2-Chloro-1,3-dimethylimidazolinium Chloride. 2. Its Application to the Construction of Heterocycles through Dehydration Reactions

Toshio Isobe

Central Research Laboratory, Shiratori Pharmaceutical Co. Ltd., 6-11-24 Tsudanuma, Narashino, Chiba 275-0016, Japan

Tsutomu Ishikawa*

Faculty of Pharmaceutical Sciences, Chiba University, 1-33 Yayoi, Inage, Chiba 263-8522, Japan

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2-Chloro-1,3-dimethylimidazolinium chloride (DMC) (**1**) can act as a powerful dehydrating equivalent to DCC (**2**) under nearly neutral conditions. Its application to the construction of heterocycles through dehydration reactions is described.

Introduction

In the preceding paper in this issue[1] we showed that 2-chloro-1,3-dimethylimidazolinium chloride (DMC) (**1**) was a good dehydrating agent and that **1** could be superior to dicyclohexylcarbodiimide (DCC) (**2**) (Chart 1). In this paper we describe the additional capability of **1** to construct heterocycles based on dehydration reactions.

Results and Disscusion

Sydnone Synthesis. It is well-known that sydnones are easily synthesized by the cyclodehydration of N-substituted *N*-nitroso-α-amino acids.[2] Thus, we at first compared the versatility of DMC (**1**) to that of related reagents[3] such as the bromo equivalent in the preparation of 1,2,3-oxadiazole (sydnone) from *N*-nitroso-*N*-phenylglycine. Treatment of the *N*-nitroso derivative with either **1** or its analogues under standard conditions[1] led to the expected cyclodehydration (Table 1[4]). The sydnone was prepared in an excellent yield, when either **1** (run 1 in Table 1) or its hexafluorophosphate derivative (run 2 in Table 1) was used. On the other hand, use of the bromo analogues resulted in moderate yields (runs 3 and 4 in Table 1). The unsatisfactory yields obtained in the latter cases could be due to the instability of the bromo equivalent of **1**. Therefore, we decided to use DMC (**1**) in the following heterocycle constructions.

Four-Membered Rings: Azetidin-2-one Construction. There are numerous modifications for the preparation of azetidin-2-ones by interaction of acid halides with imines in the presence of bases,[5] and a wide variety of β-lactams are available by these reactions. We attempted their preparation from carboxylic acids using DMC (**1**). Carboxylic acids were treated with imines in the presence of **1** and triethylamine to afford expected β-lactams in good yields (Table 2[6]). It is known that the stereochemistries of the products are dependent upon the substituents present on the carboxylic acids used. In our case a similar tendency was observed.[7]

Chart 1

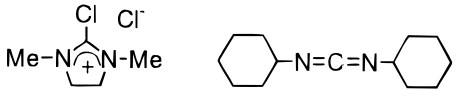
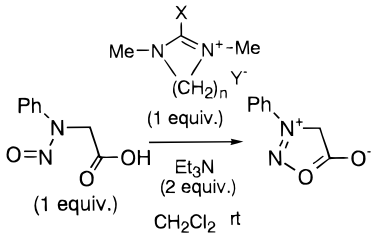


Chart 1

Table 1. Effectivity of DMC Analogues on Preparation of a Sydnone from an *N*-Nitroso-*N*-phenylglycine



runs	DMC analogs X	Y	n	time (min)	yields[a] (%)
1[4]	Cl	Cl	2	60	93
2[4]	Cl	PF_6	2	17	100
3[4]	Br	Br	2	120	64
4[4]	Br	Br	3	120	40

[a] Nonoptimized, isolated yield.

(1) Isobe, T.; Ishikawa, T. *J. Org. Chem.* **1999**, *64*, 6984.

(2) Clapp, L. B. In *Comprephensive Heterocyclic Chemistry*; Katritzky, A., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984, Vol. 6, pp 376−378.

(3) 2-Chloro-1,3-dimethylimidazolinium hexafluorophosphate (CIP) was prepared by treatment of an aqueous solution of DMC (**1**) with ammonium hexafluorophosphate (NH_4PF_6). It was obtained as nonhygroscopic colorless prisms, mp 231 °C dec [see Okamura, H.; Kawamoto, H.; Shiraishi, H. Eur. Patent EP 162308, 1985; *Chem. Abstr.* **1986**, *104*, 159540. Kiso, Y.; Fujiwara, Y.; Kimura, T.; Nishitani, A.; Akaji, K. *Int. J. Peptide Protein Res.* **1992**, *40*, 308]. CIP is now commercially available from Fluka (¥17500/5 g in Japan: this corresponds to $145.8/5 g, based on the exchange rate of ¥120/$ of Japanese yen to U.S. dollars). Other DMC analogues were similarly synthesized from the corresponding reactants and/or reagents according to the preparation method of **1** (see the Supporting Information).

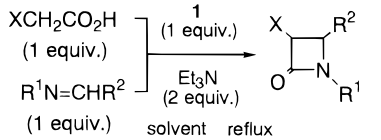
(4) Reference to the product in Table 1 is as follows. Thoman, C. J.; Voaden, D. J. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 962.

(5) Davies, D. E.; Storr, R. C. In *Comprephensive Heterocyclic Chemistry*; Katritzky, A., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 7, pp 247−267.

(6) References to the products in Table 2 are as follows. (a) Runs 1, 3, and 5: Georg, G. I.; Mashava, P. M.; Guan, X. *Tetrahedron Lett.* **1991**, *32*, 581. (b) Run 2: Isobe, T. Jpn. Kokai Tokkyo Koho JP 07 330721, 1995; *Chem. Abstr.* **1996**, *124*, 289241. (c) Run 4: Arrieta, A.; Aizpurua, J. M.; Palomo, C. *Tetrahedron Lett.* **1984**, *25*, 3365.

10.1021/jo9909756 CCC: $18.00
Published on Web 08/24/1999

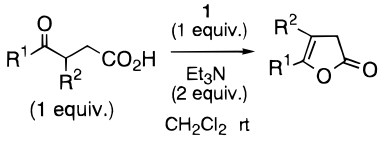
Table 2. Preparation of Azetidin-2-ones by Reaction of Carboxylic Acids and Imines



runs	X[a]	$\frac{R^1}{R^2}$	sol[b]	time (h)	yields[c] (%) cis/trans
1[6a]	PhO	$\frac{4\text{-(MeO)Ph}}{\text{Ph}}$	CH	3	64/0
2[6b]	PhO	$\frac{\text{Ph(CH}_2)_2}{\text{S}}$	CH	7	61/0
3[6a]	MeO	$\frac{4\text{-(MeO)Ph}}{\text{Ph}}$	DE	7	60.5/20.5
4[6c]	PTIm	$\frac{4\text{-(MeO)Ph}}{\text{Ph}}$	CH	4	0/76
5[6a]	Vn	$\frac{4\text{-(MeO)Ph}}{\text{Ph}}$	CH	2	0/64

[a] PTIm = phthalimido; Vn = vinyl. [b] sol = solvent, CH = chloroform; DE = 1,2-dichloroethane. [c] Nonoptimized, isolated yield.

Table 3. Preparation of *β,γ*-Butenolides from *γ*-Keto Acids

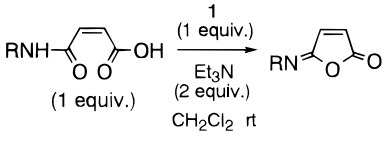


runs	R^1	R^2	time (h)	yields[a] (%)
1[9a]	4-(Me)Ph	H	18	56
2[9b]	2,3,4-(MeO)$_3$Ph	H	1	100
3[9c]			22	78

[a] Nonoptimized, isolated yield.

Five-Membered Rings. (1) With One Heteroatom. Furanones have been prepared by treatment of *γ*-keto acids with acetic anhydride through an intramolecular condensation.[8] Our modification using DMC (**1**) led to an alternative synthesis of *β,γ*-butenolides from the corresponding *γ*-keto acids (Table 3[9]). Furthermore, *γ*-imino-*α,β*-butenolides were obtained in moderate to good yields when maleic acid monoamides were used as starting materials (Table 4[10]).

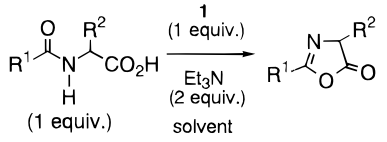
Table 4. Preparation of *γ*-Imino-*α,β*-butenolides from Maleic Acid Monoamides



run	R	time (h)	yields[a] (%)
1[10a]	Ph	19	81
2[10b]	Ph(CH$_2$)$_2$	18	57
3[10c]		24	53

[a] Nonoptimized, isolated yield.

Table 5. Preparation of 5-Oxazolidinones from *N*-Acyl-α-amino Acids



runs	$\frac{R^1}{R^2}$	sol[a]	temp / time (h)	yields[b] (%)
1[12a]	$\frac{4\text{-(Me)Ph}}{\text{Me}}$	DM	rt/4	56
2[12b]	$\frac{^i\text{Pr}}{\text{PhCH}_2}$	DE	1. rt/1 2. reflux/2	56
3[12b]	$\frac{4\text{-(Me)Ph}}{\text{MeS(CH}_2)_2}$	DE	1. rt/1 2. reflux/10	31
4[12b]	$\frac{4\text{-(Me)Ph}}{^i\text{Bu}}$	DM	rt/41	22

[a] sol = solvent, DM = dichloromethane; DE = 1,2-dichloroethane. [b] Nonoptimized, isolated yield.

(2) With Two Hetreoatoms. 1,3-Oxazolidin-5-ones have been prepared by the reaction of *N*-benzylideneglycine with acid chlorides or the reaction of α-amino acids with a ketone.[11] Treatment of *N*-acyl-α-amino acids with DMC (**1**) afforded 5-oxazolidinones through intramolecular condensation (Table 5[12]). The reaction of *N*-acylglycines under similar conditions in the presence of aldehydes led to the formation of 2-alkylidene-5-oxazolidinones (Table 6[13]). In these cases, the isolated yields were lower than expected in that TLC analysis showed a single spot attributable to the expected product. It appears that loss of product occurs during workup. The methyl ester[14] of the starting amino acid was isolated in 77% yield after purification by column chromatography (SiO_2) using solvent containing MeOH (Scheme 1), when *N*-isobutyrylphenylalanine was used as a starting material (see run 2 in Table 5). Thus, despite the instabilities

(7) Georg, G. I.; Mashava, P. M.; Guan, X. *Tetrahedron Lett.* **1991**, *32*, 581.

(8) Donnelly, D. M.; Storr, R. C. In *Comprephensive Heterocyclic Chemistry*, Katritzky, A., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 4, pp 658−684.

(9) References to the products in Table 3 are as follows. (a) Run 1: Sakurai, K.; Matsumoto, H.; Adachi, J. *Yakugaku Zasshi* **1968**, *88*, 919; *Chem. Abstr.* **1968**, *69*, 94792. (b) Run 2: Isobe, T. Jpn, Kokai Tokkyo Koho JP 08 134054, 1996; *Chem. Abstr.* **1996**, *125*, 142531. (c) Run 3: Chan, C. C.; Farmer, P. S. *Pharmazie* **1986**, *41*, 835.

(10) References to the products in Table 4 are as follows. (a) Run 1: Sauers, C. K. *J. Org. Chem.* **1969**, *34*, 2275. (b) Run 2: Takase, I.; Matsuyama, T.; Kawamura, T. *Kobunshi Ronbunshu* **1992**, *49*, 513; *Chem. Abstr.* **1992**, *117*, 70395. (c) Run 3: Capraro, H. G.; Rihs, G.; Martin, P. *Helv. Chim. Acta* **1983**, *66*, 633.

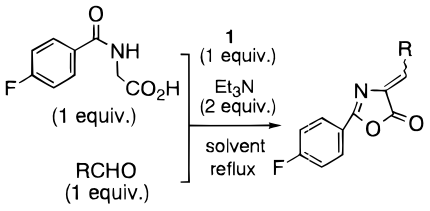
(11) Boyd, G. V. In *Comprephensive Heterocyclic Chemistry*; Katritzky, A., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 6, pp 229−232.

(12) References to the products in Table 5 are as follows. (a) Run 1: Marquez, A.; Chuaqui, C. A.; Rodriguez, H.; Zagal, L. *Tetrahedron* **1985**, *41*, 2341. (b) Runs 2−4: Isobe, T.; Hosogai, A. Jpn. Kokai Tokkyo Koho JP 08 027132, 1996; *Chem. Abstr.* **1996**, *124*, 343280.

(13) Reference to the products in runs 1 and 2 in Table 6 is as follows. Isobe, T.; Hosogai, A. Jpn. Kokai Tokkyo Koho JP 08 027132, 1996; *Chem. Abstr.* **1996**, *124*, 343280.

(14) Glaser, R.; Geresh, S. *Tetrahedron* **1979**, *35*, 2381.

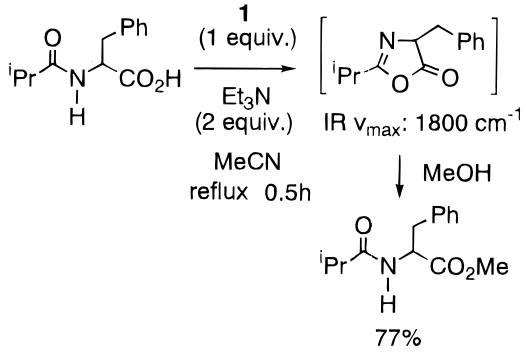
Table 6. Preparation of 4-Alkylidene-5-oxazolidinones from *N*-Acyl-α-amino Acids in the Presence of Aldehydes



runs	R	sol[a]	time (h)	yields[b] (%)
1[13]	4-(MeO)Ph	DE	4	52[c]
2[13]		MeCN	3	46[c]

[a] sol = solvent, DE = 1,2-dichloroethane. [b] Nonoptimized, isolated yield. [c] The geometries of the alkylidene residues have not been determined.

Scheme 1

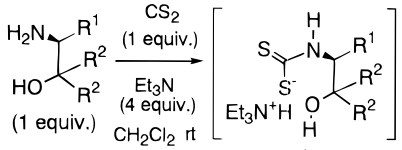


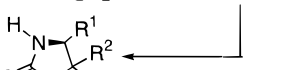
of products causing lower isolated yields in several cases, this simple method is useful for the preparation of 5-oxazolidinones because of the limited number of reports on their synthesis.[11]

The standard preparation of 1,3-oxazolidin-2-ones is by treatment of β-amino alcohols with phosgene or its synthetic equivalents.[11] The corresponding thiocarbonyl compounds, 1,3-oxazolidine-2-thiones, were isolated in moderate to excellent yields when β-amino alcohols were treated with **1** in the presence of carbon disulfide (CS_2) (Table 7[15]).

(3) With Three Hetreoatoms. The most widely applicable route to 2,5-dialkyl-, 2-alkyl-5-aryl-, or 2,5-diaryl-1,3,4-oxadiazoles is the thermal or acid-catalyzed cyclization of 1,2-diacylhydrazines.[16] Treatment of diacylhydrazines with DMC (**1**) afforded the corresponding 1,3,4-oxadiazoles in excellent yields (Table 8[17]). These compounds were also directly prepared by the reaction of acylhydrazines and carboxylic acids (Table 9[18]). On the other hand, 1,3,4-oxadiazole-5-thiones are synthesized by the reaction of acylhydrazines with thiophosgene.[16] The

Table 7. Preparation of 1,3-Oxazolidin-2-thiones from 2-Amino Alcohols and Carbon Disulfide

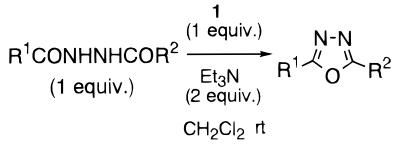




runs	R^1	R^2	time (h)	yields[a] (%)
1[15a]	$PhCH_2$	H	20	98
2[15b]	^iBu	Ph	19	96
3[15b]	$PhCH_2$	^nBu	16	53

[a] Nonoptimized, isolated yield.

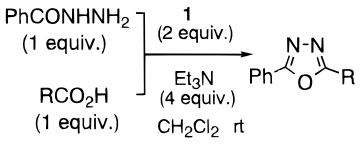
Table 8. Preparation of 1,3,4-Oxadiazoles from Diacylhydrazines



runs	R^1	R^2	time (h)	yields[a] (%)
1[b]	Ph	Ph	16	86
2[17a]	4-(Me)Ph	4-(Me)Ph	21	100
3[17b]	4-(F)Ph	4-(F)Ph	20	100

[a] Nonoptimized, isolated yield. [b] The product is commercially available.

Table 9. Direct Preparation of 1,3,4-Oxadiazoles by Reaction of Acylhydrazines and Carboxylic Acids



runs	R	time (h)	yields[a] (%)
1[18a]	4-(Cl)Ph	90	83
2[18b]		19	85
3[18c]	^tBu	18	56

[a] Nonoptimized, isolated yield.

thiones were efficiently obtained by treatment of the adducts prepared between acylhydrazines and CS_2 with **1** under conditions similar to those described in Table 7 (Table 10[19]).

Many thioamides are converted into 1,2,4-thiadiazoles on treatment with a variety of oxidizing agents.[20] The yields of the thiazoles obtained are widely variable,

(15) References to the products in Table 7 are as follows. (a) Run 1: Delaunay, D.; Toupet, L.; Le Corre, M. *J. Org. Chem*. **1995**, *60*, 6604. (b) Runs 2 and 3: Isobe, T.; Fukuda, K.; Takashi, M. Jpn. Kokai Tokkyo Koho JP 09 124621, 1997; *Chem. Abstr*. **1997**, *127*, 50634.

(16) Hill, J. In *Comprephensive Heterocyclic Chemistry*; Katritzky, A., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 6, pp 440−445.

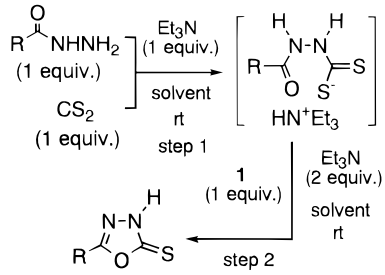
(17) References to the products in Table 8 are as follows. (a) Run 2: Siegrist, A. E. *Helv. Chim. Acta* **1967**, *50*, 906. (b) Run 3: Hayes, F. N.; Rogers, B. S.; Ott, D. G. *J. Am. Chem. Soc.* **1955**, *77*, 1850.

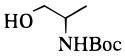
(18) References to the products in Table 9 are as follows. (a) Run 1: Sain, B.; Sandhu, J. S. *Indian J. Chem*. **1992**, *31B*, 768. (b) Run 2: ref 17b. (c) Run 3: Rigo, B.; Cauliez, P.; Fasseur, D.; Couturier, D. *Synth. Commun*. **1986**, *16*, 1665.

(19) References to the products in Table 10 are as follows. (a) Run 2: Hashimoto, N.; Deguchi, H.; Kojima, T.; Miyazaki, H. Jpn. Kokai Tokkyo Koho JP 03 163435, 1991; *Chem. Abstr*. **1992**, *116*, 162398. (b) Runs 3−5: Isobe, T. Jpn. Kokai Tokkyo Koho JP 07 258234, 1995; *Chem. Abstr*. **1996**, *124*, 176109.

(20) Franz, J. E.; Dhingra, O. P. In *Comprephensive Heterocyclic Chemistry*; Katritzky, A., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 6, pp 492−501.

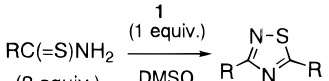
Table 10. Preparation of 1,3,4-Oxadiazole-2(3*H*)-thiones from Hydrazides and Carbon Disulfide



runs	R	sol[a]	time (h) step 1	time (h) step 2	yields[b] (%)
1[c]	Ph	PhH/MeCN (2:3)	6	3	95
2[19a]		DM/MeCN (1:1)	4	3	58
3[19b]		DMF	3	3	93
4[19b]		DMF	4	1	75
5[19b]		DM	5	3	58

[a] sol = solvent, DM = dichloromethane. [b] Nonoptimized, isolated yield. [c] The product is commercially available.

Table 11. Preparation of Thiadiazoles from Thioamides



runs	R	time (h)	yields[a] (%)
1[21a]	Ph	26	93
2[21b]		66	93

[a] Nonoptimized, isolated yield.

depending on the thioamides, the oxidizing agent, and the conditions used. We examined the effectiveness of the combination of DMC (**1**) and dimethyl sulfoxide (DMSO) on the conversion. Self-condensation of 2 mol of a thioamide with **1** in the presence of DMSO smoothly occurred to afford 1,2,4-thiadiazoles in excellent yields (Table 11[21]). The proposed mechanism of the cyclization is shown in Scheme 2.

Six-Membered Rings: 3,1-Benzoxazine Construction. 3,1-Benzoxazin-4-ones are synthesized by the cyclodehydration of *N*-acylanthranilic acids with acetic anhydride, phosphorus oxychloride, or thionyl chloride.[22] The use of DMC (**1**) as a reagent led to the alternative formation of the benzoxazinones in excellent yields (Table 12[23]).

Scheme 2

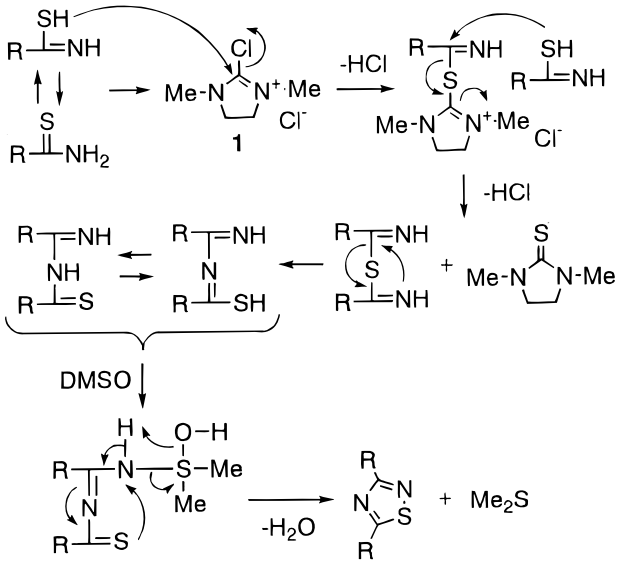
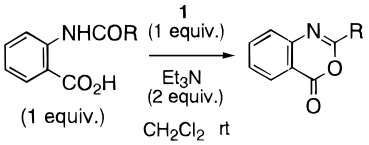
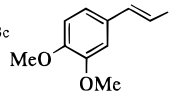


Table 12. Preparation of 4-Oxo-3,1-benzoxazines from *N*-Acylanthranilic Acids



runs	R	time (h)	yields[a] (%)
1[23a]	Et	18	100
2[23b]	2-(NO_2)Ph	17	93
3[23c]		4	95

[a] Nonoptimized, isolated yield.

Conclusions

Thus, DMC (**1**) has been shown to be useful for the construction of a representative range of heterocycles. It is reasonably expected that **1** should be applicable to other synthetic procedures based on dehydration reactions in addition to the heterocycle constructions decribed here, because of its strong dehydrating ability. In a future paper we will further discuss some additional uses of DMC (**1**) in chlorination, oxidation, reduction, and rearrangement of organic compounds.

Experimental Section

General comments and a basic procedure for the reaction using **1** were given in the preceding paper in this issue.[1]

Supporting Information Available: The preparation method of DMC analogues and selected spectroscopic data for compounds described in our patents. This material is available free of charge via the Internet at http://pubs.acs.org.

JO9909756

(21) References to the products in Table 11 are as follows. (a) Run 1: Howe, R. K.; Franz, J. E. *J. Org. Chem.* **1974**, *39*, 962. (b) Run 2: Podolesov, B. D.; Jordanovska, V. B. *J. Serb. Chem. Soc.* **1985**, *50*, 119; *Chem. Abstr.* **1987**, *106*, 4944).

(22) Sainsbury, M. In *Comprephensive Heterocyclic Chemistry*; Katritzky, A., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 3, pp 1018−1031.

(23) References to the products in Table 12 are as follows. (a) Run 1: Reid, W.; Valentin, J. *Chem. Ber.* **1968**, 101, 2106. (b) Run 2: Bain, D. I.; Smalley, R. K. *J. Chem. Soc. C* **1968**, 1593. (c) Run 3: Kojima, M.; Tsutsumi, N.; Ujiie, A.; Naito, J. *Oyo Yakuri* **1984**, *28*, 623; *Chem. Abstr.* **1985**, *102*, 55825.