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Intramolecular Cyclization with Nitrenium Ions Generated from N-Chloro-N-methoxyamides in Neutral Conditions

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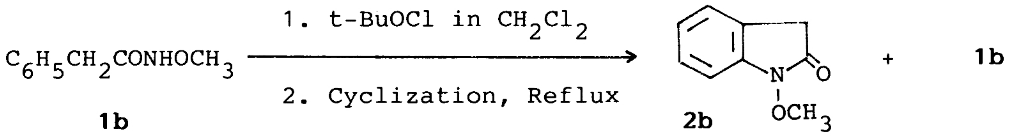
Intramolecular aromatic substitution by a N-chloro-N-methoxyamide group to a suitably situated aromatic ring in the molecule is performed by using anhydrous zinc acetate and nitromethane as solvent to give nitrogen heterocycles in good yield.

Previously we published an intramolecular electrophilic aromatic substitution with a nitrenium ion generated from N-chloro-N-methoxyamides to give nitrogen heterocycles.1) This reaction requires a silver salt to abstract a chlorine atom and trifluoroacetic acid (TFA) to stabilize a nitrenium ion,2) which is long-lived enough to react with an aromatic ring. However, this reaction is not applicable for large scale preparation because TFA has to be removed by evaporation under low temperature or has to be neutralized with sodium carbonate in order not to decompose the product and large amounts of fine insoluble materials appeared are removed by suction with great difficulty, and is also not applicable for a compound bearing acid-sensitive groups. We have decided to improve these shortcomings and to be able to use this reaction for a large scale preparation.

Recently, Glover's group3) published the same kind of intramolecular cyclization by using silver tetrafluoroborate in methanol or benzene, although they dealt with rather special compounds. We tried the synthesis of 1-methoxy-2-oxindole (**2b**) following their method and could obtain **2b** in poor yeild.4) On the course of our investigation of this cyclization reaction, we found that **2b** could be obtained in 30% yield from N-chloro-N-methoxyphenylacetamide with zinc chloride in dichloromethane accompanying the recovery of the starting amide (**1b**) (60%).

Table 1. Synthesis of **2b** in Various Conditions



Run	Reagent	Mol. equi.	Solvent	Reaction time	Product (%, yield)
1	Ag_2CO_3	2	CH_2Cl_2	6 h	**1b** (80.7)
2	Ag_2CO_3	2	CH_3NO_2	5 min	**2b** (3.1), **1b** (36.2), (46.4)a)
3	$SnCl_2$ $2H_2O$	3	CH_2Cl_2	5 h	**1b** (96.6)
4	$Cu(OAc)_2$	3	TFA	6 hb)	**1b** (93.8)
5	$Zn(OAc)_2$	5	CH_2ClCH_2Cl	4 h	**1b** (91.3)
6	$Zn(OAc)_2$	5	CH_3CN	4 h	**2b** (4.2), **1b** (23.6)
7	$Zn(OAc)_2$	5	C_2H_5OH	1 h	**1b** (15.8), (20.4)a,c)
8	$Zn(OAc)_2$ $2H_2O$	5	CH_3NO_2	40 min	**2b** (33.4), **1b** (52.0)
9	$Zn(OAc)_2$	3	CH_3NO_2	3 min	**2b** (73.8), **1b** (10.6)
10	$Zn(OAc)_2$	5	CH_3NO_2	3 min	**2b** (79.5), **1b** (13.9)

a) Yield of $C_6H_5CH_2CO_2CH_3$. b) Ice cooling. c) Yield of $C_6H_5CH_2CO_2C_2H_5$, 41.5%.

Table 2. Cyclization of N-Methoxyamides in Refluxing Nitromethane5)

Run	Starting material	Reaction time/min	Product (%, yield)
1	**1a**	2	-----a)
2	**1b**	3	**2b** (82.8)
3	**1c**	5	**2c** (93.8)
4	**1d**	5	**2d** (73.2)
5	**3a**	3	**4** (25.9)
6	**3b**	2	**5** (69.6)
7	**6b**	5b)	**7b** (60.7)
8	**6c**	4c)	**7c** (95.3)

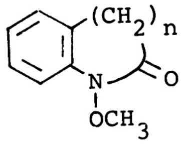
a) Many unidentifiable products. b) Reaction temp (RT), 60 °C. c) RT, 75 °C.

$C_6H_5(CH_2)_nCONHOCH_3$

1

a: n=0; **b**: n=1

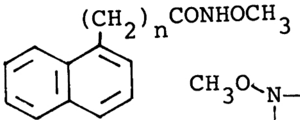
c: n=2; **d**: n=3



2b-d

b: n=1; **c**: n=2

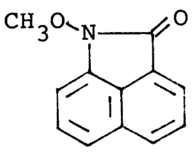
d: n=3



3a,b

a: n=0

b: n=1



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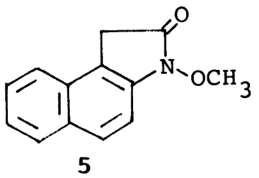

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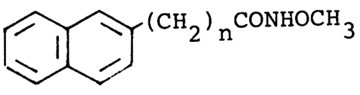
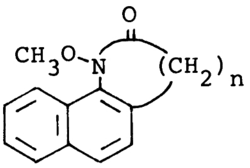


6b,c

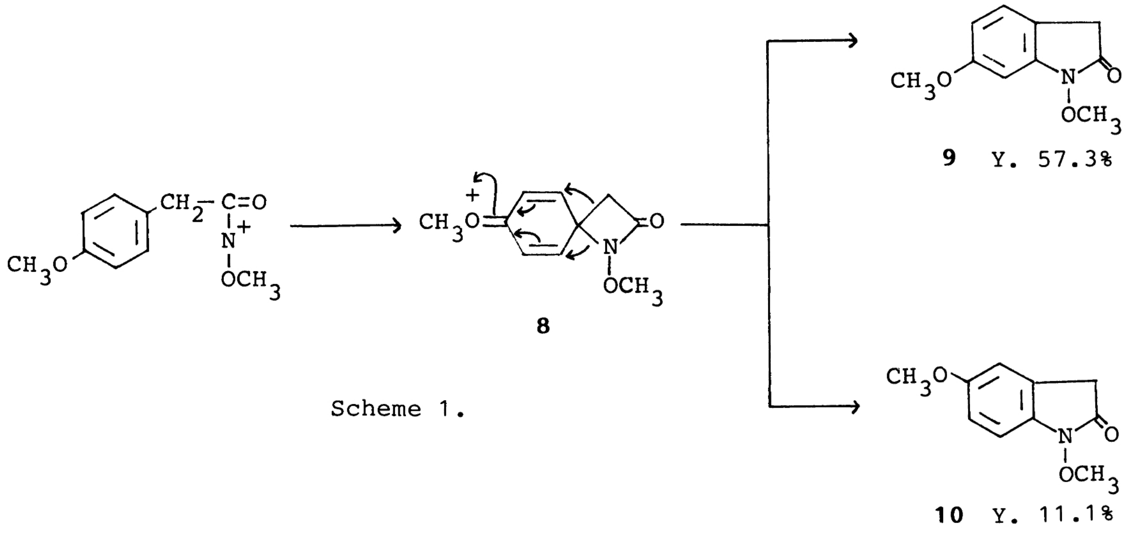
b: n=1; **c**: n=2



7b,c

b: n=1; **c**: n=2

This and Glover's results prompted us to investigate further the practical synthesis of nitrogen heterocycles without using TFA and expensive silver salts. After efforts to form **2b** from **1b** without using TFA, we have finally discovered that anhydrous zinc acetate shows an excellent ability for the cyclization in nitromethane (Table 1, Runs 9 and 10). It is worth to note that **2b** was not obtained in good yield with hydrated zinc acetate. Interestingly, **2b** was scarcely obtained with silver carbonate in nitromethane. Several N-chloro-N-methoxyamides were submitted to this reaction with optimum conditions and the results are presented in Table 2. A typical procedure is as follows: To N-methoxyphenylacetamide (**1b**, 14.84 g, 89.83 mmol) in dichloromethane (120 ml), t-butyl hypochlorite (12.19 ml, 107.8 mmol) was added with cooling. After 10-20 min, the solvent was evaporated in vacuo. The residue dissolved in nitromethane (10 ml) was added to the refluxing nitromethane (824 ml) suspended with anhydrous zinc acetate (82.42 g, 449.2 mmol). After 7 min insoluble materials were filtered off and washed with ethyl acetate (100 ml). The solvents combined were evaporated in vacuo and the residue was dissolved in ethyl acetate (900 ml), which was washed with 10% sodium bicarbonate (300 ml), saturated brine (2x200 ml) and dried (Na_2SO_4). After evaporation of the solvent in vacuo, recrystallization of the residue (14.6 g, mp 74-77 °C) from benzene-hexane and subsequent silica gel column chromatography of the mother solution using benzene-ethyl acetate (5:1,v/v) for elution gave pure 1-methoxy-2-oxindole (**2b**) (12.14 g, Y. 82.8%, mp 82-84 °C). As for the mechanism of this reaction, it is plausible to assume the intermediacy of a nitrenium ion which attacks the electron rich position of an aromatic ring.



Scheme 1.

From N-chloro-N-methoxy(p-methoxyphenyl)acetamide the two regioisomers (**9** and **10**)[6] were obtained as shown in Scheme 1. This is rationalized by way of the presence of a spiro intermediate (**8**) produced by the electrophilic intramolecular ipso attack with a nitrenium ion. The present method has the following practical advantages: simple operation; short reaction time; easy work up.[7]

References

1) Y. Kikugawa and M. Kawase, J. Am. Chem. Soc., 106, 5728 (1984).
2) T. Okamoto, K. Shudo, and T. Ohta, J. Am. Chem. Soc., 97, 7184 (1975).
3) S. A. Glover, A. Goosen, C. W. McCleland, and J. L. Schoonraad, J. Chem. Soc., Parkin Trans. 1, 1984, 2255.
4) Following Glover's method by using N-chloro-N-methoxyphenylacetamide as a starting material, we have obtained N-methoxy-N-phenylphenylacetate (32%) and 1-methoxy-2-oxindole (**2b**) (15%) with $AgBF_4$ for 24 h in benzene, and methyl phenylacetate (92%) in methanol. It is evident that TFA plays an important role for the generation and stabilization of a nitrenium ion.
5) All products were identified by the spectral data and elemental analyses.
6) They were characterized by the spectral data and elemental analyses, and also identified by reductive conversion with Pd/C in methanol for 27 h to 5- and 6-methoxy-2-oxindoles [A. H. Beckett, R. W. Daisley, and J. Walken, Tetrahedron, 24, 6093 (1968)].
7) Insoluble materials are easily filtered off and nitromethane is azeotropically removed with ethyl acetate.

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