

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

Jin Hee Ahn,^{*} Hye-Min Kim,[†] Seung Kyu Kang, Jae Du Ha, Eul Kgun Yum,^{*}
Duk Keun An,[‡] Joong-Kwon Choi, and Sung Soo Kim

Medicinal Science Division, Korea Research Institute of Chemical Technology, Daejeon 305-600, Korea

^{*}E-mail: jhahn@kRICT.re.kr

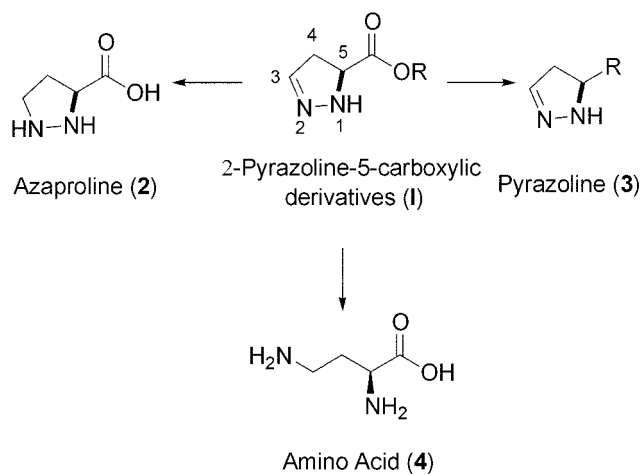
[†]Department of Chemistry, Chungnam National University, Yuseong 305-764, Korea

[‡]Department of Chemistry, Kangwon National University, ChunChon 200-701, Korea

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.

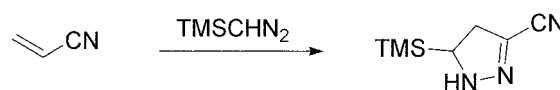


Scheme 1

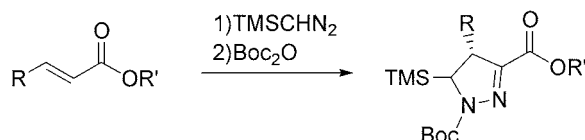
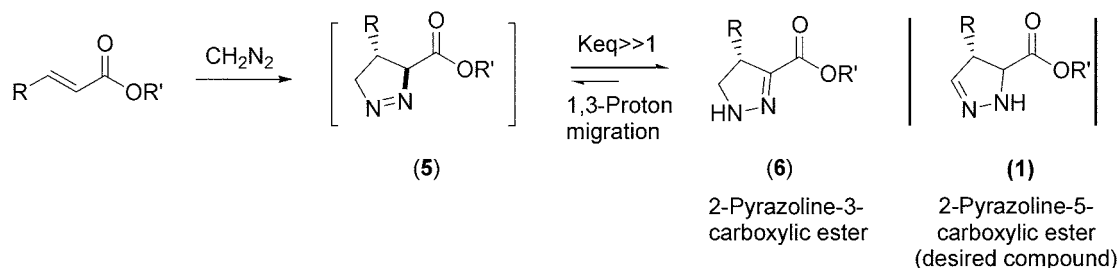
But, prior studies³⁻⁵ on the cycloadditions of α,β -unsaturated ester with diazoalkanes or trimethylsilyldiazomethane had indicated that the pyrazoline (5) initially formed in such cycloadditions readily isomerized (1,3-proton migration) to the corresponding conjugated 2-pyrazoline-3-carboxylic ester (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 trimethylsilyldiazomethane with α,β -unsaturated amide for the synthesis of 2-pyrazoline-5-carboxamide.

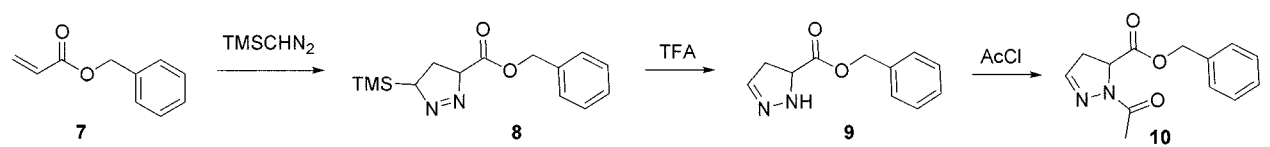
These reports prompted us to attempt synthesis of 2-pyrazoline-5-carboxylic ester, amide and nitrile through controlling the reaction before 1,3-proton migration. Therefore, under several conditions, we investigated cycloaddition reaction of α,β -unsaturated ester, amide and nitrile with trimethylsilyldiazomethane.



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

^aIsolated 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

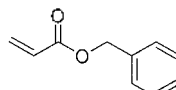
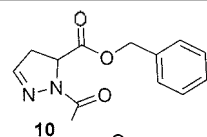
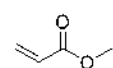
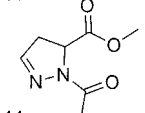
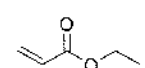
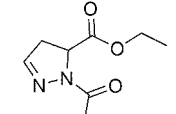
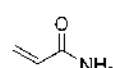
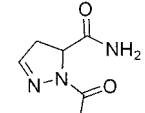

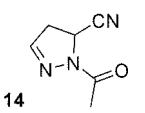
of 1.5 eq or 1.2 eq of trimethylsilyldiazomethane also gave satisfactory results. Based on these preliminary results, the application of this procedure to α,β -unsaturated esters, amide or nitrile was investigated.

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)

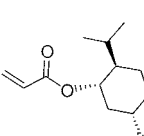
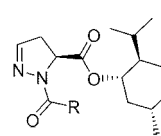
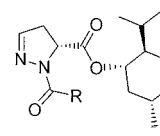
Next stage was the adoption of chirality at 5-position of 2-pyrazoline-5-ester. There have been reports by two groups that chiral alkene (alkenyl oxazolidinone⁷ or alkenyl sultam⁴) was treated with trimethylsilyldiazomethane to yield chiral 5-substituted pyrazoline, but they used an expensive camphorsultam⁴ 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 configuration, NOE experiments carried out with diastereomeric **15a** and **15b**.

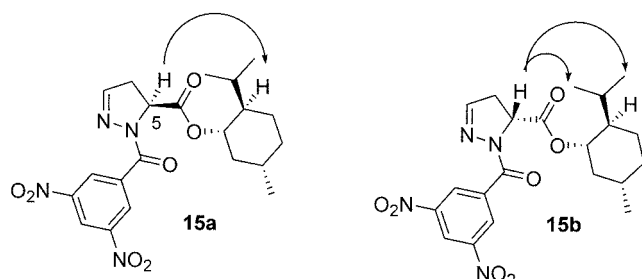
Table 2. Reaction of α,β -unsaturated carboxylic derivative with TMSCHN₂

Entry	Substrate	Time	Product	Yield ^a
7		tol:Hex, rt 3 h		85%
8		tol:Hex, rt 3 h		80%
9		tol:Hex, rt 3 h		91%
10		tol:Hex, rt 15 h		60%
11		tol:Hex, rt 3 h		70%

^aIsolated yield**Table 3.** Reaction of α,β -unsaturated carboxylic derivative with TMSCHN₂

Substrate	Product	yield ^a
	 15a  15b	86%
R = 3,5-dinitrophenyl	43% : 43%	
Diastereomers were easily separated by column chromatography		
R = Phenyl	43% : 43%	
Diastereomers were separated by column chromatography		

^aIsolated yield



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 pyrazoline 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, diastereoselectivity was 6 : 4. (data not shown)

In conclusion, we have directly synthesized 2-pyrazoline-5-carboxylic ester, amide and nitrile using trimethylsilyldiazomethane 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 °C. 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 °C. 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-1H-pyrazole-5-carboxylate (**10**) (120 mg, 80%); $^1\text{H NMR}$ (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): $^1\text{H NMR}$ (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): $^1\text{H NMR}$ (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): $^1\text{H NMR}$ (200 MHz, $\text{DMSO}-d_6$) 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): $^1\text{H NMR}$ (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): $^1\text{H NMR}$ (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**): $^1\text{H NMR}$ (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.

References

- Fuehi, N.; Doi, T.; Harada, T.; Urban, J.; Cao, B.; Kahn, M.; Takahashi, T. *Tetrahedron Lett.* **2001**, *42*, 1305.
- Kim, H. O.; Lum, C.; Lee, M. S. *Tetrahedron Lett.* **1997**, *38*, 4935.
- Whitlock, G. A.; Carreira, E. M. *Helv. Chim. Acta* **2000**, *83*, 2007.
- Mish, M. R.; Guerra, F. M.; Carreira, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 8379.
- Barluenga, J.; Fernandes-Mari, F.; Viado, A. L.; Aguilar, E.; Olano, B.; Garcia-Granda, S.; Moya-Rubiera, C. *Chem. Eur. J.* **1999**, *5*, 883.
- Seyferth, D.; Dow, A. W.; Menzel, H.; Flood, T. C. *J. Am. Chem. Soc.* **1968**, *90*, 1080.
- Kanemasa, S.; Kanai, T. *J. Am. Chem. Soc.* **2000**, *122*, 10710.