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## Acyloxy group exchange in *N*-acyloxy-*N*-alkoxyamides<sup>†</sup>

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Vasily G. Shtamburg,<sup>a</sup> Alexandr V. Tsygankov,<sup>a</sup> Evgeniy A. Klots<sup>a</sup> and Remir G. Kostyanovsky<sup>\*b</sup>

<sup>a</sup> Department of Chemistry, Dnepropetrovsk National University, 49050 Dnepropetrovsk, Ukraine.

Fax: + 38 056 776 5833; e-mail: [heterosycle@ff.dsu.dp.ua](mailto:heterosycle@ff.dsu.dp.ua)

<sup>b</sup> N. N. Semenov Institute of Chemical Physics, Russian Academy of Sciences, 119991 Moscow, Russian Federation.

Fax: +7 095 651 2191; e-mail: [kost@chph.ras.ru](mailto:kost@chph.ras.ru)

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Acyloxy group exchange at the nitrogen atom proceeds in the interaction of *N*-acyloxy-*N*-alkoxyureas, *N*-acyloxy-*N*-alkoxybenzamides and *N*-acyloxy-*N*-alkoxycarbamates with Na and K carboxylates in MeCN.

The first *N*-acyloxy-*N*-alkoxy-*N*-*tert*-alkylamine has been synthesised earlier.<sup>1</sup> In *N*-acyloxy-*N*-alkoxyureas, *N*-acyloxy-*N*-alkoxycarbamates and *N*-acyloxy-*N*-alkoxybenzamides, the acyloxy group is an anionic leaving group, and nucleophilic substitution can take place.<sup>2–4</sup> In *N*-acyloxy-*N*-alkoxybenzamides, the nucleophilic substitution of the acyloxy group

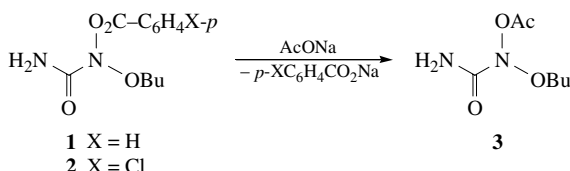
proceeds under the action of amines,<sup>3,4</sup>  $\text{NaN}_3$ <sup>5,6</sup> and alkaline hydrolysis,<sup>7</sup> but the initially formed products are unstable and undergo decomposition. *N*-Acyloxy-*N*-alkoxysubstituted ureas and carbamates afford corresponding stable *N,N*-dialkoxy derivatives under alcoholysis.<sup>2</sup> The possibility of selective nucleophilic substitution at the nitrogen atom in these *N*-acyloxy-*N*-alkoxyamides under the action of different nucleophiles is ambiguous because of both competitive nucleophilic attacks

<sup>†</sup> Geminal systems, part 51. Previous communication see ref. 2.

at other electrophilic centres and redox reactions.<sup>2</sup> In this connection, the search of nucleophiles that selectively attack the nitrogen atom and yield relatively stable initial products of the nucleophilic substitution is needed. In this work, the carboxylate anions were chosen as such selective nucleophiles. It should be mentioned that the acyloxy group substitution by another acyloxy group is discussed in our article for the first time.

We found that the acyloxy group exchange at the nitrogen atom occurs when *N*-acyloxy-*N*-alkoxy-substituted ureas, benzamides and carbamates react with Na and K carboxylates in MeCN (18–23 °C) and, as a rule, it is not accompanied by competitive processes.<sup>‡</sup>

In the case of *N*-acyloxy-*N*-alkoxyureas, when Na carboxylates were used, the reaction did not proceed to the end, and a mixture of starting and final ureas was obtained. Probably, it is a consequence of the reversibility of this reaction. The separation of the mixture of both Na carboxylates and the repeating treatment by a new portion of Na carboxylate increases the yield of the product. Thus, the successive treatment of *N*-benzoyloxy-*N*-butyloxyurea **1** by two portions of AcONa yields the mixture of urea **1** and *N*-acetoxy-*N*-butyloxyurea **3** in a ratio of 70:30. The mixture of ureas **2** and **3** in a ratio of 27:73 was obtained from *N*-*p*-chlorobenzoyloxy-*N*-butyloxyurea **2** after stirring with AcONa for 80 h (Scheme 1).



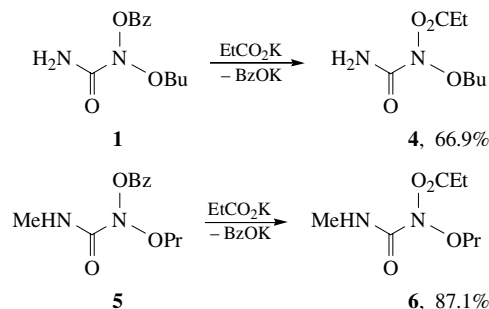
**Scheme 1** Reagents and conditions: for **1**, 3 equiv. AcONa, MeCN, 20–23 °C, (a) 30 h, (b) 20 h; for **2**, 4.5 equiv. AcONa, MeCN, 20 °C, (a) 80 h, (b) 104 h.

<sup>‡</sup> The standard method of the acyloxy group exchange in *N*-acyloxy-*N*-alkoxyamides. (A). A solution of *N*-benzoyloxy-*N*-butyloxyurea **1** (0.452 g, 1.793 mmol) in MeCN (30 ml) and EtCO<sub>2</sub>K (1.57 g, 14 mmol) was stirred for 37 h at 18–20 °C; the solid was filtered off and washed with Et<sub>2</sub>O (15 ml); the filtrate was concentrated *in vacuo*; the residue was extracted with Et<sub>2</sub>O (20 ml); the extract was evaporated *in vacuo*. The residue was dissolved in MeCN (25 ml); the solution was stirred with EtCO<sub>2</sub>K (1.57 g, 14 mmol) for 83 h; the solid was filtered off and washed with Et<sub>2</sub>O (20 ml). The filtrate was evaporated *in vacuo*; the residue was extracted with Et<sub>2</sub>O (20 ml); the ether was removed *in vacuo*, yielding 0.245 g (66.9%) of *N*-propionyloxy-*N*-butyloxyurea **4** as a colourless liquid. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ: 0.95 [t, 3H, NO(CH<sub>2</sub>)<sub>3</sub>Me, <sup>3</sup>J 7 Hz], 1.22 [t, 3H, O<sub>2</sub>CCH<sub>2</sub>Me, <sup>3</sup>J 7.2 Hz], 1.39 [t qu, 2H, NO(CH<sub>2</sub>)<sub>2</sub>CH<sub>2</sub>Me, <sup>3</sup>J 7 Hz], 1.68 (quint, 2H, NOCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>Me, <sup>3</sup>J 7 Hz), 2.46 (qu, 2H, O<sub>2</sub>CCH<sub>2</sub>Me, <sup>3</sup>J 7.2 Hz), 4.09 (t, 2H, NOCH<sub>2</sub>, <sup>3</sup>J 7 Hz), 5.64 (br. s, 1H, NH), 5.97 (br. s, 1H, NH). Found (%): C, 46.93; H, 8.02; N, 13.94. Calc. for C<sub>8</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub> (%): C, 47.05; H, 7.90; N, 13.72. According to Scheme 5, compound **4** was obtained in 82% yield.

(B). A solution of compound **7** (0.5 g, 1.82 mmol) in MeCN (23 ml) and AcOK (0.98 g, 10 mmol) were stirred for 55 h at 20 °C; the solid was filtered off and washed with CH<sub>2</sub>Cl<sub>2</sub> (7 ml). The filtrate was evaporated *in vacuo*; the residue was extracted with CH<sub>2</sub>Cl<sub>2</sub> (10 ml); the extract, was evaporated *in vacuo*. 0.38 g of a colourless liquid was obtained. According to <sup>1</sup>H NMR spectrum, it is a mixture of *N*-acyloxy-*N*-methoxycarbamates **7** and **8** in a molar ratio of 42:58. An additional treatment with two portions of AcOK followed by distillation *in vacuo* yielded pure *N*-acetoxy-*N*-methoxycarbamate **8** (0.17 g, 53%).<sup>2</sup>

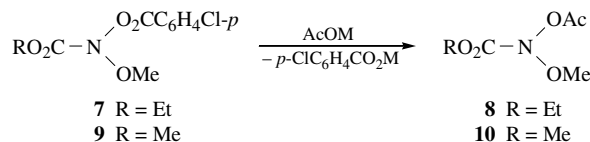
Standard method for the synthesis of *N*-acyloxy-*N*-alkoxyamides. A solution of *N*-chloro-*N*-ethoxyurethane **15**<sup>2</sup> (1.12 g, 7.3 mmol) in MeCN (40 ml) and *p*-ClC<sub>6</sub>H<sub>4</sub>CO<sub>2</sub>Na (2.6 g, 14.6 mmol) were stirred for 55 h at 18–20 °C; the solid was filtered off and washed with CH<sub>2</sub>Cl<sub>2</sub> (30 ml). The filtrate was evaporated *in vacuo*; the residue was extracted with CH<sub>2</sub>Cl<sub>2</sub> (10 ml). The extract was evaporated *in vacuo*; hexane (4 ml) was added. The mixture was kept at –2 °C; the precipitate was filtered and washed with hexane (3 ml). 1.27 g (63.6%) of ethyl *N*-*p*-chlorobenzoyloxy-*N*-methoxycarbamate **7** was obtained as colourless crystals, mp 25–27 °C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ: 1.35 (t, 3H, CO<sub>2</sub>CH<sub>2</sub>Me, <sup>3</sup>J 7.2 Hz), 3.97 (s, 3H, OMe), 4.36 (qu, 2H, CO<sub>2</sub>CH<sub>2</sub>Me, <sup>3</sup>J 7.2 Hz), 7.47 (d, 2H, C<sub>6</sub>H<sub>4</sub>, <sup>3</sup>J 8.4 Hz), 8.03 (d, 2H, C<sub>6</sub>H<sub>4</sub>, <sup>3</sup>J 8.4 Hz). IR (ν/cm<sup>-1</sup>): 1790 (C=O), 1780 (C=O). Found (%): C, 48.11; H, 4.62; N 5.02. Calc. for C<sub>11</sub>H<sub>12</sub>ClNO<sub>5</sub> (%): C, 48.28; H, 4.42; N, 5.12.

The repeated treatment of this mixture by a fresh portion of AcONa (104 h) yielded pure *N*-acetoxy-*N*-butyloxyurea **3** in 42% yield. The more complete *N*-acyloxy group exchange was achieved by the interaction of *N*-benzoyloxy-*N*-alkoxyureas with K carboxylates. By the twofold treatment with EtCO<sub>2</sub>K, ureas **1** and **5** were fully converted into corresponding *N*-propionyloxy-*N*-alkoxyureas **4**<sup>†</sup> and **6**, respectively (Scheme 2).



**Scheme 2** Reagents and conditions: for **4**, 7.8 equiv. EtCO<sub>2</sub>K, MeCN, 18–20 °C, (a) 37 h, (b) 83 h; for **6**, 5.3 equiv. EtCO<sub>2</sub>K, MeCN, 22 °C, (a) 61 h, (b) 12 h.

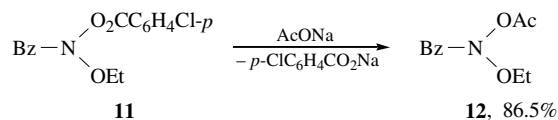
The interaction of ethyl *N*-chlorobenzoyloxy-*N*-methoxycarbamate **7** with two portions of AcONa yielded ethyl *N*-acetoxy-*N*-methoxycarbamate **8**. The ratio of carbamates **7** and **8** in the reaction mixture was 71:29 (Scheme 3).



**Scheme 3** Reagents and conditions: for R = Et, 3.6 equiv. AcONa, MeCN, 20 °C, (a) 32 h, (b) 41 h; 5.5 equiv. AcOK, MeCN, 20 °C, (a) 55 h, (b) 65 h, (c) 86 h; for R = Me, 3 equiv. AcOK, MeCN, 20 °C, (a) 44 h, (b) 165 h.

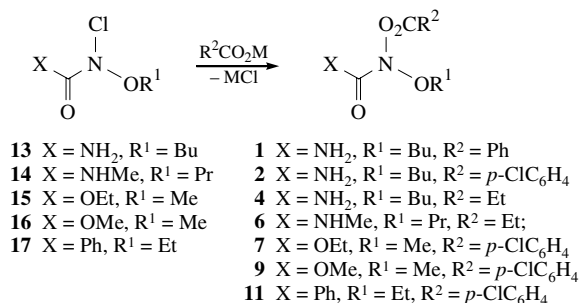
The replacement of AcONa by AcOK also results in more complete exchange of acyloxy group: the ratio of compounds **7** and **8** is 42:58.<sup>‡</sup> An additional treatment by two portions of AcOK followed by distillation of the reaction mixture gives pure carbamate **8** in 53% yield. By analogy, methyl *N*-*p*-chlorobenzoyloxy-*N*-methoxycarbamate **9** is converted into methyl *N*-acetoxy-*N*-methoxycarbamate **10** with a 75% yield by treatment with two portions of AcOK.

*N*-*p*-Chlorobenzoyloxy-*N*-ethoxybenzamide **11** reacts more actively than carbamate **7**, and after stirring with two portions of AcONa, compound **11** is converted into *N*-acetoxy-*N*-ethoxybenzamide **12** (Scheme 4).



**Scheme 4** Reagents and conditions: 5.7 equiv. AcONa, MeCN, 20 °C, (a) 48 h, (b) 73 h.

Compounds **3**, **5**, **8**, **10** and **12** were described earlier;<sup>2</sup> new compounds **1**, **2**, **7**,<sup>‡</sup> **9** and **11** were obtained by the reactions



**Scheme 5** Reagents and conditions: 2.5 equiv. R<sub>2</sub>CO<sub>2</sub>M, M = Na, K, MeCN, 20 °C, 25–55 h.

of corresponding *N*-chloro-*N*-alkoxyamides **13–17** with Na and K carboxylates. Analogously, the counter synthesis of *N*-propionyloxy-*N*-alkoxyureas **4, 6** was performed by the reactions of *N*-chloro-*N*-alkoxyureas **13, 14** with EtCO<sub>2</sub>K (Scheme 5).

Thus, the following compounds were obtained.

*N*-Benzoyloxy-*N*-butyloxyurea **1**: yield 90.9%, viscous colourless oil, mp 18–20 °C. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ: 0.93 [t, 3H, O(CH<sub>2</sub>)<sub>3</sub>Me, <sup>3</sup>J 7 Hz], 1.40 [t qu, 2H, O(CH<sub>2</sub>)<sub>2</sub>CH<sub>2</sub>Me, <sup>3</sup>J 7 Hz], 1.72 (quint, 2H, OCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>Me, <sup>3</sup>J 7 Hz), 4.19 (t, 2H, NOCH<sub>2</sub>, <sup>3</sup>J 7 Hz), 5.80 (br. s, 2H, NH<sub>2</sub>), 7.47 (t, 2H, Ph, <sup>3</sup>J 7.2 Hz), 7.58 (t, 1H, Ph, <sup>3</sup>J 7.2 Hz), 8.10 (d, 2H, Ph, <sup>3</sup>J 7.2 Hz). Found (%): C, 57.07; H, 6.28; N, 11.34. Calc. for C<sub>12</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub> (%): C, 57.13; H, 6.39; N, 11.10.

*N*-p-Chlorobenzoyloxy-*N*-butyloxyurea **2**: yield 75%, colourless crystals, mp 79–80 °C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ: 0.93 [t, 3H, NO(CH<sub>2</sub>)<sub>3</sub>Me, <sup>3</sup>J 7.2 Hz], 1.39 [t qu, 2H, NO(CH<sub>2</sub>)<sub>2</sub>CH<sub>2</sub>Me, <sup>3</sup>J 7.2 Hz], 1.71 (quint, 2H, NOCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>Me, <sup>3</sup>J 7.2 Hz), 4.17 (t, 2H, NOCH<sub>2</sub>, <sup>3</sup>J 7.2 Hz), 6.10 (br. s, 2H, NH<sub>2</sub>), 7.46 (d, 2H, C<sub>6</sub>H<sub>4</sub>, <sup>3</sup>J 8.4 Hz), 8.03 (d, 2H, C<sub>6</sub>H<sub>4</sub>, <sup>3</sup>J 8.4 Hz). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ: 13.7 (Me), 19.0, 30.0 (CH<sub>2</sub>), 75.6 (CH<sub>2</sub>O), 125.9 [C(4)], 129.0 [C(3), C(5)], 131.4 [C(2), C(6)], 140.5 [C(1)], 160.3 (H<sub>2</sub>NC=O), 163.9 (C=O). Found (%): C, 50.14; H, 5.42; N, 9.61. Calc. for C<sub>12</sub>H<sub>15</sub>ClN<sub>2</sub>O<sub>4</sub> (%): C, 50.27; H, 5.27; N, 9.77.

*N*-Propionyloxy-*N*-propyloxy-*N*'-methylurea **6**: yield 77%, colourless liquid. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ: 0.95 (t, 3H, NOCH<sub>2</sub>CH<sub>2</sub>Me, <sup>3</sup>J 6.9 Hz), 1.21 (t, 3H, NO<sub>2</sub>CCH<sub>2</sub>Me, <sup>3</sup>J 7.5 Hz), 1.71 (t qu, 2H, NOCH<sub>2</sub>CH<sub>2</sub>Me, <sup>3</sup>J 6.9 Hz), 2.45 (qu, 2H, NO<sub>2</sub>CCH<sub>2</sub>Me, <sup>3</sup>J 7.5 Hz), 2.90 (d, 3H, NHMe, <sup>3</sup>J 5.1 Hz), 4.03 (t, 2H, NOCH<sub>2</sub>, <sup>3</sup>J 6.9 Hz), 6.42 (br. s, 1H, NH). Found (%): C, 47.22; H, 8.15; N, 13.48. Calc. for C<sub>8</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub> (%): C, 47.05; H, 7.90; N 13.72.

*Methyl N*-p-chlorobenzoyloxy-*N*-methoxycarbamate **9**: yield 77%, colourless crystals, mp 33–34 °C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ: 3.92 (s, 3H, NOME), 3.97 (s, 3H, CO<sub>2</sub>Me), 7.47 [d, 2H, C(3)H, C(5)H, <sup>3</sup>J 8.4 Hz], 8.03 [d, 2H, C(2)H, C(6)H, <sup>3</sup>J 8.4 Hz]. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ: 55.3 (NOME), 63.4 (CO<sub>2</sub>Me), 125.6 [C(4)], 129.2 [C(3), C(5)], 131.5 [C(2), C(6)], 140.8 [C(1)], 158.5 (CO<sub>2</sub>Me), 163.7 (C=O). Found (%): C, 46.11; H, 3.92; N, 5.20. Calc. for C<sub>10</sub>H<sub>10</sub>ClNO<sub>5</sub> (%): C, 46.26; H, 3.88; N, 5.39.

*N*-p-Chlorobenzoyloxy-*N*-ethoxybenzamide **11**: yield 90%, colourless viscous oil. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ: 1.31 (t, 3H, NOCH<sub>2</sub>Me, <sup>3</sup>J 7 Hz), 4.34 (qu, 2H, NOCH<sub>2</sub>Me, <sup>3</sup>J 7 Hz), 7.41 (t, 2H, Ph, <sup>3</sup>J 7.5 Hz), 7.42 (d, 2H, C<sub>6</sub>H<sub>4</sub>, <sup>3</sup>J 8.7 Hz), 7.53 (t, 1H, Ph, <sup>3</sup>J 7.5 Hz), 7.84 (d, 2H, Ph, <sup>3</sup>J 7.5 Hz), 7.94 (d, 2H, C<sub>6</sub>H<sub>4</sub>, <sup>3</sup>J 8.7 Hz). Found (%): C, 59.87; H, 4.63; N, 4.16. Calc. for C<sub>16</sub>H<sub>14</sub>ClNO<sub>4</sub> (%): C, 60.10; H, 4.41; N, 4.38.

Thus, the acyloxy group exchange in *N*-acyloxy-*N*-alkoxyamides was performed for the first time.

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