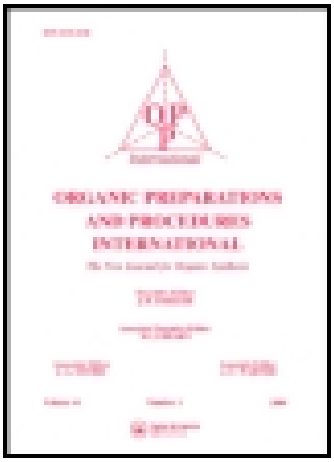


Organic Preparations and Procedures International: The New Journal for Organic Synthesis

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/uopp20

SYNTHESIS OF 2,4(1H,3H)-QUINAZOLINEDIONE AND 3-SUBSTITUTED 2,4(1H,3H)-QUINAZOLINEDIONES

J. S. Petrov [a c] & G. N. Andreev [b]

[a] Institute of Organic Chemistry, Bulgarian Academy of Sciences , 1113, Sofia, BULGARIA

[b] Department of Chemistry , University of Plovdiv , 4000, Plovdiv, BULGARIA E-mail:

[c] Department of Chemistry , University of Plovdiv , 24 Tzar Assen Street, 4000, Plovdiv, Bulgaria E-mail:

Published online: 06 Feb 2009.

To cite this article: J. S. Petrov & G. N. Andreev (2005) SYNTHESIS OF 2,4(1H,3H)-QUINAZOLINEDIONE AND 3-SUBSTITUTED 2,4(1H,3H)-QUINAZOLINEDIONES, Organic Preparations and Procedures International: The New Journal for Organic Synthesis, 37:6, 560-565, DOI: 10.1080/00304940509354986

To link to this article: http://dx.doi.org/10.1080/00304940509354986

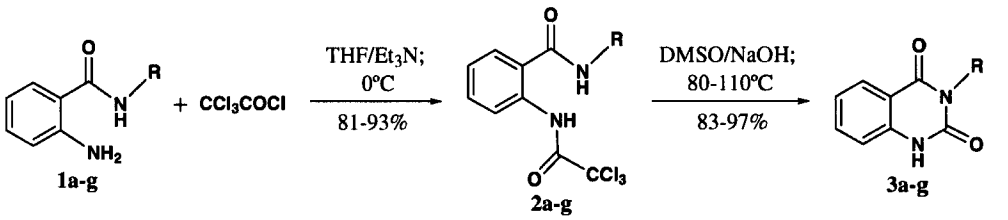
SYNTHESIS OF 2,4(1*H*,3*H*)-QUINAZOLINEDIONE AND 3-SUBSTITUTED 2,4(1*H*,3*H*)-QUINAZOLINEDIONES

Submitted by J. S. Petrov*† and G. N. Andreev‡
(06/03/05)

† *Institute of Organic Chemistry, Bulgarian Academy of Sciences*
1113 Sofia, BULGARIA
‡ *Department of Chemistry, University of Plovdiv*
4000 Plovdiv, BULGARIA
E-mail: petrov@argon.acad.bg

In the recent decades 2,4(1*H*,3*H*)-quinazolinediones have attracted attention because of their biological activity as anticonvulsants, psychosedatives, hypotensive compounds or inhibitors of puromycin-sensitive aminopeptidase showing tumor cell invasion inhibiton.[1-3] Quinazolinediones are also useful synthetic materials in heterocyclic chemistry.[4,5]

We report here a new synthetic method for preparation of 2,4(1*H*,3*H*)-quinazolinedione and its 3-substituted analogs based on the cyclization of 2-[(trichloroacetyl)amino]benzamides. The approach includes three steps, namely synthesis of *N*-substituted 2-aminobenzamides **1**, trichloroacetylation of the latter compounds to 2-[(trichloroacetyl)amino]benzamides **2**, and their base-induced intramolecular cyclization leading to 2,4(1*H*,3*H*)-quinazolinediones **3** (*Scheme 1*).



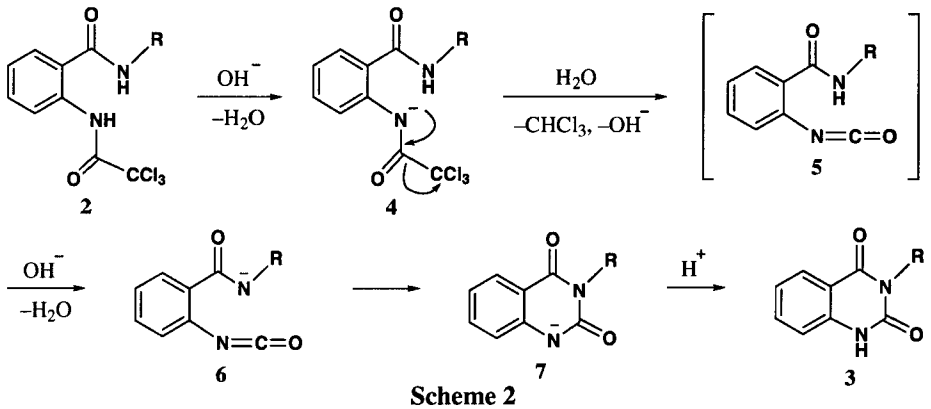
a) R = C_6H_5; b) R = 4-(*i*-C_3H_7)C_6H_4; c) R = 4-$CH_3OC_6H_4$, d) R = $C_6H_5CH_2$, e) R = 3,4-(CH_2O_2)$C_6H_3CH_2$; f) R = 4-$ClC_6H_4CH_2$, g) R = H

Scheme 1

N-Substituted 2-aminobenzamides **1** were obtained by the reaction of isatoic anhydride with primary amines by a procedure similar to those described in literature.[1,6] 2-[(Trichloroacetyl)amino]benzamides **2** were prepared by treatment of benzamides **1** with trichloroacetyl chloride as *N*-acylating reagent for amines.[7] Higher yields were reached by using of tetrahydrofuran instead of diethyl ether[7], and the reaction was carried out in the presence of triethylamine. The last step of the approach to the synthesis of quinazolinediones **3** is an intramolecular cyclization (*Scheme 1*) of the corresponding 2-[(trichloroacetyl)amino]benzamides **2**. The reaction proceeded when dimethyl sulfoxide solution of **2** in the presence of excess of anhydrous sodium hydroxide was stirred at elevated temperature. The quinazolinediones **3** were collected after acidification of the mixture.

A probable pathway of the reaction of 2-[(trichloroacetyl)amino]benzamides **2** to 2,4(1*H*,3*H*)-quinazolinediones **3** is shown in *Scheme 2*. Treatment of **2** with sodium hydroxide

leads to deprotonation of its trichloroacetylamino moiety. Under the influence of electron withdrawing trichloromethyl group of **4**, formation of 2-isocyanatobenzamide **5** occurs with the accompanying evolution of trichloromethane. Hydroxide ion in the presence of polar aprotic solvent (DMSO) is sufficiently basic to deprotonate the nitrogen atom of benzamido group of **5** and to form 2-isocyanatobenzamide anion **6**. When R is benzyl, removal of proton from the nitrogen atom of the benzamido group is more difficult than in the case when R is phenyl. This is in accordance with the necessity of a higher temperature of the reaction mixture and a longer reaction time for the reaction when R is benzyl to proceed (**3d-f**, *Table 5*). Intramolecular nucleophilic attack on the electron-deficient carbon atom of the isocyanato group of **6** leads to ring closure and formation of anion of quinazolinedione **7**. Subsequent acidification produced the corresponding quinazolinedione **3**.



Scheme 2

The method presented is a useful addition to the existing methods for the synthesis of 3-(un)substituted 2,4(1*H*,3*H*)-quinazolinediones because it avoids the use of highly toxic phosgene as a reagent for quinazolinedione ring closure.[1,6] Our procedure also avoids the use of isocyanates. The latter compounds, which in many cases are unstable and inconvenient for storage, are used as reactants in the syntheses of ureido derivatives which are subsequently cyclized to the corresponding quinazolinediones.[4,8-10]

EXPERIMENTAL SECTION

Isatoic anhydride and 2-aminobenzamide are commercially available (Merck). Melting points were determined on a "Boetius PHMK 05" hot-stage melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FTIR 1750 spectrometer. ^{1}H-NMR spectra were obtained on a Perkin-Elmer R-24B spectrometer at 60 MHz, on a Tesla BS-487-C spectrometer at 80 MHz and on a Bruker WM 250 spectrometer at 250 MHz in DMSO-d_6 with TMS as an internal reference. Mass spectra were determined on a HP 6890 GC System/HP5973 MSD.

2-Amino-*N*-phenylbenzamide (1a). Typical Procedure.- To a stirred solution of isatoic anhydride (3.26 g, 20 mmol) in DMF (10 mL) heated at 80°C was added dropwise a solution of aniline (1.86 g, 20 mmol) in DMF (5 mL) over a period of 30 min. After 4 h of additional stirring

at the same temperature, the mixture was cooled and cold water (60 mL) was added with stirring. The resulting precipitate was collected, washed with cold water (2 x 10 mL) and dried at 60°C. Recrystallization (diethyl ether) afforded 3.34 g (79%) of **1a**. Compounds **1b-f** were obtained in a similar way (*Table 1*).

Table 1. Reaction Conditions, Yields, Melting Points and Elemental Analyses of **1**

Cmpd	Reac. Cond. Temp. (°C)	Time (h)	Yield (%)	mp (°C) (solvent)	*lit.* mp (°C)	Calcd (Found) C	H	N
1a	80	4.5	79	128-130 (Et_2O)	130-131[11]	----	----	----
1b	60	6.0	89	126-128 (PhH)	----	75.56 (75.28)	7.13 (7.19)	11.01 (11.12)
1c	60	5.75	88	119-121 (PhH/ Et_2O)	119[12]	----	----	----
1d	25-60[a]	3.75	95	124-126 (PhH)	124-125[13]	----	----	----
1e	25-60[a]	4.5	94	133-134 (EtOH)	----	66.66 (66.58)	5.22 (5.25)	10.36 (10.23)
1f	25-60[a]	4.0	92	139-141 (EtOH)	----	64.50 (64.67)	5.03 (5.14)	10.74 (10.71)

a The addition of the amine was started at rt (25°C) and the reaction temperature rose to 60°C approximately without applying of additional heating.

Table 2. IR and ^{1}H-NMR Spectral Data of **1**

Cmpd	IR (cm^{-1}) ν_{NH}	ν_{CO}	^{1}H-NMR[a] [DMSO-d_6/TMS, δ, *J* (Hz)]
1a	3420, 3296	1645	9.97, br s, 1H, CONH; 7.75-7.64, m, 2H, ArH; 7.61, dd, *J* = 7.9, 1.4, 1H, ArH; 7.38-7.26, m, 2H, ArH; 7.23-7.13, m, 1H, ArH; 7.11-7.00, m, 1H, ArH; 6.74, dd, *J* = 8.2, 1.0, 1H, ArH; 6.63-6.52, m, 1H, ArH; 6.29, br s, 2H, NH_2
1b	3434, 3328	1643	9.89, br s, 1H, CONH; 7.59, br d, 2H, ArH and 1H, ArH overlapping; 7.22-7.09, m, 3H, ArH; 6.72, d, *J* = 8.2, 1H, ArH; 6.56, br t, 1H, ArH; 6.28, br s, 2H, NH_2; 2.84, sept, *J* = 6.9, 1H, $CH(CH_3)_2$; 1.18, d, *J* = 6.9, 6H, $CH(CH_3)_2$
1c	3440, 3351 3307	1641	9.96, br s, 1H, CONH; 7.86-6.41, m, 8H, ArH and 2H, NH_2 overlapping; 3.73, s, 3H, OCH_3
1d	3472, 3359 3303	1631	8.85, br t, 1H, CONH; 7.76-6.97, m, 7H, ArH; 6.88-6.38, m, 2H, ArH and 2H, NH_2 overlapping; 4.46, d, *J* = 6, 2H, $PhCH_2$
1e	3443, 3344 3286	1616	8.79, br t, 1H, CONH; 7.60, dd, *J* = 8, 1, 1H, ArH; 7.35-7.05, m, 1H, ArH; 7.04-6.38, m, 5H, ArH and 2H, NH_2 overlapping; 6.02, s, 2H, $O-CH_2-O$; 4.35, d, *J* = 6, 2H, $Ar-CH_2$
1f	3473, 3359 3309	1632	8.84, br t, 1H, CONH; 7.79-7.01, m, 6H, ArH; 6.88-6.33, m, 2H, ArH and 2H, NH_2 overlapping; 4.41, d, *J* = 6, 2H, $Ar-CH_2$

a) The spectra of **1a, b** were recorded on a Bruker WM 250 spectrometer at 250 MHz and those of **1c-f** on a Tesla BS-487-C spectrometer at 80 MHz.

2-[(Trichloroacetyl)amino]benzamides 2a-g. General Procedure.- To a solution of 2-aminobenzamide **1** (10 mmol) in 25 mL of THF was added Et_3N (1.01 g, 10 mmol). At ice-bath temperature and with stirring, a solution of trichloroacetyl chloride (1.96 g, 10.8 mmol) in THF (25 mL) was added dropwise over a period of 1.5 h. The reaction mixture was stirred for a further 3 h and allowed to stand overnight. The precipitate was collected and suspended in water (40 mL). The suspended solid was collected to afford **2**. The filtrate was evaporated to dryness and water (30 mL) was added to the residue with stirring. The suspension was filtered again to give an additional amount of **2**. The two crops were combined and recrystallized from ethanol to give the pure compound **2** (*Table 3*).

Table 3. Yields, Melting Points and Elemental Analyses of **2**

Cmpd	Yield (%)	mp (°C) (solvent)	Molecular Formula	Calcd (Found) C	H	N
2a	88	199-201 (EtOH)	$C_{15}H_{11}Cl_3N_2O_2$	50.38 (50.64)	3.10 (3.26)	7.83 (7.71)
2b	93	188.5-190.5 (95% EtOH)	$C_{18}H_{17}Cl_3N_2O_2$	54.09 (54.13)	4.29 (4.27)	7.01 (7.03)
2c	88	177-179 (95% EtOH)	$C_{16}H_{13}Cl_3N_2O_3$	49.57 (49.76)	3.38 (3.39)	7.23 (7.24)
2d	88	139-141 (EtOH)	$C_{16}H_{13}Cl_3N_2O_2$	51.71 (51.45)	3.53 (3.51)	7.54 (7.42)
2e	89	145-146.5 (EtOH)	$C_{17}H_{13}Cl_3N_2O_4$	49.12 (49.37)	3.15 (3.21)	6.74 (6.91)
2f	81	129-130 (EtOH)	$C_{16}H_{12}Cl_4N_2O_2$	47.32 (47.08)	2.98 (3.05)	6.90 (6.82)
2g	85	195-197 (EtOH)	$C_9H_7Cl_3N_2O_2$	38.40 (38.35)	2.51 (2.46)	9.95 (9.94)

Table 4. IR and ^{1}H-NMR Spectral Data of **2**

Cmpd	IR (cm^{-1}) ν_{NH}	ν_{CO}	^{1}H-NMR[a] [DMSO-d_6/TMS, δ, *J* (Hz)]
2a	3285 3193	1720 1636	8.36, dd, *J* = 8, 1, 1H, ArH; 8.09, dd, *J* = 8, 1, 1H, ArH; 7.92-7.06, m, 7H, ArH
2b	3286 br	1728 1635	10.67, br s, 1H, ArCONH; 8.44 br d, 1H, ArH; 8.10 br d, 1H, ArH; 7.94-7.19, m, 6H, ArH; 3.10-2.68, m, 1H, CH(CH_3)$_2$; 1.19, d, *J* = 7, 6H, CH(CH_3)$_2$
2c	3294 br	1726 1632	8.40, d, *J* = 8, 1H, ArH; 8.08, br d, 1H, ArH; 7.66, d, *J* = 9, 2H, ArH and 2H, ArH overlapping; 6.98, d, *J* = 9, 2H, ArH; 3.73, s, 3H, OCH_3
2d	3334 3288	1722 1632	9.74, br t, 1H, ArCONH; 8.50, d, *J* = 8, 1H, ArH; 8.17-7.95, m, 1H, ArH; 7.68, br t, 1H, ArH; 7.56-7.02, m, 6H, ArH; 4.56, d, *J* = 6, 2H, Ph-CH_2
2e	3309 3240	1718 1707 1631	9.60, br t, 1H, ArCONH; 8.46, d, *J* = 8, 1H, ArH; 8.02, br d, 1H, ArH; 7.71, br t, 1H, ArH; 7.40, br t, 1H, ArH; 6.94, d, *J* = 7, 2H, ArH and 1H ArH overlapping; 6.03, s, 2H, O-CH_2-O; 4.44, d, *J* = 7, 2H, Ar-CH_2
2f	3299 3192	1715 1629	9.61, br t, 1H, ArCONH; 8.48, d, *J* = 8, 1H, ArH; 8.05, br d, 1H, ArH; 7.73, br t, 1H, ArH; 7.54-7.06, m, 5H, ArH; 4.56, d, *J* = 6, 2H, Ar-CH_2
2g	3395 3187	1707 1681 1658	13.43, br s, 1H, $NHCOCCl_3$; 8.75-7.83, m, 2H, ArH and 2H, $ArCONH_2$ overlapping; 7.80-7.50, m, 1H, ArH; 7.45-7.10, m, 1H, ArH

a) The spectra of **2a-f** were recorded on a Tesla BS-487-C spectrometer at 80 MHz and this of **2g** on Perkin-Elmer R-24B spectrometer at 60 MHz.

Table 5. Reaction Conditions, Yields, Melting Points and Elemental Analyses of **3**

Cmpd	Reaction Conditions		Yield	mp (°C)	*lit.* mp	Calcd (Found)		
	Temp. (°C)	Time (h)	(%)	(solvent)	(°C)	C	H	N
3a	80	4.5	93	281-283 (AcOH)	280-282[8]	----	----	----
3b	90	4.0	96	253-254 (EtOH)	$C_{17}H_{16}N_2O_2$	72.84 (72.60)	5.75 (5.84)	9.99 (9.82)
3c	90	3.5	94	303-304.5 (EtOH)	$C_{15}H_{12}N_2O_3$ 297-299[14]	67.16 (67.14)	4.51 (4.55)	10.44 (10.39)
3d	110	6.0	94	226-228 (EtOH)	227[15]	----	----	----
3e	110	6.0	91	262-263.5 (EtOH)	$C_{16}H_{12}N_2O_4$	64.86 (64.92)	4.08 (4.16)	9.46 (9.72)
3f	100	5.0	97	241-242.5 (EtOH)	$C_{15}H_{11}ClN_2O_2$	62.84 (63.13)	3.87 (3.98)	9.77 (10.01)
3g	90	3.0	83	>300 (EtOH)	> 300[16]	----	----	----

Table 6. IR and ^{1}H-NMR Spectral Data of **3**

Cmpd	IR (cm^{-1})		^{1}H-NMR [250 MHz, DMSO-d_6/TMS, δ, *J* (Hz)]
	ν_{NH}	ν_{CO}	
3a	3245 3199 3144	1732 1650	11.53, br s, 1H, NH; 7.93, dd, *J* = 8.2, 1.5, 1H, ArH; 7.73-7.65, m, 1H, ArH; 7.52-7.17, m, 7H, ArH
3b	3197 3129	1726 1661	11.52, br s, 1H, NH; 7.92, dd, *J* = 8.1, 1.4, 1H, ArH; 7.72-7.64, m, 1H, ArH; 7.33, d, *J* = 8.3, 2H, ArH; 7.20, d, *J* = 8.3, 2H, ArH and 2H, ArH overlapping; 2.95, sept, *J* = 6.9, 1H, $CH(CH_3)_2$; 1.24, d, *J* = 6.9, 6H, $CH(CH_3)_2$
3c[a]	3195 3128	1720 1662	11.48, br s, 1H, NH; 7.91, dd, *J* = 8.2, 1.5, 1H, ArH; 7.71-7.63, m, 1H, ArH; 7.20, d, *J* = 8.9, 2H, ArH and 2H ArH overlapping; 6.99, d, *J* = 8.9, 2H, ArH; 3.79, s, 3H, OCH_3
3d	3192 3128	1713 1666 1656	11.51, br s, 1H, NH; 7.93, dd, *J* = 8.2, 1.5, 1H, ArH; 7.70-7.61, m, 1H, ArH; 7.33-7.16, m, 7H, ArH; 5.08, s, 2H, Ph-CH_2
3e	3189 3128	1714 1662	11.48, br s, 1H, NH; 7.99-7.88, m, 1H, ArH; 7.69-7.60, m, 1H, ArH; 7.24-7.14, m, 2H, ArH; 6.92-6.68, m, 3H, ArH; 5.95, s, 2H, OCH_2O; 4.97, s, 2H, Ar-CH_2
3f	3192 3129	1720 1657	11.53, br s, 1H, NH; 7.93, dd, *J* = 8.4, 1.5, 1H, ArH; 7.71-7.62, m, 1H, ArH; 7.38-7.31, m, 4H, ArH; 7.25-7.15, m, 2H, ArH; 5.06, s, 2H, Ar-CH_2
3g[b]	3256 3196	1725 1703 1674	11.22, br s, 2H, NH; 7.88, dd, *J* = 8.4, 1.5, 1H, ArH; 7.67-7.58, m, 1H, ArH; 7.22-7.10, m, 2H, ArH

a) Mass spectrum: *m/z* (%) 268 (M^+, 100); 146 (62); 119 (51); 92 (20); 64 (7). b) Mass spectrum: *m/z* (%) 162 (M^+, 100); 119 (83); 92 (48); 64 (14).

3-Phenyl-2,4(1*H*,3*H*)-quinazolinedione (3a). Typical Procedure.- To a solution of *N*-phenyl-2-[(trichloroacetyl)amino]benzamide (**2a**) (1.79 g, 5 mmol) in DMSO (12 mL) was added powdered sodium hydroxide (0.5 g, 12.5 mmol). The mixture was stirred at 80°C for 4.5 h. After cooling (cold-water bath), the mixture was diluted with cold water (70 mL). The resultant mixture was acidified to pH~2 with 10% sulfuric acid. The precipitated product was collected and recrystallized from (acetic acid) to afford 1.11 g (93%) compound **3a**. Compounds **3b-g** were obtained in a similar way (*Table 5*).

REFERENCES

* Current address: Department of Chemistry, University of Plovdiv, 24 Tzar Assen Street, 4000 Plovdiv, Bulgaria, e-mail: petrov@argon.acad.bg

1. S. Hayao, H. J. Havera, W. G. Strycker, T. J. Leipzig, R. A. Kulp and H. E. Hartzler, *J. Med. Chem.*, **8**, 807 (1965).

2. W. Meuldermans, J. Hendrickx, R. Woestenborghs, A. van Peer, W. Lauwers, J. De Cree and J. Heykants, *Arzneim.-Forsch./Drug Res.*, **38**, 789 (1988).

3. H. Kakuta, A. Tanatani, K. Nagasawa and Y. Hashimoto, *Chem. Pharm. Bull.*, **51**, 1273 (2003).

4. N. P. Peet and P. B. Anzeveno, *J. Heterocyclic Chem.*, **16**, 877 (1979).

5. (a) H. Miki, *Heterocycles*, **19**, 7 (1982); (b) M. A. Badawy, Y. A. Ibrahim and A. M. Kadry, *J. Heterocyclic Chem.*, **21**, 1403 (1984); (c) J. Michel, J. J. Toulmé, J. Vercauteren and S. Moreau, *Nucleic Acids Res.*, **24**, 1127 (1996).

6. R. L. Jacobs, *J. Heterocyclic Chem.*, **7**, 1337 (1970).

7. L. Spiegel and P. Spiegel, *Ber.*, **40**, 1730 (1907).

8. B. Taub and J. B. Hino, *J. Org. Chem.*, **26**, 5238 (1961).

9. A. Kamal and P. B. Sattur, *Heterocycles*, **26**, 1051 (1987).

10. J.-W. Chern, F.-J. Shish, C.-D. Chang, C.-H. Chan and K.-C. Liu, *J. Heterocyclic Chem.*, **25**, 1103 (1988).

11. G. Wagner and L. Rothe, *Pharmazie*, **24**, 513 (1969).

12. M. S. Manhas and S. G. Amin, *J. Heterocyclic Chem.*, **14**, 161 (1977).

13. O. C. Dermer and J. King, *J. Org. Chem.*, **8**, 168 (1943).

14. J. Garin, E. Melendez, F. L. Merchan, T. Tejero and E. Villarrova, *Synthesis*, 406 (**1983**).

15. R. P. Staiger and E. C. Wagner, *J. Org. Chem.*, **18**, 1427 (1953).

16. T. Yoshida, N. Kambe, S. Murai and N. Sonoda, *Bull. Chem. Soc. Jpn*, **60**, 1793 (1987).