CYCLIZATION WITH NITRENIUM IONS GENERATED FROM *N*-METHOXY- OR *N*-ALLYLOXY-*N*-CHLOROAMIDES WITH ANHYDROUS ZINC ACETATE. SYNTHESIS OF *N*-HYDROXY- AND *N*-METHOXYNITROGEN HETEROCYCLIC COMPOUNDS

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Abstract ---- Electrophilic intramolecular aromatic substitution with an *N*-methoxy- or an *N*-allyloxy-acylnitrenium ion, generated by treatment of an *N*-methoxy- or an *N*-allyloxy-*N*-chloroamide with anhydrous zinc acetate in nitromethane, leads to formation of a nitrogen heterocyclic compound bearing an *N*-methoxy- or *N*-allyloxy group. The latter is readily converted to the corresponding *N*-hydroxy compound by palladium-catalyzed removal of the allyl group.

The divalent positively-charged nitrogen species, known as the nitrenium ion, has been extensively investigated in recent years.[1] The *N*-acyl-*N*-alkoxynitrenium ion is an excellent source of electrophilic nitrogen and has proved to have great utility in synthesis.[2] Successful use of this species is due mainly to the fact that the nitrenium ion is stabilized by the electron donating effect of the neighboring methoxy group;[3] the ion is thus long-lived enough to react with an aromatic ring. The synthetic utility of such ions

will be enhanced further by the development of simpler methods of generation of them from readily available reagents.

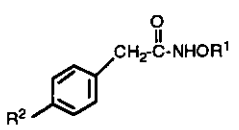
In previous work, we described an intramolecular electrophilic aromatic substitution with a nitrenium ion generated from *N*-chloro-*N*-methoxyamides with anhydrous zinc acetate in nitromethane to give nitrogen heterocyclic compounds bearing an *N*-methoxy function.[2c] This method overcomes shortcomings of previous methods,[2a,b,d] and is applicable to large scale preparations. The method was successfully applied by us for the synthesis of the alkaloid, eupolauramine,[4] and for new oxindoles related to the alkaloid, gelsemine, by others.[5]

We now report full details of our studies, including synthesis of *N*-hydroxynitrogen heterocyclic compounds from the corresponding *N*-allyloxy compounds by palladium-catalyzed removal of the allyl group.[6] This process constitutes a new convenient route to nitrogen heterocyclic compounds bearing an *N*-hydroxy function.

Results and Discussion

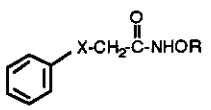
Synthesis of *N*-Methoxynitrogen Heterocyclic Compounds---We have investigated practical syntheses of nitrogen heterocyclic compounds without use of silver salts or trifluoroacetic acid (TFA).[2a,d] The cyclization reaction is strongly affected by the nature of the transition metal salts and the solvent used. Several transition metal salts ($SnCl_2 \cdot 2H_2O$, $ZnBr_2$, $ZnCl_2$, ZnI_2, $Zn(OAc)_2$, $Zn(OAc)_2 \cdot 2H_2O$, Ag_2CO_3, $CoCl_2 \cdot 6H_2O$, $CoCl_2$, $Co(OAc)_2$, $Cu(OAc)_2$, and $CuCl_2$) and solvents (dichloromethane, 1,2-dichloroethane, acetonitrile, ethanol, TFA, and nitromethane) were examined; the combination of $Zn(OAc)_2$ and nitromethane proved to be the best. Treatment of **1a** with *tert*-butyl hypochlorite in dichloromethane afforded in quantitative yield the corresponding *N*-chloro compound, which was added to a hot (70-100 °C) solution of nitromethane containing a 5-fold molar excess of $Zn(OAc)_2$. After a few min, the reaction was complete and **7a** was obtained after the usual work-up. Various *N*-methoxyamides (**1**-**6**) were reacted in this way to produce *N*-methoxy heterocyclic compounds (**7**-**14**), and the results are presented in Table 1. Interestingly, there is

great difference in reactivity between $Zn(OAc)_2$ and $Zn(OAc)_2 \cdot 2H_2O$. The coordination with two water molecules in the latter leads to a monomeric compound of distorted octahedral structure.[7] On the other hand, $Zn(OAc)_2$ forms a three dimensional polymeric network. The Zn ions are in a slightly distorted tetrahedral environment[7] and may be assumed to have a higher ability to abstract a chlorine atom as an anion than $Zn(OAc)_2 \cdot 2H_2O$. Reaction of *N*-chloro-*N*-methoxyphenylacetamide with $ZnCl_2$ in nitromethane at room temperature (5 min) led to 1-methoxy-2-oxindole (**7a**) (15.5%) and the corresponding 5-chloro derivative (**8a**) (41.2%). The latter product is rationalized by way of the intermediate (**17**), produced by pairing of **16** with chloride ion. Elimination of HCl or H_2 from **17** gives **7a** or **8a** as shown in Scheme 1.



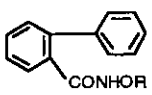
1

a : $R^1 = CH_3$, $R^2 = H$
b : $R^1 = CH_3$, $R^2 = CH_3$
c : $R^1 = CH_3$, $R^2 = CH_3O$
d : $R^1 = CH_3$, $R^2 = C_6H_5$
e : R^1 = allyl, $R^2 = H$
f : $R^1 = H$, $R^2 = H$



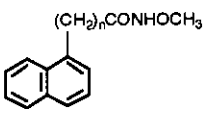
2

a : R = CH_3, X = CH_2
b : R = CH_3, X = CH_2CH_2
c : R = CH_3, X = O
d : R = allyl, X = CH_2
e : R = H, X = CH_2
f : R = allyl, X = O
g : R = H, X = O



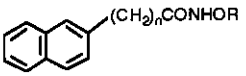
3

a : R = CH_3
b : R = allyl
c : R = H



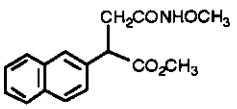
4

a : n = 0
b : n = 1



5

a : n = 1, R = CH_3
b : n = 2, R = CH_3
c : n = 2, R = C_2H_5
d : n = 2, R = allyl
e : n = 2, R = H

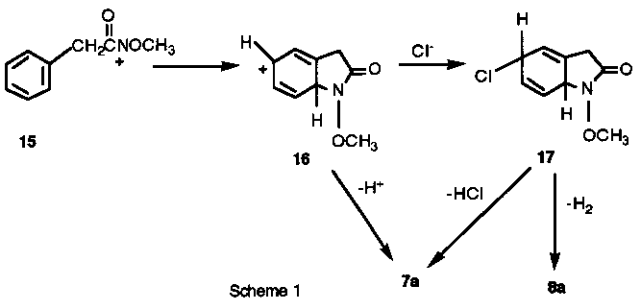


6

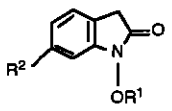
Table 1. Synthesis of nitrogen heterocyclic compounds from *N*-methoxyamides

Entry	Starting material	Reaction time (min) [a]	Product	Yield (%) [b]
1	**1a**	3	**7a**	83
2	**1b**	5	**7b**	76
3	**1c**	1	**7c**, **8b** [c]	57, 11
4	**1d**	8	**7d**	77
5	**2a**	5	**9a**	94
6	**2b**	5	**9b**	73
7	**2c**	4	**9c**	77
8	**3a**	26	**10a**	87
9	**4a**	3	**11**	26
10	**4b**	2	**12**	70
11	**5a**	5 [d]	**13a**	61
12	**5b**	4 [e]	**13b**	95
13	**5c**	5	**13c**	73
14	**6**	7	**14**	88

[a] Reflux. [b] Overall yield of chlorination of *N*-methoxyamides and cyclization. [c] See Ref. 2c. [d] 60 °C. [e] 75 °C.

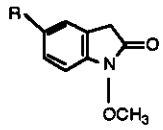


Scheme 1



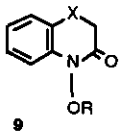
7

a : $R^1 = CH_3$, $R^2 = H$
b : $R^1 = CH_3$, $R^2 = CH_3$
c : $R^1 = CH_3$, $R^2 = CH_3O$
d : $R^1 = CH_3$, $R^2 = C_6H_5$
e : R^1 = allyl , $R^2 = H$
f : $R^1 = H$, $R^2 = H$



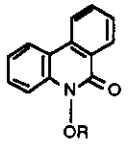
8

a : R = Cl
b : $R = CH_3O$



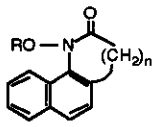
9

a : $R = CH_3$, $X = CH_2$
b : $R = CH_3$, $X = CH_2CH_2$
c : $R = CH_3$, X = O
d : R = allyl , $X = CH_2$
e : R = H , $X = CH_2$
f : R = allyl , X = O
g : R = H , X = O



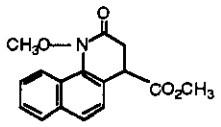
10

a : $R = CH_3$
b : R = allyl
c : R = H



13

a : n = 1 , $R = CH_3$
b : n = 2 , $R = CH_3$
c : n = 2 , $R = C_2H_5$
d : n = 2 , R = allyl
e : n = 2 , R = H



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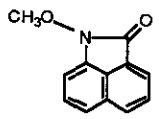

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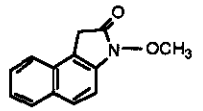
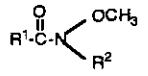


12



18 : $R^2 = Cl$ **19** : $R^2 = C_6H_5$

a : $R^1 = C_6H_5$
b : $R^1 = CH_3(CH_2)_6$
c : $R^1 = C_6H_5CH{=}CH$

Table 2. Synthesis of *N*-allyloxy- and *N*-hydroxynitrogen heterocyclic compounds

Entry	Starting material	*N*-allyloxy compound	Yield(%)[a]	*N*-hydroxy compound	Yield(%)[b]
1	**1e**	**7e**	54	**7f**	83
2	**2d**	**9d**	47	**9e**	82
3	**2f**	**9f**	58	**9g**	85
4	**3b**	**10b**	84	**10c**	70[c]
5	**5c**	**13d**	74	**13e**	71

[a] Total yield of chlorination and cyclization. [b] Yield of deprotection. [c] Crude yield.

N-Chloro derivatives of *N*-methoxybenzamide (**18a**), -octanamide (**18b**), and -cinnamamide (**18c**) were submitted to intermolecular reaction with a 50-fold molar excess of benzene under the same reaction conditions to give the corresponding *N*- phenyl derivatives (**19a-c**) in yields of 75.2%, 72.4%, and 67.4%, respectively.

Synthesis of *N*-Hydroxynitrogen Heterocyclic Compounds from the Corresponding *N*-Allyloxy Compounds---Various synthetic methods have been introduced recently for the synthesis of *N*-hydroxynitrogen heterocyclic compounds;[8] there is, however, no versatile method generally applicable. Demethylation of the *N*-methoxy compounds (**7-14**) with $AlCl_3$-Me_2S[9] revealed, in some cases, concomitant

introduction of the methylthio moiety on aromatic rings.[10] Thus, the selection of a suitable protecting group is an important step in this synthetic methodology. Benzyl and methoxyethoxymethyl (MEM) groups have been used for the *O*-protection of phenylacetohydroxamic acid, but cyclization by use of $Zn(OAc)_2$-CH_3NO_2 or Ag_2CO_3-TFA of the *N*-chloro compounds bearing these groups failed;[11] very likely, the corresponding *N*-acylnitrenium ion is short-lived due to spontaneous decomposition to a benzyl or MEM cation and a nitroso carbonyl compound. The latter compound is readily hydrolyzed to the corresponding carboxylic acid during work-up.

In the case of an *O*-acyl derivative, the corresponding nitrenium ion would be strongly destabilized by the adjacent *O*-acyl groups and would decompose without cyclization. Finally, we found that allyloxy is a suitable protecting group for our purpose. Intramolecular cyclization of *N*-allyloxy-*N*-chloroamides and deprotection of the allyl group by palladium-catalyzed reaction with triethylammonium formate[6] proceeds smoothly and the corresponding *N*-hydroxy compounds are obtained in moderate to good yield. The results are presented in Table 2.

Although the synthetic methods for aliphatic hydroxamic acids are well documented,[12] the methods for the synthesis of cyclic hydroxamic acids are limited. Therefore, the present method provides a convenient method for the synthesis of cyclic hydroxamic acids.

EXPERIMENTAL

Melting points are uncorrected. ^1H Nmr spectra were measured at 60 or 270 MHz with tetramethylsilane (Me_4Si) as an internal reference and $CDCl_3$ as the solvent, unless otherwise noted. Low and high resolution mass spectra (MS) were obtained with a direct inlet system at 70 eV. Elemental analyses were performed in the Microanalytical Laboratory of this University. Hydroxamic acids were prepared according to the published procedure.[12,13] *N*-Alkoxyamides except **5c** were prepared by the Schotten-Baumann reaction, using the corresponding acid chlorides and alkoxyamines.[2] *N*-Allyloxyamides and **5c** were prepared from the corresponding hydroxamic acids in

the presence of an equimolar amount of NaH in *N*,*N*-dimethylformamide (DMF) with allyl bromide and ethyl iodide, respectively. Physical data of all new products are presented in Table 3.

General Procedure for the Intramolecular Cyclization of *N*-Alkoxyamides---The intramolecular cyclization of *N*-methoxyamides and **5c** were performed by the reported method.[2c] The results are summarized in Table 1.

Intermolecular Reaction of *N*-Chloro-*N*-methoxycinnamamide (18c) with Benzene---Compound (**18c**) (290.6 mg, 1.64 mmol) was added with stirring to a mixture of benzene (7.3 ml), nitromethane (15 ml), and $Zn(OAc)_2$ (1.5 g, 8.2 mmol) at 50 °C. After 1.5 h, insoluble materials were filtered off, washed with ethyl acetate (20 ml), and the organic solvents were concentrated. The residue was diluted with ethyl acetate (50 ml). The organic layer was washed with 5% aq. $NaHCO_3$ (30 ml), brine (20 ml), dried over Na_2SO_4, and concentrated. The crude products were chromatographed on a column of silica gel. First elution with benzene-ethyl acetate (20:1) afforded an unknown compound (11.8 mg) and further elution with the same solvent mixture afforded *N*-methoxy-*N*-phenylcinnamamide (**19c**) (280.0 mg, 67.4%), mp 65-67 °C (from Et_2O). ^1H nmr δ 3.75 (3H, s, MeO), 6.97 (1H, d, J=16, -C<u>H</u>=CHCO-), 7.50-7.62 (10H, m, ArH), 7.80 (1H, d, J=16, -CH=C<u>H</u>CO-); ν_{max} (nujol)/cm^{-1} 1650 (C=O); m/z 253 (M^+, 0.32%), 131 (100%). Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found C, 76.07; H, 6.09; N, 5.44.

General Procedure for the Cyclization of *N*-Allyloxyamides---To an *N*-allyloxyamide (2 mmol) in dichloromethane (6 ml) was added *t*-butyl hypochlorite (0.27 ml, 2.4 mmol) with cooling. After 20-30 min, the solvent was concentrated. The residue was added to nitromethan (20 ml) containing anhydrous zinc acetate (1.83 g, 10 mmol) at 60 °C. After 10 min, insoluble materials were filtered off, washed with ethyl acetate (20 ml), and the combined solvents were concentrated. The residue was diluted with ethyl acetate (50 ml). The organic layer was washed with 5% aq. $NaHCO_3$ (30 ml), brine (20 ml), dried over Na_2SO_4, and concentrated. The crude product was

chromatographed on a column of silica gel with benzene-ethyl acetate (5:1) as an eluent to give an *N*-allyloxynitrogen heterocyclic compound.

Table 3. Physical and analytical data of new nitrogen heterocyclic compounds

Compounds (Formula)	mp ℃ (Solvent)	Found (%) (requires) C	H	N	Ir ν_{max} (KBr)/cm^{-1}	Nmr δ	m/z M^+
7c ($C_{10}H_{11}NO_3$)	121-122 (Benzene-Hexane)	62.17 (62.17)	5.74 (5.74)	6.97 (7.25)	1710	3.40(2H,s,CH_2),3.82(3H,s,MeO),3.97(3H,s,MeO), 6.58(1H,dd,*J* = 2.2,8.4,5-H),6.60(1H,s,7-H),7.16 (1H,d,*J*=8.4,4-H) [a]	193
7d ($C_{15}H_{13}NO_2$)	95-97 (Ether-Hexane)	75.10 (75.30)	5.47 (5.48)	5.71 (5.85)	1725	3.49(2H,s,CH_2),4.02(3H,s,MeO),7.18-7.55(8H,m, ArH)	239
8b ($C_{10}H_{11}NO_3$)	78-79 (Ether)	62.03 (62.17)	5.63 (5.74)	6.96 (7.25)	1720	3.45(2H,s,CH_2),3.77(3H,s,MeO),3.95(3H,s,MeO), 6.87-6.90(2H,m,4-H,7-H),6.93-6.96(1H,m,6-H) [a]	193
9d ($C_{12}H_{13}NO_2$)	Oil	———			1695 [b]	2.46-3.10(4H,m,CH_2CH_2),4.56(2H,d,*J*=5.94,OCH_2), 5.13-5.56(2H,m,CH=CH_2),5.73-6.36(1H,m,CH=CH_2), 6.89-7.43(4H,m,ArH)	203
9f ($C_{11}H_{11}NO_3$)	Oil	———			1700 [b]	4.50-4.59(2H,m,OCH_2CH=CH_2),4.61(2H,s,OCH_2), 5.17-5.58(2H,m,CH=CH_2),5.66-6.43(1H,m,CH=CH_2), 6.76-7.43(4H,m,ArH)	205
10b ($C_{16}H_{13}NO_2$)	98-100 (Benzene-Hexane)	76.20 (76.48)	5.35 (5.21)	5.38 (5.57)	1660	4.78(2H,d,*J*=5.94,OCH_2),5.17-5.63(2H,m,CH=CH_2), 5.83-6.56(1H,m,CH=CH_2),7.07-7.92(5H,m,ArH), 8.07-8.73(3H,m,ArH)	251
10c [c] ($C_{20}H_{15}NO_2$)	132 (Benzene)	79.68 (79.72)	5.18 (5.02)	4.51 (4.65)	1645	5.30(2H,s,PhCH_2),7.10-7.92(10H,m,ArH×2), 8.10-8.73(3H,m,ArH)	301
11 ($C_{12}H_9NO_2$)	136-138 (Ether)	72.47 (72.35)	4.50 (4.55)	6.77 (7.03)	1710	4.31(3H,s,MeO),7.17(1H,d,*J*=6.8,8-H),7.59(1H,dd, *J*=6.8,8.1,7-H),7.67(1H,d,*J*=8.1,6-H),7.84(1H,dd, *J*=6.8,8.1,4-H),8.05(1H,d,*J*=6.8,5-H),8.20(1H,d, *J*=8.1,3-H) [a]	199
13b ($C_{14}H_{13}NO_2$)	65-66 (Ether)	74.18 (73.99)	5.95 (5.77)	6.02 (6.16)	1695	2.57-3.23(4H,m,2×CH_2),3.63(3H,s,MeO),7.23-7.57(3H,m,ArH),7.62-7.90(2H,m,ArH),8.40-8.73 (1H,m,ArH)	227
13c ($C_{15}H_{15}NO_2$)	Oil	——— [d]			1690 [b]	1.21(3H,t,*J*=6.93,CH_3),2.53-3.23(4H,m,CH_2CH_2), 3.86(2H,q,*J*=6.93,CH_2),7.07-7.92(5H,m,ArH), 8.46-8.79(1H,m,ArH)	241
13d ($C_{16}H_{15}NO_2$)	Oil	———			1690 [b]	2.43-3.20(4H,m,CH_2CH_2),4.31(2H,d,*J*= 5.94,OCH_2), 4.89-5.36(2H,m,CH=CH_2),5.53-6.23(1H,m,CH=CH_2), 7.07-7.92(5H,m,ArH),8.43-8.79(1H,m,ArH)	253
13e ($C_{13}H_{11}NO_2$)	162-163 (Ethyl acetate)	72.93 (73.23)	5.35 (5.20)	6.35 (6.57)	1670 3120	2.59-3.30(4H,m,CH_2CH_2),6.92-7.96(5H,m,ArH), 8.56-8.89(1H,m,ArH),9.68(1H,br,OH)	213

[a] 270MHz, solvent : CD_3COCD_3. [b] Neat. [c] *O*-Benzyl **10c**. As a poor combustion analysis was obtained probably due to a trace impurity with metal chelation, **10c** was converted to benzyl ether with NaH and benzyl bromide in DMF (61.4%).
[d] High ms m/z (M^+): 205.1102. Found: 205.1084.

General Procedure for Removal of the Allyl Group---A mixture of an *N*-allyloxynitrogen heterocyclic compound (4 mmol), $Pd(OAc)_2$ (90mg, 0.4 mmol), Ph_3P (420 mg, 1.6 mmol), formate reagent ($5HCOOH \cdot 2Et_3N$) (5.19 g), and 80% aq. EtOH (15 ml) was stirred under reflux for 10 min. Insoluble materials were filtered off, washed with ethyl acetate (5 ml), and the organic layer was diluted with ethyl acetate (45 ml). The organic layer was washed with brine (30 ml), dried over Na_2SO_4, and concentrated. The crude product was chromatographed on a column of silica gel with benzene-ethyl acetate (2:1) as an eluent to give an *N*-hydroxynitrogen heterocyclic compound. The results are summarized in Table 2.

REFERENCES AND NOTES

1. P. G. Gassman, *Acc. Chem. Res.*, 1970, **3**, 26; K. Shudo, T. Ohta, and T. Okamato, *J. Am. Chem. Soc.*, 1981, **103**, 645; R. A. Abramovitch and R. Jeyaraman, Azides and Nitrenes, ed. by E.F.V. Scriven, Academic Press, New York,1984, pp. 297-357; R. A. Abramovitch, M. M. Cooper, R. Jeyaraman, and G. Rusek, *Tetrahedron Lett.*, 1986, **27**, 3705; H. Takeuchi, T. Adachi, and H. Nishiguchi, *J. Chem. Soc., Chem. Commun.*, 1991, 1524.
2. (a) Y. Kikugawa and M. Kawase, *J. Am. Chem. Soc.*, 1984, **106**, 5728; (b) S. A. Glover, A. Goosen, C. W. McCleland, and J. L. Schoonraad, *J. Chem. Soc., Perkin Trans. 1*, 1984, 2255; (c) Y. Kikugawa and M. Shimada, *Chem. Lett.*, 1987, 1771; (d) M. Kawase, T. Kitamura, and Y. Kikugawa, *J. Org. Chem.*, 1989, **54**, 3394.
3. S. A. Glover and A. P. Scott, *Tetrahedron*, 1989, **45**, 1763.
4. Y. Kikugawa, M. Kawase, Y. Miyake, T Sakamoto, and M. Shimada, *Tetrahedron Lett.*, 1988, **29**, 4297; M. Kawase, Y. Miyake, T. Sakamoto, M. Shimada, and Y. Kikugawa, *Tetrahedron*, 1989, **45**, 1653.
5. I. Fleming, R. C. Moses, M. Tercel, and J. Ziv, *J. Chem. Soc., Perkin Trans. 1*, 1991 617.
6. T. Yamada, K. Goto, Y. Mitsuda, and J. Tsuji, *Tetrahedron Lett.*, 1987, **28**, 4557.
7. A. V. Capilla, and R. A. Aranda, *Cryst. Struct. Commun.*, 1979, **8**, 795.

8. M. Somei, H. Sato, and C. Kaneko, *Heterocycles*, 1983, **20**, 1797; S.-I. Murahashi, T. Oda, T. Sugahara, and Y. Masui, *J. Chem. Soc., Chem. Commun.*, 1987, 1471; Idem, *J. Org. Chem.*, 1990, **55**, 1744; A. S. Kende and J. Thurston, *Synth. Commun.*, 1990, **20**, 2133.
9. M. Kawase, T. Kitamura, M. Shimada, and Y. Kikugawa, *Synth. Commun.*, 1990, **20**, 887.
10. Demethylation of **13b** resulted in removal of the methoxy function and introduction of a methylthio group at the *para* position of the aromatic ring in 60.3% yield. The details will be published elsewhere.
11. *N*-Benzyloxy-*N*-chlorophenylacetamide was submitted to the cyclisation reaction to give 1-benzyl-2-oxindole (6%) and phenylacetic acid (45%).
12. S. A. Sandler and W. Karo, Organic Functional Group Preparations, 2nd Edition, Academic Press, Inc., 1989, Vol. 3, pp. 482-522.
13. A. Liguori, G. Sindona, G. Romeo, and N. Uccella, *Synthesis*, 1987, 168.

Received, 25th March, 1993