Hydride Transfer Reaction Products in the Aminomethylation of Styrene

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Aminomethylation of styrene with formaldehyde and dimethylamine leads to *N*-methylbenzenepropanamine (*1*), *N*-(3-phenylpropyl)benzenepropanamine (*3*), and α -methylenebenzenepropanal (*4*) as major products. The ratio of *1*, *3* and *4* is considerably influenced by the ratio of the reactants. The best yield of *1* is obtained by using dimethylamine in excess. Styrene in excess favors the formation of *3*, and equivalent amounts of reactants afford the best yield of *4*. Using formaldehyde in excess leads to the complete *N*-methylation of *1* and *3*. When styrene reacts with formaldehyde and diethylamine or diisopropylamine the most important aminomethylation products are *N*-ethylbenzenepropanamine (*11*) or *N*-isopropylbenzenepropanamine (*12*), respectively, and *3* and *4* in both cases. The formation of the major products in the aminomethylation of styrene can be explained by the hydride transfer mechanism represented earlier as one competing mechanism for the aminomethylation of certain bicyclic alkenes. The *N*-methylation of amine *1* and *3*, when formaldehyde is used in excess, is due to Eschweiler methylation under aminomethylation conditions.

The products in the aminomethylation of alkenes with formaldehyde and a secondary amine are unsaturated tertiary amines and amino alcohols.¹⁰ However, certain alkenes react under these aminomethylation conditions to give mainly an aldehyde² and secondary amines.^{3–6} In the first case, the intermediates are carbocations, which undergo a proton elimination or a nucleophilic attack by water^{7,8} (carbocation mechanism). The formation of an unsaturated amine can also be formulated as an ene reaction.^{9,10} For aminomethylation leading to an aldehyde and amines a special hydride ion transfer (hydride transfer mechanisms) is encountered.^{2,3} These competing mechanisms have been found to occur in the aminomethylation of certain, mainly bicyclic, alkenes studied in our laboratory.^{4–6,9,10}

Several 1-alkenes, among them certain styrenes, were recently reported to undergo both the ene and hydride transfer reactions in the aminomethylation.¹¹ As the major product in the re-

action of *N,N*-dimethylmethyleneiminium ions with styrene one secondary amine, namely *N*-methylbenzenepropanamine (*1*) was isolated. One of the three major products was assumed to be *N,N*-diisopropylbenzenepropanamine (*2*), when diisopropylamine and trioxane were used in the aminomethylation of styrene.

Since the aminomethylation of styrene with *N,N*-dimethylmethyleneiminium ions with regard to the hydride transfer mechanism should also produce *N*-(3-phenylpropyl)benzenepropanamine (*3*) and α -methylenebenzenepropanal (*4*) as major products (Scheme 1) and as the formation of *2* in the aminomethylation conditions is quite surprising, we were interested in re-examining the aminomethylation of styrene.

Results

When styrene was heated with paraformaldehyde and dimethylammonium chloride in acetic acid, all the three expected compounds *1*, *3* and *4* were formed as major products. Amine *1*, reported in

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Scheme 1.

the recent study,¹¹ was isolated as *p*-toluenesulfonamide, amine 3 as hydrochloride and aldehyde 4 as semicarbazone. The structural elucidations of 3 and 4 are based on mass and NMR spectral data. The melting points of the derivatives are in accordance with the literature. The minor products in this aminomethylation, according to mass spectra, were 3-(dimethylamino)-1-phenyl-1-propanol acetate (5), *N*-methyl-*N*-(3-phenylpropyl)-benzenepropanamine (6), and *N*-methyl-*N*-(3-phenylpropyl)-3-phenyl-2-propen-1-amine (7) in addition to *N,N*-dimethylbenzenepropanamine (8) and *N,N*-dimethyl-3-phenyl-2-propen-1-

amine (9) mentioned in the recent study.¹¹ The yields of the major products are presented in Table 1.

In the second experiment styrene was allowed to react with *N,N,N',N'*-tetramethyldiaminomethane as described¹¹ except that nitrogen flushing of the reaction flask was not performed. By employing the same separation methods as in the first experiment, the three major products 1, 3 and 4 could be isolated (yields in Table 1). The minor aminomethylation products of this experiment were not examined. The same compounds 1, 3 and 4 formed when styrene reacted with 1-

Table 1. Yields of the major aminomethylation products of styrene.

Reactants/mol			Products %/mol		
Styrene/formaldehyde/dimethylamine			1	3	4
0.1	0.1	0.1	0.019	0.008	0.052
0.5	0.1	0.1	0.023	0.017	0.040
0.1	0.1	0.5	0.049	0.0015	0.0008
0.06	0.3	0.06	^b	^c	0.010
Styrene/[(CH ₃) ₂ N] ₂ CH ₂					
0.13	0.14		0.035	0.0059	0.013
Styrene/(CH ₃) ₂ NCH ₂ Cl					
0.1	0.1		0.018	0.008	0.014
Styrene/formaldehyde/amine 1					
0.015	0.015	0.015	—	0.0011	^d
Styrene/formaldehyde/amine 3					
0.0075	0.0075	0.0075	—	0.0043 ^e	0.0015

^a1 as *p*-toluenesulfonamide, 3 as hydrochloride, 4 as semicarbazone. ^bProduct amine 8. ^cProduct amine 6, the yield of 8 + 6 4.8 g, the ratio by GLC 75:25. ^dPresence of 4 in the product mixture was determined only qualitatively by GLC. ^eFormation of 3 during this aminomethylation was confirmed by allowing styrene to react with perdeuterioparaformaldehyde and 3. According to the mass spectrum amine obtained is 3, where four (4 %), three (2 %), two (31 %) or none (63 %) of the hydrogens in the carbons adjacent to nitrogen are substituted with deuteriums.

chloro-*N,N*-dimethylmethanamine in acetonitril (see Table 1). The same minor products 6, 7, 8 and 9 as in the first experiment and 3-dimethylaminophenyl-1-propanol (10) instead of its acetate 5 were determined by mass spectra.

To obtain information about the influence of reactant ratios on the yields of the main products the heating of styrene, paraformaldehyde and dimethylammonium chloride in acetic acid was repeated using each of the reactants in five fold excess. The use of styrene in excess clearly increased the yield of amine 3, whereas the change in the yields of 1 and 4 was small. The use of dimethylammonium chloride in excess caused changes in the yields of all three main products. The yield of 1 increased and the yields of 3 and 4 decreased strongly. The use of paraformaldehyde in excess and a prolonged reaction time led to the *N*-methylation of both amines 1 and 3.

To check the hydride transfer mechanism for the aminomethylation of styrene both amine 1 and 3 were used to generate iminium ions. The reaction of styrene, paraformaldehyde and 1 hydrochloride gave amine 3 and aldehyde 4 (Table 1). Employing amine 3 hydrochloride as the amine gave 4. A considerable amount of starting compound 1 was present in the product mixture in this case (Table 1).

The aminomethylation of styrene with formaldehyde and diethylammonium chloride gave *N*-ethylbenzenepropanamine (11) as the major product as reported¹¹ and also amine 3 and aldehyde 4. The minor products in this case were not examined.

The aminomethylation of styrene with trioxane and diisopropylamine in dioxane was repeated several times, both as reported¹¹ and analogously with the first experiment mentioned above. The only major product in the very low amine part of the product mixture was the reported¹¹ *N*-isopropylbenzenepropanamine (12). The minor products in the amine part were *N*-isopropyl-*N*-methylbenzenepropanamine (13), *N,N*-diisopropyl-3-phenyl-2-propen-1-amine (14), 3-(diisopropylamino)-1-phenyl-1-propanol acetate (15), *N*-(3-phenylpropyl)benzenepropanamine (3) and *N*-methyl-*N*-(3-phenylpropyl)benzenepropanamine (6). To study the presence of *N,N*-diisopropyl-3-phenylbenzenepropanamine (2) in the product mixture, a mass spectrum at an *m/z* value of 219, corresponding to the molecular ion of 2,

was also measured using chemical ionisation. However, no peak could be detected at this *m/z* value.

Discussion

The above results reveal that the major products in the reaction of styrene, formaldehyde and dimethylamine *via* the hydride transfer mechanism are secondary amines 1 and 3 and aldehyde 4. The mechanism for this case is depicted in Scheme 2. Step a) in Scheme 2 is the same as in the recent publication,¹¹ steps a), b) and c) together are analogous to the aminomethylation mechanism of norbornene³ and d) analogous to the formation of an α -methylene aldehyde in the aminomethylation of 2-methylenenorbornane.⁵ The formation of 3 and 4, when 1 was used instead of dimethylamine in the aminomethylation of styrene, confirms the steps b), c) and d). The similar use of 3 instead of dimethylamine and the formation of 4 in addition to 3 itself are in accordance with steps c) and d).

The ratio of the starting compounds in the aminomethylation of styrene has a considerable effect on the yields of 1, 3 and 4. The use of dimethylamine in excess favors the formation of 1. Styrene in excess produces more 3. The best yield of 4 is achieved by using equivalent amounts of starting compounds. The yield ratio of 1, 3 and 4 remains unchanged when formaldehyde and dimethylamine are replaced by an equivalent amount of *N,N,N',N'*-tetramethyldiaminomethane or 1-chloro-*N,N*-dimethylaminomethane.

The formation of *N*-ethylbenzenepropanamine (11), 3 and 4 from styrene, formaldehyde and diethylamine as major products is in accordance with the mechanism in Scheme 2. Similarly, the formation of *N*-isopropylbenzenepropanamine (12), 3 and 4 can be explained with the mechanism analogous to that in Scheme 2. The low yield of 12 and the very low yields of 3 and 4 in this case are due to the steric hindrance in the hydride transfers. The only major product in this synthesis was 12. This is contrary to the results published in the recent report,¹¹ where *N,N*-diisopropylbenzenepropanamine (2) is believed to be the most important component among the two other products 12 and 14. The conclusion drawn from the mass spectral measurements and gas chromatographic analysis is that no 2 was formed

Scheme 2.

from styrene, formaldehyde and diisopropylamine in our experiments.

The formation of most minor products in the aminomethylation of styrene can be explained by the carbocation mechanism. The ene-reaction,¹² which implies a hydrogen in the allylic position, is not possible in the case of styrene. Minor products, formed *via* the carbocation mechanism from styrene, formaldehyde and dimethylamine are *N,N*-dimethyl-3-phenyl-2-propen-1-amine (9) as reported,¹¹ the corresponding acetate 5 and alcohol 10 and the unsaturated amine 7 formed *via* 1 as an intermediate. The other minor products in this case are tertiary amines 6 and 8. They are clearly Eschweiler methylation products of the amines 3 and 1, respectively. When formaldehyde is used in excess, the methylation is complete, and 6 and 8 are major products instead of 3 and 1. These kinds of *N*-methylations, which are also associated with an intramolecular 1,3-hydride transfer have been discussed in an earlier report.¹³

Experimental

Heating of styrene with paraformaldehyde and dimethylammonium chloride. Typical procedure. Styrene (10.5 g, 0.1 mol), paraformaldehyde (3.0 g, equivalent to 0.1 mol of formaldehyde) and dimethylammonium chloride (8.2 g, 0.1 mol) were heated in acetic acid (50 ml) for 5 h at 115°C. Water (300 ml) and ether (50) were added and the mixture was allowed to stand at 5°C overnight. The resulting solid product was separated from the mixture by filtration, washed with ether and water and dried. The yield of *N*-(3-phenylpropyl)benzenepropanamine (3) hydrochloride, melting at 205–206°C, (lit.¹⁴ 202–203°C), was 2.4 g (0.008 mol). The amine 3 salt (0.5 g) was decomposed in hot water (30 ml) by solid potassium carbonate to give *N*-(3-phenylpropyl)benzenepropanamine (3), which was distilled in a bulb tube oven at 160°C/2.7 kPa. Yield nearly quantitative.

MS *m/z* (% rel. int.): 253 (6, M), 148 (64, M – PhCH₂CH₂), 117 (7), 105 (4), 91 (66), 77 (7), 65 (8), 44 (100). Mol. wt., obs. 253.1830, calc. for C₁₈H₂₃N 253.1847.

^1H NMR (100 MHz): δ 1.09 (1H, s), 1.78 (4H), 2.62 (8H), 7.20 (10H).

^{13}C NMR (25.05 MHz): δ 142.2, 128.3 and 125.7 (Ph), 49.5, 33.7 and 31.6 (CH_2).

The acidic filtrate of the reaction mixture was extracted four times with 50 ml of ether. The combined ethereal extracts were dried with calcium sulfate. The residue after the evaporation of the solvents, followed by treatment with semicarbazide hydrochloride (8.2 g) and sodium acetate (8.2 g) in an ethanol (80 ml) and water (30 ml) mixture gave 10.5 g (0.052 mol) semicarbazone of α -methylenebenzenepropanal, m.p. 185–186°C (from ethanol, lit.¹⁵ m.p. 187–189°C). The semicarbazone was decomposed with oxalic acid in boiling water to give α -methylenebenzenepropanal (4), which was distilled in a bulb tube oven at 70°C/2.7 kPa.

MS m/z (% rel. int.): 146 (85, M), 115 (100), 91 (93), 78 (59), 65 (68), 51 (43), 39 (48). Mol. wt., obs. 146.0750, calc. for $\text{C}_{10}\text{H}_{10}\text{O}$ 146.0732.

^1H NMR (100 MHz): δ 3.56 (2H, s), 6.06 (2H, d, J 4.0 Hz), 7.24 (5H, m), 9.59 (1H, s).

^{13}C NMR (25.05 MHz): δ 193.9 (C=O), 149.9 (α -C), 138.1, 129.1, 128.3 and 126.4 (Ph), 135.1 (olefinic CH_2), 34.1 (benzylic CH_2).

The acidic filtrate of the reaction mixture was then made alkaline with a cold saturated sodium hydroxide solution. The amines were extracted into ether. The main component of this part, *N*-methylbenzenepropanamine (1), was separated as *p*-toluenesulfonamide (yield 5.7 g, 0.019 mol, m.p. 40.5–41.5°C from ethanol, lit.¹⁶ m.p. 41.8–42.4°C), followed by hydrolysis¹⁷ with 48% hydrobromic acid. The spectral data of 1 are similar to those described in the literature.¹¹ The minor components in this amine fraction are: 3-(dimethylamino)-1-phenyl-1-propanol acetate (5) with a MS m/z (% rel. int.) 221 (M, 10), 178 (24), 117 (6), 104 (16), 91 (19), 77 (20), 58 (100); *N*-methyl-*N*-(3-phenylpropyl)benzenepropanamine (6) with a MS m/z (% rel. int.) 267 (M, 20), 162 (100), 91 (50), 58 (100), 44 (14), lit.¹⁸ 267 (M, 50), 162 (100), 91 (77), 58 (77); *N*-methyl-*N*-(phenylpropyl)-3-phenyl-2-propen-1-amine (7) with a MS m/z (% rel. int.) 265 (M, 3), 174 (4), 160 (20), 146 (4), 117 (100), 91 (33), 77 (7), 58 (18), 44 (21); *N,N*-dimethylbenzenepropanamine (8) with a MS m/z (% rel. int.) 163 (M, 28), 117 (8), 104 (11), 91 (44), 77 (14), 58 (100); and *N,N*-dimethyl-3-phenyl-2-propen-1-amine (9) with a MS m/z (% rel. int.) 161 (M, 92), 146 (35), 117 (92),

115 (94), 91 (80), 84 (58), 70 (100), 58 (100), 42 (75).

Heating of styrene with N,N,N',N'-tetramethyldiaminomethane. Styrene (13.2 g, 0.13 mol), *N,N,N',N'*-tetramethyldiaminomethane (13.8 g, 0.14 mol), sulfuric acid (23 g, 0.23 mol) and acetic acid (150 ml) were heated for 5 h. The acetic acid was removed and the major products were isolated: *N*-methylbenzenepropanamine (1) as *p*-toluenesulfonamide, yield 10.6 g (0.025 mol), *N*-(3-phenylpropyl)benzenepropanamine (3) as hydrochloride, yield 1.7 g (0.0059 mol) and α -methylenebenzenepropanal (4) as semicarbazone, yield 2.72 g, (0.013 mol).

Heating of styrene with 1-chloro-N,N-dimethylmethanamine. Styrene (10.6 g, 0.1 mol) and 1-chloro-*N,N*-dimethylmethanamine (9.7 g, 0.1 mol) were heated in acetonitrile (100 ml) for 12 h. Acetonitrile was evaporated, the major products isolated and the minor products detected by mass spectra. The three major products were *N*-methylbenzenepropanamine (1), yield 5.4 g (0.018 mol) as *p*-toluenesulfonamide, *N*-(3-phenylpropyl)benzenepropanamine (3), yield 2.35 g (0.008 mol) as hydrochloride and α -methylenebenzenepropanal (4), yield 2.93 g (0.014 mol) as semicarbazone. The minor components were amines 6, 7, 8, 9 and 3-dimethylamino-1-phenyl-1-propanol (10) with a MS m/z (% rel. int.) 179 (M, 10), 105 (13), 77 (16), 58 (100).

Heating of styrene with trioxane and diethylammonium chloride. Styrene (12.8 g, 0.12 mol), trioxane (3.8 g, equivalent to 0.12 mol of formaldehyde), and diethylammonium chloride (13.1 g, 0.12 mol) were refluxed in acetic acid (150 ml) in the presence of phosphoric acid (23 g, 0.23 mol). Most of the acetic acid was evaporated and the neutral products were separated from amines by extraction. Yield of amine 3 hydrochloride was 0.15 g (0.0005 mol). The presence of aldehyde 4 among the neutrals was detected only by a mass spectrum. Distilling the crude amine (3.3 g) gave *N*-ethylbenzenepropanamine (11), b.p. 53–58°C/9 Pa, yield 0.9 g (0.005 mol), ^1H NMR is as described.¹¹

MS m/z (% rel. int.): 163 (M, 16), 117 (8), 91 (32), 58 (100).

^{13}C NMR (25.05 MHz): δ 142.2, 128.4, 128.3 and 125.7 (Ph), 49.3, 44.1, 33.8 and 31.7 (CH_2), 15.2 (CH_3).

Heating of styrene with trioxane and diisopropylamine. Styrene (12.8 g, 0.12 mol), trioxane

(10.8 g, equivalent to 0.36 mol of formaldehyde), diisopropylamine (12.2 g, 0.12 mol), phosphoric acid (23 g, 0.23 mol) and acetic acid (145 ml) were refluxed for 5 h. Most of the acetic acid was evaporated and the neutral products were separated from amines by extraction. α -Methylenebenzenepropanal is among the neutral products according to mass spectrum. The major product in the amine part is *N*-isopropylbenzenepropanamine (12), yield 0.7 g (0.004 mol).

MS m/z (% rel. int.): 177 (M, 45), 162 (100), 117 (10), 91 (70), 72 (78). Mol. wt., obs. 177.1547, calc. for $C_{12}H_{15}N$ 177.1517.

1H NMR (100): δ 1.03 (6H, d, J 6.2 MHz), 1.95–1.63 (2H, m), 2.89–2.56 (5H, m).

^{13}C NMR (25.05 MHz): δ 141.9, 128.1 and 125.5 (Ph), 48.6 (CH_2), 47.0 (CH), 33.8 and 32.0 (CH_2), 23.0 (CH_3).

The minor components in the amine part are *N*-isopropyl-*N*-methylbenzenepropanamine (13) with a MS m/z (% rel. int.) 191 (M, 10), 176 (23), 107 (10), 91 (28), 86 (100), 72 (20); *N,N*-diisopropyl-3-phenyl-2-propen-1-amine (14) with a MS m/z (% rel. int.) 217 (M, 8), 202 (20), 117 (100), 91 (10); 3-(diisopropylamino)-1-phenyl-1-propanol acetate (15) with a MS m/z (% rel. int.) 277 (M, 6), 262 (42), 114 (100), 98 (4), 91 (6), 72 (18), 56 (34), 43 (32); *N*-(3-phenylpropyl)benzenepropanamine (3), and *N*-methyl-*N*-(3-phenylpropyl)benzenepropanamine (6).

Apparatus. MS analyses were recorded on a Kratos MS 80 RF spectrometer at 70 eV. 1H NMR and ^{13}C NMR spectra were run on a JEOL FX 100 instrument using $CDCl_3$ as a solvent. The gas chromatographic analyses were performed on a Carlo Erba Fractovap 2900 instrument equipped with capillary columns OV-101 (25 m) or SE-54 (16 m).

References

1. Hellmann, H. and Opitz, G. *α -Aminoalkylierung*, Verlag Chemie, Weinheim 1960, p. 90.
2. Krieger, H. and Manninen, K. *Tetrahedron Lett.* (1966) 6483.
3. Manninen, K. *Acta Univ. Oul. A2 Chem. 1* (1972).
4. Manninen, K. and Haapala, J. *Acta Chem. Scand. B28* (1974) 433; Manninen, K. *Finn. Chem. Lett.* (1980) 146.
5. Södervall, M. *Acta Univ. Oul. A67, Chem. 7* (1978).
6. Yrjänheikki, E. *Acta Univ. Oul. A103, Chem. 11* (1980).
7. Hennion, G. F., Price, C. C. and Wolff, V. C. Jr. *J. Amer. Chem. Soc.* 77 (1955) 4633.
8. Schmidle, C. J. and Mansfield, R. C. *J. Amer. Chem. Soc.* 77 (1955) 4636.
9. Krieger, H., Arstila, A. and Koskenniska, L. *University of Oulu, Report Series in Chemistry n:o 10* (1983).
10. Krieger, H., Lumme, H., Petäjä, T., Talvitie, A. and Vainio, U.-M. *University of Oulu, Report Series in Chemistry n:o 18* (1984).
11. Cohen, T. and Onopchenko, A. *J. Org. Chem.* 48 (1983) 4531.
12. Hoffmann, H. M. R. *Angew. Chem.* 81 (1969) 597.
13. Manninen, K. *Acta Chem. Scand. B28* (1974) 603.
14. Kindler, K., Melamed, G. and Matthies, D. *Justus Liebigs Ann. Chem.* 644 (1961) 23.
15. Hayashi, Y., Nagano, Y., Hongyo, S. and Teramura, K. *Tetrahedron Lett.* (1974) 1299.
16. Cope, A. C. and McElvain, S. M. *J. Amer. Chem. Soc.* 53 (1931) 1587.
17. Snyder, H. R. and Heckert, R. E. *J. Amer. Chem. Soc.* 74 (1952) 2006; Snyder, H. R. and Geller, H. C. *Ibid.* 74 (1952) 4864.
18. Kuehne, M. E. and Shannon, P. J. *J. Org. Chem.* 42 (1977) 2082.

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