ester with trimethylsilyl diazomethane.

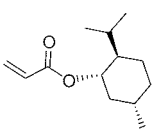
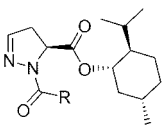
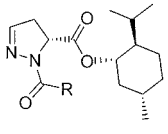
As shown in Table 3, when (1*S*, 2*R*, 5*S*)-(+)-menthol was used as a chiral auxiliary, although none of diastereoselectivity was obtained (1 : 1), both of diastereomers were easily separated by column chromatography. To determine the absolute configuation, NOE experiments carried out with diastereomeric **15a** and **15b**.

Table 2. Reaction of α,β-unsaturated carboxylic derivative with $TMSCHN_2$

Entry	Substrate	Time	Product	Yield[a]
7		tol:Hex, rt 3 h	 **10**	85%
8		tol:Hex, rt 3 h	 **11**	80%
9		tol:Hex, rt 3 h	 **12**	91%
10		tol:Hex, rt 15 h	 **13**	60%
11		tol:Hex, rt 3 h	 **14**	70%

[a]Isolated yield

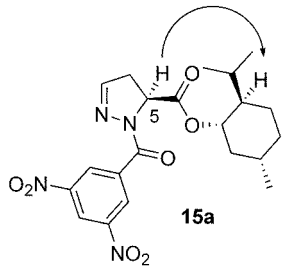
Table 3. Reaction of α,β-unsaturated carboxylic derivative with $TMSCHN_2$

Substrate	Product		yield[a]
	 **15a**	 **15b**	86%

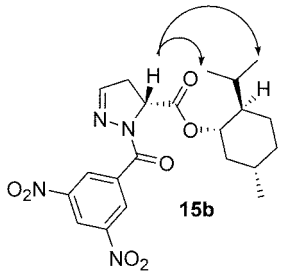
R = 3,5-dinitrophenyl 43% : 43%
Diastereomers were easily seperated by column chromatography

R = Phenyl 43% : 43%
Diastereomers were seperated by column chromatography

[a]Isolated yield



15a



15b

In the case of compound **15a**, the proton at C5 of pyrazoline ring and methine proton of menthol showed a positive NOE effect (0.96%). Also, in **15b**, the proton at C5 of pyrazolin ring and methyl proton of menthol indicated a NOE effect. So, pyrazoline **15a** and **15b** possess S and R configuration, respectively.

Meanwhile, using (−)-8-phenylmenthol, under the same reaction conditions, diasteroselectivtiy was 6 : 4. (data not shown)

In conclusion, we have directly synthesized 2-pyrazoline-5-carboxylic ester, amide and nitrile using trimethylsilyl-diazomethane from the corresponding α,β-unsaturated ester, amide and nitrile.

Experimental Procedure

Typical procedure for the preparation of 2-pyrazoline-5-carboxylic derivatives. To a solution of benzyl acrylate (**7**) (100 mg, 1.0 mmol) in toluene (5 mL) was added trimethylsilyldiazomethane (1.5 mL, 1.5 mmol) at room temperature. After being stirred for 3 h, the reaction mixture was evaporated. The resulting oil was dissolved in CH_2Cl_2 and trifluoroacetic acid (0.11 mL, 3.0 mmol) was added at 0 ^oC. After being stirred for 1 h, the reaction mixture was evaporated. The resulting oil was dissolved in CH_2Cl_2 and acetyl chloride (0.11 mL, 1.50 mmol) and triethylamine (0.28 mL, 2.0 mmol) were added at 0 ^oC. After being stirred for 1 h, the mixture was quenched with water and extracted with CH_2Cl_2. The organic layer was dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography to afford **benzyl 1-acetyl-4,5-dihydro-1*H*-pyrazole-5-carboxylate** (**10**) (120 mg, 80%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.35 (s, 5H) 6.85 (s, 1H) 5.19 (t, *J* = 13.5 Hz, 2H) 4.85 (dd, *J* = 12.3, 6.0 Hz, 1H) 3.23 (d, *J* = 18.6, 12.6 Hz, 1H) 2.91 (dd, *J* = 18.6, 5.7 Hz, 1H) 2.34 (s, 3H); mass spectrum *m/e* (relative intensity) 246 (M^+, 5) 111 (29) 69 (100).

2-Acetyl-3,4-dihydro-2H-pyrazole-3-carboxylic acid methyl ester (**11**); ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.86 (s, 1H) 4.79 (dd, *J* = 12.4, 6.1 Hz, 1H) 3.75 (s, 3H) 3.24 (ddd, *J* = 18.7, 12.4, 1.6 Hz, 1H) 2.94 (ddd, *J* = 18.7, 6.3, 1.8 Hz, 1H) 2.33 (s, 3H); mass spectrum *m/e* (relative intensity) 170 (M^+, 12) 111 (17) 69 (100) 43 (38).

2-Acetyl-3,4-dihydro-2H-pyrazole-3-carboxylic acid ethyl ester (**12**); ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.87 (s, 1H) 4.79 (dd, *J* = 12.3, 6.0 Hz, 1H) 4.72 (q, *J* = 14.1, 6.9 Hz, 2H) 3.25 (dd, *J* = 18.6, 12.6 Hz, 1H) 2.95 (dd, *J* = 18.6, 5.7 Hz, 1H) 2.34 (s, 3H) 1.29 (t, *J* = 7.2 Hz, 3H); mass spectrum *m/e* (relative intensity) 184 (M^+, 6) 169 (2) 111 (16) 69 (100) 43 (29).

2-Acetyl-3,4-dihydro-2H-pyrazole-3-carboxylic acid amide (**13**); ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.49 (brs, 1H) 7.07-7.06 (m, 2H) 4.54 (dd, *J* = 12.3, 7.6 Hz, 1H) 3.19 (ddd, *J* = 18.8, 12.1, 1.7 Hz, 1H) 2.81 (ddd, *J* = 18.8, 5.9, 2.1 Hz, 1H) 2.16 (s, 3H).

2-Acetyl-3,4-dihydro-2H-pyrazole-3-carbonitrile (**14**); ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.96 (s, 3H) 5.00 (dd, *J* = 10.5, 7.7 Hz, 1H) 3.34-3.28 (m, 2H) 2.33 (s, 3H); mass spectrum *m/e* (relative intensity) 137 (M^+, 10) 84 (41) 43 (100).

2-(3,5-Dinitrobenzoyl)-3,4-dihydro-2H-pyrazole-3-carboxylic acid 2-isopropyl-5 methylcyclohexyl ester (**15a**); ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.16 (d, *J* = 2.0 Hz, 1H) 9.12 (d, *J* = 2.0 Hz, 2H) 7.08 (s, 1H) 5.05 (dd, *J* = 12.0, 5.6 Hz, 1H) 4.79 (dt, *J* = 10.8, 4.4 Hz, 1H) 3.34 (ddd, *J* = 19.3, 12.4, 1.6 Hz, 1H) 3.01 (ddd, *J* = 18.9, 5.6, 1.6 Hz, 1H) 2.06-1.92 (m, 2H) 1.75-1.67 (m, 3H) 1.55-1.43 (m, 3H) 1.39-1.05 (m, 1H) 0.95-0.80 (m, 10); mass spectrum *m/e* (relative intensity) 237 (M^+, 15) 195 (18) 83 (69) 43 (100).

(**15b**); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.09 (s, 1H) 5.03 (dd, *J* = 12.0, 6.0 Hz, 1H) 4.77 (dt, *J* = 10.8, 4.4 Hz, 1H) 3.41 (ddd, *J* = 18.9, 5.6, 1.6 Hz, 1H) 3.03 (ddd, *J* = 18.9, 5.6, 1.6 Hz, 1H) 2.12-2.05 (m, 1H) 1.82 (dt, *J* = 6.8, 2.8 Hz, 1H) 1.74-1.66 (m, 3H) 1.55-1.36 (m, 2H) 1.21 (d, *J* = 19.7 Hz, 1H) 1.07 (d, *J* = 10.8 Hz, 1H) 0.98-0.76 (m, 9H); mass spectrum *m/e* (relative intensity) 237 (M^+, 11) 195 (19) 138 (34) 83 (100).

Acknowledgment. This research was supported by the Center for Biological Modulators of the 21st Century Frontier R&D Program, the Ministry of Science and Technology, Korea.

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