

AlCl₃-mediated Regioselective Migration of a Methoxy Group of *N*-Methoxy-*N*-phenylamides to the *ortho* Position of the Phenyl Ring

Yasuo Kikugawa* and Masahiro Shimada

Faculty of Pharmaceutical Sciences, Josai University, 1-1 Keyakidai, Sakado, Saitama 350-02, Japan

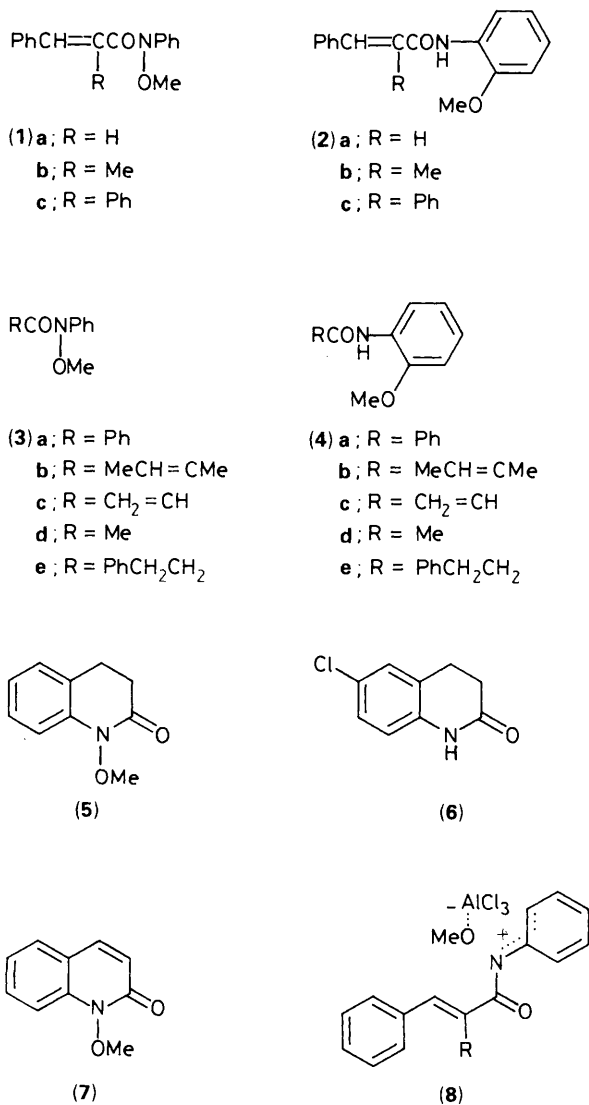
AlCl₃-mediated decomposition of *N*-methoxy-*N*-phenylamides in dichloroethane leads to regioselective intramolecular migration of the methoxy group from the nitrogen to the *ortho* position of the phenyl ring *via* a tight ion pair intermediate.

Although acid-catalysed hydrolysis of *N*-hydroxy-*N*-phenylacetamides in protic solvents has been studied^{1a} in detail and found to give aminophenols through preferential hydrolysis of the amide group over N–O bond heterolysis, there have been no reports, to our knowledge, concerning the reaction of *N*-phenylhydroxamic acids with Lewis acids in aprotic solvents, although *N*-phenylhydroxamic acids have been reacted with benzene in the presence of trifluoromethanesulphonic acid to form aminobiphenyl derivatives.²

In this Communication we report that AlCl₃-mediated decomposition of *N*-methoxy-*N*-phenylamides in dichloroethane (DCE) provides a new source of *N*-acyl-*N*-arylnitrenium ions³ and leads to the nucleophilic intramolecular

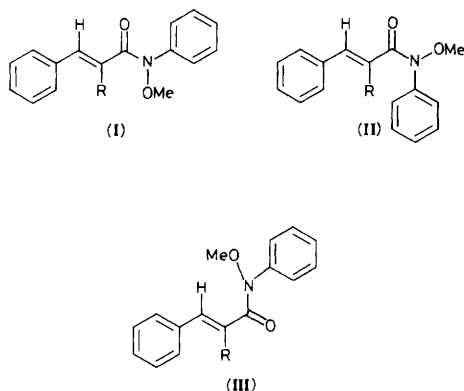
migration of the methoxy group from the nitrogen to the *ortho* position of the phenyl ring. We have investigated the reaction of *N*-methoxy-*N*-phenylcinnamamide (**1a**) with various Lewis acids (ZnCl₂, SnCl₄, FeCl₃, BF₃·Et₂O, and AlCl₃) in aprotic solvents (CH₂Cl₂, PhCl, MeNO₂, CS₂, and DCE) and found that the methoxy group migrated from the nitrogen, with AlCl₃[†] in DCE, to the *ortho* position of the phenyl ring in 79.4% yield; there was no migration to the *para* position. Two equiv. of AlCl₃ to (**1a**) were needed to obtain a high yield of *N*-(2-methoxyphenyl)cinnamamide (**2a**), and the use of 1.2 equiv. of AlCl₃ lowered the yield [**2a**, 31.9%; (**1a**), 60.9%; 45 h]. Prolonged reaction time or a higher reaction temperature brought about the demethylation of (**2a**). Several *N*-methoxy-*N*-phenylamides were reacted in this way, and the results are presented in Table 1.

Cinnamamides (**1b** and **c**) bearing α -substituent groups rearranged rapidly in high yields (runs 2,3), while *N*-methoxycarbostryls [1-methoxy-2(1H)-quinidinones] (**5**) and (**7**) did not, even with prolonged reaction times (runs 9 and 10). The most interesting aspect of this reaction is that rearrangement of (**1**) and (**3**) gave exclusively *N*-(*o*-methoxyphenyl)amides (**2**) and (**4**). The complete absence of the corresponding *para*-substituted products can be accounted for by assuming an intramolecular mechanism with a tight ion pair intermediate (**8**) which was formed by AlCl₃-mediated N–O bond heterolysis. A radical mechanism is not supported, as addition of a radical scavenger *N,N*-diphenylpicrylhydrazil did not affect this rearrangement. The configuration of the carbonyl oxygen and the methoxy oxygen in an *N*-methoxyamide group seems to influence the rate of this reaction. *N*-Phenylhydroxamic acids primarily have a configuration in which the two oxygens are on the same side;⁴ however, (**1b** and **c**) are assumed to have a configuration where the two oxygens are on opposite sides owing to steric hindrance by the phenyl group.[‡] Therefore, two moles of AlCl₃ co-ordinate with the oxygens to form a 2:1 complex, which enhances the rate of heterolytic N–O bond cleavage. On the other hand, (**5**) and (**7**) apparently have a configuration with two oxygens on the same side and one mole of AlCl₃ co-ordinates with these oxygens to form a 1:1 complex,⁵ which retards the N–O bond cleavage. Even if the N–O bond is cleaved, the *ortho* position becomes remote from the methoxide anion generated but the latter is



[†] Cinnamanilide (*N*-phenyl-3-phenylprop-2-enamide) (28.9%), *o*-chlorocinnamanilide (*o*-chloro-*N*-phenyl-3-phenylprop-2-enamide) (9.6%), and *N*-methoxy-*N*-phenyl-3-phenylprop-2-enamide (**1a**), (44.4%) were obtained with FeCl₃ and (**1a**) was recovered quantitatively with other acids.

[‡] The structures of cinnamamides are postulated as (I)–(III). (*E*)-Cinnamic acids were used as starting materials and the β -H signal (δ 7.80) of (**1a**) was shifted downfield owing to the deshielding effect of a carbonyl group compared with the corresponding H chemical shifts of (**1b**) (δ 6.84) and (**1c**) (δ 7.27), which supports the theory that the predominant structures of (**1a**, **b**, and **c**) are (I) (R = H) or (II) (R = H), (III) (R = Me), and (III) (R = Ph), respectively.

**Table 1.** Rearrangement of *N*-methoxy-*N*-phenylamides.^a

Run	Starting material	Time/min	Product %
1	(1a)	120	(2a) (79.4)
2	(1b)	25	(2b) (84.0)
3	(1c)	27	(2c) (95.3)
4	(3a)	37	(4a) (59.6), (3a) (6.1)
5	(3b)	50	(4b) (69.2), (3b) (13.5)
6	(3c)	960	(4c) (32.0) ^b
7	(3d)	140	(4d) (22.8), (3d) (57.9)
8	(3e)	120	(4e) (41.7), ^c (3e) (27.4)
9	(5)	1440	(5) (30.0), (6) (49.3) ^d
10	(7)	4320	(7) (77.9)

^a The reactions were carried out at room temperature with AlCl₃ (2 equiv.) in DCE. All new compounds reported in this Communication have been fully characterised by spectroscopic methods and elemental analyses. ^b Plus ca. 50% of a mixture of the *p*-chloroanilide and demethylated (4c). ^c Plus 18.6% of demethylated (4e). ^d A positive charge of a nitrenium ion generated by N–O bond heterolysis shifted to C-6 where a chloride anion was trapped.

held by AlCl₃, which still will be co-ordinated on the carbonyl oxygen side. The configuration of the methoxyamide group of other amides changes under different reaction conditions.

Compound (1a) was subjected to thermolysis (150 °C, 3 h), by which some *N*-acyloxy-*N*-arylamides were decomposed to give *N*-(*o*-acyloxyaryl)amides,⁶ to recover the starting material in 94.9% yield. Usually, liquid *N*-methoxy-*N*-arylamides may be distilled below 150 °C under reduced pressure, and crystalline compounds can be stored for several years without decomposition. *N*-Acetoxy-*N*-phenylacetamide was subjected to this AlCl₃-mediated decomposition and *ortho*-substituted products were not obtained; however, *p*-chloroacetanilide and the starting material were isolated in 40.5% and 12.9% yields, respectively. However, *N*-ethoxy- and *N*-hydroxy-*N*-phenylamides were decomposed with AlCl₃ to give the corresponding *N*-(*o*-ethoxy- and hydroxy-phenyl)-amides in moderate yields.

Received, 23rd June 1989; Com. 9/02664I

References

- (a) M. Novak, G. A. Bonham, L. K. Mohler, and K. M. Peet, *J. Org. Chem.*, 1988, **53**, 3903; (b) Y. Konda, M. Onda, A. Hirano, and S. Omura, *Chem. Pharm. Bull.*, 1980, **28**, 2987.
- Y. Endo, T. Ohta, K. Shudo, and T. Okamoto, *Heterocycles*, 1977, **8**, 367; G. Capozzi, A. Chimirri, S. Grasso, and G. Romeo, *ibid.*, 1984, **22**, 1759.
- R. A. Abramovitch and R. Jeyaraman, in 'Azides and Nitrenes,' ed. E. F. V. Scriven, Academic Press, New York, 1984, pp. 297–357.
- L. Bauer and O. Exner, *Angew. Chem., Int. Ed. Engl.*, 1974, **13**, 376.
- H. Imaizumi, Y. Hashida, and K. Matsui, *Bull. Chem. Soc. Jpn.*, 1978, **51**, 1507.
- L. Horner and H. Steppan, *Liebigs Ann. Chem.*, 1957, **606**, 24; T. Tissue, M. Grassmann, and W. Lwowski, *Tetrahedron*, 1968, **24**, 999; P. G. Gassman and J. E. Granrud, *J. Am. Chem. Soc.*, 1984, **106**, 1498, 2448.