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Acyl Iodides in Organic Synthesis. Reactions with Morpholine, Piperidine, and *N*-Hydrocarbylpiperidines

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Abstract—Acyl iodides RCOI (R = Me, Ph) reacted with morpholine and piperidine to give the corresponding *N*-acyl derivatives and morpholine or piperidine hydroiodides. Reactions of acyl iodides with *N*-methyl- and *N*-ethylpiperidines involved cleavage of the exocyclic R–N bond with formation of *N*-acylpiperidine and alkyl iodide and were accompanied (to insignificant extent) by cleavage of the endocyclic N–C bond, leading to *N*-alkyl-*N*-(5-iodopentyl)acylamides. In the reaction of acetyl iodide with *N*-phenylpiperidine, the main process was cleavage of just endocyclic N–C bond to produce *N*-(5-iodopentyl)-*N*-phenylacetamide and its dehydroiodination product, *N*-(pent-4-en-1-yl)-*N*-phenylacetamide. Analogous reaction with benzoyl iodide afforded *N*-(5-iodopentyl)-*N*-phenylbenzamide in a poor yield.

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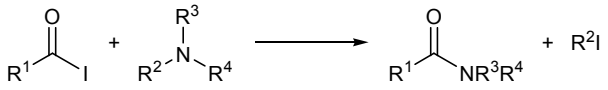
We previously showed [1] that acyl iodides react with excess primary and secondary amines in a way similar to acyl chlorides (but considerably more readily) to give the corresponding carboxylic acid amides and initial amine hydroiodides. In contrast, reactions of acyl iodides with tertiary amines occur under mild conditions in the absence of a catalyst via cleavage of N–C bond in the amine and formation of the corresponding *N*,*N*-disubstituted carboxylic acid amides and alkyl iodides (Scheme 1).

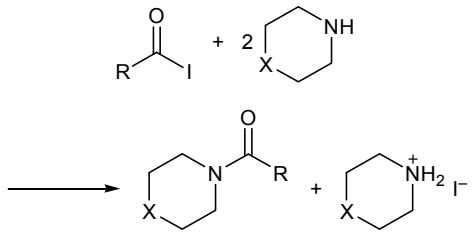
Scheme 1.



R^1 = Me, Ph; R^2 = R^3 = R^4 = Et, Bu, CH_2=$CHCH_2$; R^2 = $PhCH_2$, R^3 = R^4 = Me; R^2 = R^3 = Et, R^4 = Ph.

The N–C bond in tertiary amines is cleaved by acyl iodides most readily if one of the substituents on the nitrogen atom is a benzyl, allyl, or alkyl group. No cleavage of $N–C_{Ph}$ bond was observed under these conditions. With a view to elucidate factors responsible for cleavage of the endocyclic N–C bond in cyclic aliphatic amines and extend the synthetic potential of acyl iodides, we examined their reactions with morpholine, piperidine, and *N*-substituted piperidines. Acetyl and benzoyl iodides RCOI (R = Me, Ph) reacted with 2 equiv of morpholine or piperidine in methylene chloride at room temperature to give the corresponding *N*-acylated amines and amine hydroiodides (Scheme 2); analogous products were formed in the reactions with acyclic secondary amines. It should be noted that, unlike ethers [2], the C–O–C fragment in morpholine molecule remained intact under the given conditions.

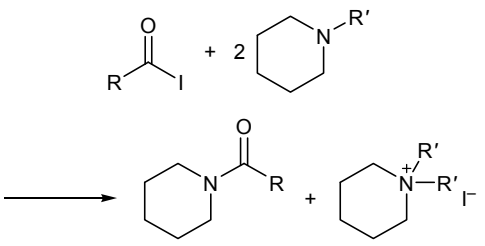
Scheme 2.



R = Me, Ph; X = CH_2, O.

The reactions of acyl iodides with *N*-methyl- and *N*-ethylpiperidines at a molar ratio of 1:2 in methylene chloride at room temperature involved mainly cleavage of the exocyclic N–C bond, which is typical of their reactions with other tertiary amines [1] (Scheme 3). The reactions with *N*-methylpiperidine were accom-

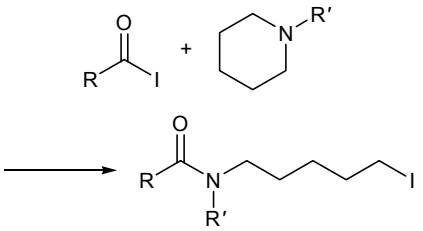
Scheme 3.



R = Me, Ph; R′ = Me, Et.

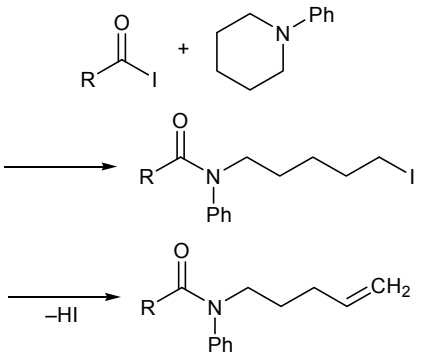
panied to an insignificant extent by cleavage of the endocyclic N–C bond, leading to *N*-alkyl-*N*-(5-iodopentyl) amides (yield 1.7 and 3.4% for R = Me and Ph, respectively; Scheme 4). No analogous side process was observed with *N*-ethylpiperidine.

Scheme 4.



Taking into account that no cleavage of N–C_{Ph} bond occurs in reactions of acyl iodides with N,N-disubstituted anilines [1], we examined their reactions with *N*-phenylpiperidine at a molar ratio of 1:1 in benzene at 80°C. As might be expected, the products were the corresponding *N*-(5-iodopentyl)-*N*-phenyl-substituted amides which were formed as a result of cleavage of the endocyclic N–C bond (Scheme 5). The yield was 12% (calculated on the reacted *N*-phenylpiperidine) for R = Me. *N*-(5-Iodopentyl)-*N*-phenylacetamide underwent dehydroiodination to (*N*-pent-4-en-1-yl)-*N*-phenylacetamide whose yield reached 81% (on the reacted *N*-phenylpiperidine). The yield of analogous product in

Scheme 5.



the reaction with benzoyl iodide was low, presumably due to steric effect of two phenyl groups, and no dehydroiodination was observed.

Our results (Schemes 3–5) are very consistent with those reported previously for reactions acyl iodides with tertiary amines [1]. In both cases, quaternary ammonium salt is formed as intermediate via addition of acyl iodide at the nitrogen atom of *N*-hydrocarbylpiperidine. When R = Alk, the adduct decomposes with cleavage of the exocyclic C–N bond and formation of alkyl iodide which then reacts with excess *N*-alkylpiperidine. If R = Ph, cleavage of the endocyclic N–C bond gives rise to 5-iodopentyl group on the nitrogen atom, which undergoes dehydroiodination (R = Me).

EXPERIMENTAL

The NMR spectra were recorded on a Bruker DPX-400 spectrometer at 400.13 MHz for ^{1}H and 100.58 MHz for ^{13}C using $CDCl_3$ as solvent and tetramethylsilane or cyclohexane as reference. The reaction mixtures and products were analyzed by GLC on a Tsvet-500 chromatograph equipped with a thermal conductivity detector and a glass column, 3 m×4 mm, packed with 10% of PSM-1000 on Inerton Super (0.125–0.150 mm); carrier gas helium. The mass spectra were obtained on a Shimadzu GCMS-QP5050A (SPB-5ms capillary column, 60 m× 250 μm, film thickness 0.25 μm; quadrupole mass analyzer, electron impact, 70 eV, ion source temperature 230°C, a.m.u. range 34–650) or LKB-2091 GC–MS instrument (SE-54 capillary column, 38 m; ion source temperature 240°C, electron impact, 60 eV).

Initial acetyl and benzoyl iodides were synthesized by reaction of the corresponding acyl chlorides with anhydrous sodium iodide [3].

Reaction of acetyl iodide with morpholine. Acetyl iodide, 0.85 g (5 mmol), was added dropwise under stirring to a solution of 0.87 g (10 mmol) of morpholine in 6 ml of methylene chloride. The mixture was stirred for 9 h at room temperature, and the precipitate was filtered off, washed with methylene chloride, and dried under reduced pressure. Yield of morpholine hydroiodide 0.51 g (47%). Found, %: C 21.05; H 5.23; I 62.1; N 6.72. C_4H_9INO. Calculated, %: C 22.43; H 4.21; I 59.35; N 6.54. *M* 214. The filtrate was evaporated to isolate 0.52 g of a mixture containing (according to the GC–MS data) 73% of unreacted morpholine [mass spectrum, *m*/*z* (I_{rel}, %): 87 (70), 71 (20), 58 (45), 43 (50)] and 27% of *N*-acetylmorpholine (yield 22%). ^{1}H NMR spectrum, δ, ppm:

2.07 s (3H, CH_3), 3.25 m (4H, CH_2O), 3.54 m (4H, CH_2N). ^{13}C NMR spectrum, δ_C, ppm: 21.42 (CH_3), 43.25 and 41.50 (CH_2N), 65.62 (CH_2O), 167.97 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 129 (8) $[M]^+$, 114 (20), 86 (70), 71 (20), 58 (45), 43 (50).

Reaction of benzoyl iodide with morpholine. Benzoyl iodide, 1.16 g (5 mmol), was added dropwise under stirring to a solution of 0.87 g (12 mmol) of morpholine in 6 ml of methylene chloride. The mixture was stirred for 6 h at room temperature, and the precipitate was filtered off, washed with methylene chloride, and dried under reduced pressure. Yield of morpholine hydroiodide 0.46 g (43%). Found, %: C 23.56; H 5.34; I 62.67; N 6.92. $C_8H_{12}IN$. Calculated, %: C 22.34; H 4.65; I 59.07; N 6.51. *M* 214. The filtrate was evaporated to isolate 0.68 g (71%) of *N*-benzoylmorpholine, mp 74°C; published data [4]: mp 74–75°C. ^1H NMR spectrum, δ, ppm: 3.28–3.77 m (8H, CH_2), 7.25–7.34 m (5H, Ph). ^{13}C NMR spectrum, δ_C, ppm: 42.42 and 47.26 (CH_2N), 66.52 (CH_2O), 127.07–135.56 (Ph), 169.23 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 191 (8) $[M]^+$, 114 (25), 105 (78), 86 (65), 77 (65), 56 (15).

Reaction of acetyl iodide with piperidine. Acetyl iodide, 2.55 g (15 mmol), was added dropwise under stirring to a solution of 1.3 g (15 mmol) of piperidine in 6 ml of methylene chloride. The mixture was stirred for 9 h at room temperature, the solvent was distilled off, and the residue was distilled under reduced pressure to isolate 0.3 g (16%) of *N*-acetylpiperidine, bp 73°C (3 mm); published data [5]: bp 226°C. ^1H NMR spectrum, δ, ppm: 1.68 m (2H, CH_2), 2.09 s (3H, CH_3CO), 3.26 m (2H, CH_2N). ^{13}C NMR spectrum, δ_C, ppm: 21.41 (**C**H_3CO), 25.01 (CH_2), 26.2 (CH_2), 47.26 (CH_2N), 168.6 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 127 (80) $[M]^+$, 112 (20), 99 (10), 84 (100), 70 (40), 56 (45), 43 (50), 15 (2).

Reaction of benzoyl iodide with piperidine. Benzoyl iodide, 1.16 g (5 mmol), was added dropwise under stirring to a solution of 1.0 g (12 mmol) of piperidine in 6 ml of methylene chloride. The mixture was stirred for 6 h at room temperature, the solvent was distilled off, and the residue was distilled under reduced pressure to isolate 0.8 g (85%) of *N*-benzoylpiperidine, bp 138°C (3 mm); published data [5]: bp 180°C (15 mm). ^1H NMR spectrum, δ, ppm: 3.28–3.77 m (8H, CH_2), 7.34–7.45 m (5H, Ph). Mass spectrum, *m*/*z* (I_{rel}, %): 189 (33) $[M]^+$, 188 (90) $[M - H]^+$, 105 (80), 84 (10), 77 (35), 51 (15).

Reaction of acetyl iodide with *N*-ethylpiperidine. Acetyl iodide, 0.90 g (5.3 mmol), was added dropwise under stirring to a solution of 1.3 g (11.5 mmol) of *N*-ethylpiperidine in 5 ml of methylene chloride. The mixture was stirred for 6 h at room temperature, the solvent was distilled off, and distillation of the residue gave 0.49 g (72%) of *N*-acetylpiperidine and 0.8 g (61%) of initial *N*-ethylpiperidine, bp 131°C, n_D^{20} = 1.4440. ^1H NMR spectrum, δ, ppm: 1.06 t (CH_2CH_3), 1.39 m (6H, CH_2), 2.26 m (4H, CH_2N), 2.36 q (CH_2CH_3). Mass spectrum, *m*/*z* (I_{rel}, %): 113 (25) $[M]^+$, 98 (100), 84 (10), 70 (7), 56 (10), 42 (30), 28 (10), 15 (3).

Reaction of acetyl iodide with *N*-methylpiperidine. Acetyl iodide, 1.0 g (6 mmol), was added dropwise under stirring to a solution of 1.18 g (12 mmol) of *N*-methylpiperidine in 5 ml of methylene chloride. The mixture was stirred for 6 h at room temperature, the solvent was distilled off, and distillation of the residue gave 0.48 g (65%) of *N*-acetylpiperidine and 0.51 g (43%) of initial *N*-methylpiperidine, bp 107°C, n_D^{20} = 1.4355. ^1H NMR spectrum, δ, ppm: 1.39 m (6H, CH_2), 2.62 s (3H, CH_3), 2.86 m (4H, CH_2N). Mass spectrum, *m*/*z* (I_{rel}, %): 98 (10) $[M - H]^+$, 84 (25), 70 (20), 58 (15), 42 (20), 28 (10), 15 (3). According to the GC–MS data, the residue (1.12 g) contained 2.42% of *N*-(5-iodopentyl)-*N*-methylacetamide. Yield 0.028 g (2%). Mass spectrum, *m*/*z* (I_{rel}, %): 252 (5) $[M - Me]^+$, 211 (20), 197 (3), 126 (100), 72 (3), 56 (4), 43 (45).

Reaction of benzoyl iodide with *N*-methylpiperidine. Benzoyl iodide, 0.78 g (34 mmol), was added dropwise under stirring to a solution of 1.11 g (11 mmol) of *N*-methylpiperidine in 5 ml of methylene chloride. The mixture was stirred for 6 h at room temperature, and the precipitate was filtered off, washed, and dried under reduced pressure. Yield of *N*,*N*-dimethylpiperidinium iodide 0.4 g (50%). Found, %: C 35.07; H 6.93; I 53.94; N 6.12. $C_8H_{12}IN$. Calculated, %: C 34.87; H 6.69; I 52.7; N 5.81. *M* 241. The solvent was distilled off from the filtrate, and the residue was distilled to isolate 0.53 g (84%) of *N*-benzoylpiperidine. According to the GC–MS data, the residue (1.25 g) contained 3.31% of *N*-(5-iodopentyl)-*N*-methylbenzamide. Yield 0.04 g (3%). Mass spectrum, *m*/*z* (I_{rel}, %): 238 (18), 223 (3), 204 (20), 197 (3), 148 (30), 134 (10), 119 (3), 105 (100), 77 (31), 51 (6).

Reaction of acetyl iodide with *N*-phenylpiperidine. Acetyl iodide, 1.86 g (11 mmol), was added dropwise under stirring to a solution of 1.76 g (11 mmol) of *N*-phenylpiperidine in 7 ml of benzene. The mixture was stirred for 3 h at 80°C, and the solvent was distilled off to isolate 1.6 g (91%) of unreacted *N*-phenylpiperidine. ^1H NMR spectrum, δ,

ppm: 1.61–1.63 m (6H, CH_2), 3.17–3.20 m (4H, CH_2N), 6.84–6.96 m and 7.25–7.27 m (5H, Ph). Mass spectrum, *m*/*z* (I_{rel}, %): 161 (70) $[M]^+$, 160 (100) $[M - H]^+$, 146 (5), 132 (15), 120 (20), 105 (35), 91 (10), 77 (45), 51 (20). According to the GC–MS data, the residue (1.25 g) contained 3.2% of *N*-(5-iodopentyl)-*N*-phenylacetamide, yield 0.04 g (12%, calculated on the reacted *N*-phenylpiperidine) {mass spectrum, *m*/*z* (I_{rel}, %): 331 (10) $[M]^+$, 316 (3), 288 (5), 238 (5), 204 (15), 197 (5), 134 (31), 119 (13), 91 (20), 77 (45), 51 (6), 43 (18)}, and 14.4% of *N*-(pent-4-en-1-yl)-*N*-phenylacetamide, yield 0.18 g (81%, calculated on the reacted *N*-phenylpiperidine) {mass spectrum, *m*/*z* (I_{rel}, %): 203 (20) $[M]^+$, 188 (13), 160 (100), 126 (20), 112 (80), 83 (10), 77 (30), 56 (60), 43 (45), 14 (25)}.

Reaction of benzoyl iodide with *N*-phenylpiperidine. Benzoyl iodide, 2.81 g (12 mmol), was added dropwise under stirring to a solution of 1.95 g (12 mmol) of *N*-phenylpiperidine in 7 ml of benzene. The mixture was stirred for 3 h at 80°C, the solvent was distilled off, and distillation of the residue gave 1.07 g (55%) of unreacted *N*-phenylpiperidine. According to the GC–MS data, the residue (1.25 g) contained 11.3% of *N*-(5-iodopentyl)-*N*-phenylbenzamide. Mass spectrum, *m*/*z* (I_{rel}, %): 393 (8) $[M]^+$, 331 (4), 288 (3), 266 (5), 211(5), 197 (20), 180 (2), 169 (5), 155 (3), 132 (3), 105 (100), 77 (31), 51 (6).

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