Russian Journal of Organic Chemistry, Vol. 41, No. 7, 2005, pp. 1011–1015. Translated from Zhurnal Organicheskoi Khimii, Vol. 41, No. 7, 2005, pp. 1034–1038.

Reformatsky Reaction of Methyl α-Bromoisobutyrate with 2-Arylmethylidenemalonic Acid Derivatives

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Received July 22, 2004

Abstract—Reformatsky reagent obtained by treatment of methyl α-bromoisobutyrate with zinc reacts with dimethyl 2-arylmethylidenemalonates to give trimethyl 2-aryl-3-methylbutane-1,1,3-tricarboxylates. The reaction of the same compound with ethyl 3-aryl-2-(4-methylphenylcarbamoyl)acrylates yields cyclic products, ethyl 4-aryl-5,5-dimethyl-1-(4-methylphenyl)-2,6-dioxopiperidine-3-carboxylates. Treatment of the latter with morpholine and phenylhydrazine leads to the corresponding 4-aryl-5,5-dimethyl-1-(4-methylphenyl)-2,6-dioxopiperidine-3-carboxylic acid morpholides and phenylhydrazides. The products are formed as a single diastereoisomer.

We previously studied Reformatsky reactions of diethyl bromomalonate with dimethyl 2-alkylidene- and 2-arylmethylidenemalonates [1]. The goal of the present work was to involve in analogous reaction 2-arylmethylidenemalonic acid derivatives with a view to obtain 1,4-addition products which could be converted into heterocycles of the 2,6-dioxopiperidine series. As starting compound we used methyl α-bromoisobutyrate which was treated with zinc to generate Reformatsky reagent **I**. The latter readily reacted with methyl 2-arylmethylidenemalonates **IIa**–**IIc** to give intermediates **IIIa**–**IIIc** whose hydrolysis resulted in formation of trimethyl 2-aryl-3-methylbutane-1,1,3-tricarboxylates **IVa**–**IVc** in high yields (Scheme 1).

The structure of products **IVa**–**IVc** was proved by elemental analysis and ^{1}H NMR spectroscopy. The ^{1}H NMR spectra of **IVa**–**IVc** contained two singlets from methyl protons in the δ region 0.93–1.15 ppm and two doublets at δ 4.04–4.06 and 3.86–3.88 ppm from protons on C^2 and C^1, respectively, with a coupling constant ^3J of 10 Hz. According to the ^{1}H NMR data, compounds **IVa**–**IVc** were formed as a single stereoisomer.

Alkyl malonates are known to readily react with amines [2]; in these reactions, one or both ester groups are converted into amide groups. We tried to perform reactions of esters **IVa**–**IVc** with *p*-toluidine and cyclohexylamine with a view to obtain the corresponding amides. However, numerous experiments with variation of the reactant ratio (**IV**–amine, 1 : 1.5 to 1 : 3), reaction time (1 to 6 h under reflux), and solvent (*o*-xylene, toluene, ethanol, 2-propanol) were unsuccessful. As a result, we isolated either unchanged initial esters or unidentified liquid substances. Presumably, the reason is steric hindrances created by bulky substituents at C^3 in molecules **IVa**–**IVc**.

Therefore, we selected another strategy for synthesizing target heterocycles of the 2,6-dioxopiperidine series via Reformatsky reaction of methyl α-bromoisobutyrate with ethyl 3-aryl-2-(4-methylphenylcarbamoyl)acrylates **Va**–**Vc** which were prepared by the procedure described in [2]. In the first stage, bromozinc intermediates **VIa**–**VIc** were formed; these intermediates underwent intramolecular cyclization to dioxopiperidine derivatives **VIIa**–**VIIc**; and hydrolysis of the latter afforded the desired ethyl 4-aryl-5,5-dimethyl-1-(4-methylphenyl)-2,6-dioxopiperidine-3-carboxylates **VIIIa**–**VIIIc** (Scheme 2). The structure of compounds **VIIIa**–**VIIIc** was confirmed by the IR and ^{1}H NMR spectral data. In the IR spectra of **VIIIa**–**VIIIc** we observed absorption bands typical of C=O groups in the piperidine ring (1695 cm^{-1}) and ester carbonyl group (~1720 cm^{-1}). The ^{1}H NMR spectra of **VIIIa**–**VIIIc** contained two doublets from the methyl groups on C^5 (δ 1.07–1.22 ppm) and two doublets from 3-H and 4-H at δ 4.63–4.65 and 3.63–3.67 ppm, respectively, ^3J = 14 Hz. According to the ^{1}H NMR data,

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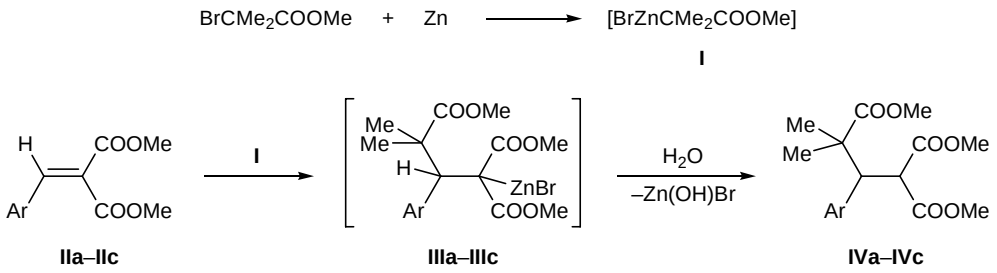
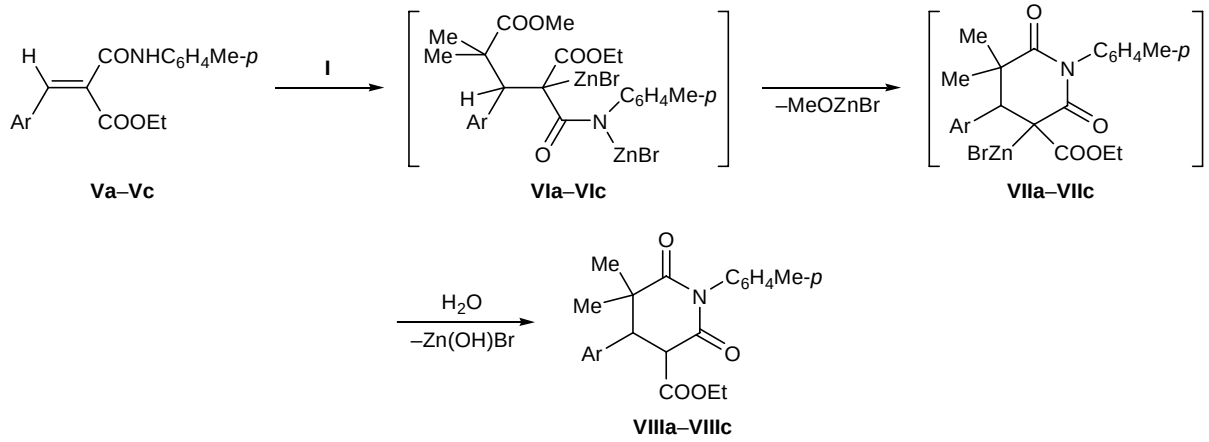
Scheme 1.



Ar = 4-BrC_6H_4 (**a**), 4-ClC_6H_4 (**b**), 3,4-$(MeO)_2C_6H_3$ (**c**).

Scheme 2.

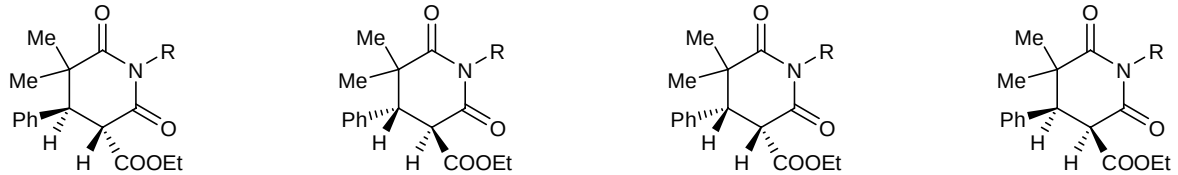


Ar = Ph (**a**), 3-BrC_6H_4 (**b**), 4-$Me_2NC_6H_4$ (**c**).

compounds **VIIIa**–**VIIIc** were formed as a single stereoisomer.

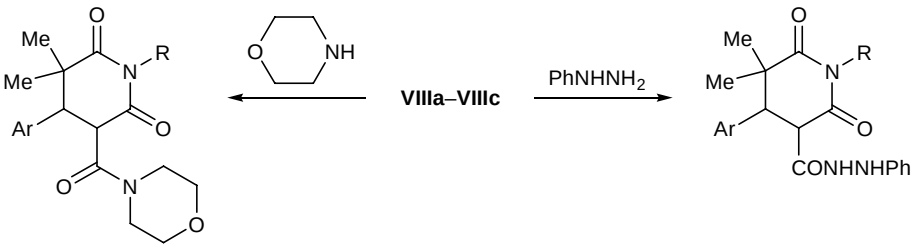
In order to obtain an additional information on the structure of compounds **VIIIa**–**VIIIc** we performed MNDO (SCF MO LCAO) quantum-chemical calculations [3] of ethyl 5,5-dimethyl-1-(4-methylphenyl)-2,6-dioxo-4-phenylpiperidine-3-carboxylate (**VIIIa**). Theoretically, compound **VIIIa** can exist as four stereoisomers **A**–**D** shown in Scheme 3. According to the calculations, the most stable stereoisomers are **A** and **B** in which the bulky phenyl and ethoxycarbonyl groups on C^3 and C^4 are maximally distant from each other. On the other hand, the spin–spin coupling constants calculated by the Karplus equation (using the Bothner-By parameters) [4] from the dihedral angles HC^3C^4H for stereoisomers **A** and **B** were equal to

Scheme 3.



R = 4-MeC_6H_4.

Scheme 4.



IXa–IXc **Xa**, **Xb**

VIII, **IX**, R = 4-MeC_6H_4, Ar = Ph (**a**), 3-BrC_6H_4 (**b**), 4-$Me_2NC_6H_4$ (**c**); **X**, R = 4-MeC_6H_4, Ar = Ph (**a**), 4-$Me_2NC_6H_4$ (**b**).

~13 Hz. Comparison of the theoretical and experimental values of $^3J_{3,4}$ suggests that ethyl 4-aryl-5,5-dimethyl-1-(4-methylphenyl)-2,6-dioxopiperidine-3-carboxylates **VIIIa**–**VIIIc** have structure **A** or **B**.

We also performed reactions of esters **VIIIa**–**VIIIc** with morpholine and phenylhydrazine and obtained the corresponding morpholides **IXa**–**IXc** and phenylhydrazides **Xa** and **Xb** (Scheme 4). The structure of compounds **IXa**–**IXc**, **Xa**, and **Xb** was confirmed by elemental analysis and ^{1}H NMR spectroscopy. Their ^{1}H NMR spectra contained two singlets from the methyl groups on C^5 (δ 1.03–1.07 and 1.19–129 ppm) and two doublets from protons on C^3 and C^4 at δ 4.41–4.96 and 3.71–3.86 ppm, respectively, $^3J_{3,4}$ = 14 Hz. Compounds **IXa**–**IXc** showed in the ^{1}H NMR spectra a broadened multiplet from methylene protons in the morpholine ring (δ 3.15–3.50 ppm), and hydrazides **Xa** and **Xb** displayed signals from the CONH and N**H**Ph protons at δ 9.70 and 6.21 ppm, respectively. The similar $^3J_{3,4}$ values for **VIIIa**–**VIIIc**, on the one hand, and **IXa**–**IXc**, **Xa**, and **Xb**, on the other, lead us to presume that the latter also have structure of diastereoisomers **A** and **B**.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer. The ^{1}H NMR spectra were measured on a Bruker spectrometer (400 MHz; TMS; **VIIIa**–**VIIIc**, **IXa**–**IXc**, **Xa**, **Xb**) and on an RYa-2310 instrument (60 MHz; HMDS; **IVa**–**IVc**) from solutions in $CDCl_3$.

Trimethyl 2-aryl-3-methylbutane-1,1,3-tricarboxylates IVa–IVc (*general procedure***).** Methyl α-bromoisobutyrate, 3.62 g (0.020 mol), was added dropwise under stirring to a mixture of 4 g (0.062 mol) of zinc prepared as fine turnings, 2 g (0.013 mol) of dimethyl arylmethylidenemalonate, 4 ml of diethyl ether, and 15 ml of benzene. The mixture was heated to initiate the reaction which then proceeded spontaneously. When the reaction was complete, the mixture was heated for 15 min on a water bath, cooled, treated with 5% hydrochloric acid, and extracted with benzene. The extract was dried over anhydrous sodium sulfate, the solvent was distilled off, and the residue was recrystallized thrice from methanol.

Trimethyl 2-(4-bromophenyl)-3-methylbutane-1,1,3-tricarboxylate (IVa). Yield 81%, mp 92–93°C. ^{1}H NMR spectrum, δ, ppm: 0.93 s and 1.13 s (3H each, 3-CH_3); 3.27 s, 3.57 s, and 3.68 s (3H each, OCH_3); 3.86 d (1H, 1-H, J = 10 Hz); 4.06 d (1H, 2-H, J = 10 Hz); 7.20–7.31 m (4H, 4-BrC_6H_4, J = 8 Hz). Found, %: C 50.80; H 5.32. $C_{17}H_{21}BrO_6$. Calculated, %: C 50.88; H 5.285.

Trimethyl 2-(4-chlorophenyl)-3-methylbutane-1,1,3-tricarboxylate (IVb). Yield 90%, mp 72–74°C. ^{1}H NMR spectrum, δ, ppm: 0.94 s and 1.15 s (3H each, 3-CH_3); 3.24 s, 3.60 s, and 3.66 s (3H each, OCH_3); 3.87 d (1H, 1-H, J = 10 Hz); 4.04 d (1H, 2-H, J = 10 Hz); 7.23–7.34 m (4H, 4-ClC_6H_4, J = 8 Hz). Found, %: C 57.17; H 5.87. $C_{17}H_{21}ClO_6$. Calculated, %: C 57.22; H 5.94.

Trimethyl 2-(3,4-dimethoxyphenyl)-4-methylbutane-1,1,3-tricarboxylate (IVc). Yield 86%, mp 70–72°C. ^{1}H NMR spectrum, δ, ppm: 0.94 s and 1.12 s (3H each, 3-CH_3); 3.25 s, 3.57 s, and 3.68 s (3H each, OCH_3); 3.86 d (1H, 1-H, J = 10 Hz); 4.06 d (1H, 2-H, J = 10 Hz); 7.20–7.32 m (3H, C_6H_3, J = 8 Hz). Found, %: C 59.11; H 6.99. $C_{19}H_{26}O_6$. Calculated, %: C 59.66; H 6.86.

Ethyl 4-aryl-5,5-dimethyl-1-(4-methylphenyl)-2,6-dioxopiperidine-3-carboxylates VIIIa–VIIIc (*general procedure***).** Ethyl α-bromoisobutyrate, 5.43 g (0.03 mol), was added dropwise under stirring to a mixture of 6 g (0.092 mol) of fine zinc turnings, 3 g (0.013 mol) of ethyl 3-aryl-2-(4-methylphenylcarba-

moyl)acrylate, 4 ml of diethyl ether, 15 ml of benzene, and 4 ml of HMPA. The mixture was heated to initiate the reaction which then proceeded spontaneously. When the reaction was complete, the mixture was heated for 30 min on a water bath, ~5 to 8 ml of THF was added, and the mixture was heated for an additional 30 min, cooled, treated with 5% hydrochloric acid, and extracted with benzene. The extract was dried over anhydrous sodium sulfate, the solvent was distilled off, and the residue was recrystallized thrice from methanol.

Ethyl 5,5-dimethyl-1-(4-methylphenyl)-2,6-dioxo-4-phenylpiperidine-3-carboxylate (VIIIa). Yield 50%, mp 168–169°C. ^{1}H NMR spectrum, δ, ppm: 1.09 s and 1.21 s (3H each, 5-CH_3), 0.89 t (3H, $OCH_2C\mathbf{H}_3$, J = 7 Hz), 3.87 q (2H, $OC\mathbf{H}_2CH_3$, J = 7 Hz), 2.53 s (3H, $C\mathbf{H}_3C_6H_4$), 3.65 d (1H, 4-H, J = 14 Hz), 4.64 d (1H, 3-H, J = 14 Hz), 7.05 d and 7.26 d (2H each, $CH_3C_6\mathbf{H}_4$, J = 8 Hz), 7.30–7.40 m (5H, C_6H_5). Found, %: C 72.61; H 6.56. $C_{23}H_{25}NO_4$. Calculated, %: C 72.80; H 6.64.

Ethyl 4-(3-bromophenyl)-5,5-dimethyl-1-(4-methylphenyl)-2,6-dioxopiperidine-3-carboxylate (VIIIb). Yield 59%, mp 128–129°C. ^{1}H NMR spectrum, δ, ppm: 1.08 s and 1.20 s (3H each, 5-CH_3), 0.88 t (3H, $OCH_2C\mathbf{H}_3$, J = 7 Hz), 3.85 q (2H, $OC\mathbf{H}_2CH_3$, J = 7 Hz), 2.55 s (3H, $C\mathbf{H}_3C_6H_4$), 3.67 d (1H, 4-H, J = 14 Hz), 4.63 d (1H, 3-H, J = 14 Hz), 7.06 d and 7.28 d (2H each, $CH_3C_6\mathbf{H}_4$, J = 8 Hz), 7.36 s (4H, 3-BrC_6H_4, J = 8 Hz). Found, %: C 60.10; H 5.19. $C_{23}H_{24}BrNO_4$. Calculated, %: C 60.27; H 5.28.

Ethyl 4-(4-dimethylaminophenyl)-5,5-dimethyl-1-(4-methylphenyl)-2,6-dioxopiperidine-3-carboxylate (VIIIc). Yield 61%, mp 185–186°C. ^{1}H NMR spectrum, δ, ppm: 1.09 s and 1.22 s (3H each, 5-CH_3), 0.90 t (3H, $OCH_2C\mathbf{H}_3$, J = 7 Hz), 3.90 s (6H, NCH_3), 3.84 q (2H, $OC\mathbf{H}_2CH_3$, J = 7 Hz), 2.56 s (3H, $C\mathbf{H}_3C_6H_4$), 3.63 d (1H, 4-H, J = 14 Hz), 4.65 d (1H, 3-H, J = 14 Hz), 7.04 d and 7.23 d (2H each, $CH_3C_6\mathbf{H}_4$, J = 8 Hz), 7.30–7.41 m (4H, 4-$Me_2NC_6\mathbf{H}_4$, J = 8 Hz). Found, %: C 70.91; H 7.02. $C_{25}H_{30}N_2O_4$. Calculated, %: C 71.07; H 7.16.

4-Aryl-5,5-dimethyl-1-(4-methylphenyl)-2,6-dioxopiperidine-3-carboxylic acid morpholides IXa–IXc and phenylhydrazides Xa and Xb (*general procedure*). Morpholine or phenylhydrazine, 0.02 mol, was added to a mixture of 0.01 mol of ethyl 4-aryl-5,5-dimethyl-1-(4-methylphenyl)-2,6-dioxopiperidine-3-carboxylate **VIIIa–VIIIc** and 20–30 ml of xylene. The mixture was heated for 4–6 h and cooled, and the precipitate was filtered off and recrystallized from ethyl acetate–acetone.

5,5-Dimethyl-1-(4-methylphenyl)-2,6-dioxo-4-phenylpiperidine-3-carboxylic acid morpholide (IXa). Yield 47%, mp 253–254°C. ^{1}H NMR spectrum, δ, ppm: 1.06 s and 1.29 s (3H each, 5-CH_3), 2.35 s (3H, $C\mathbf{H}_3C_6H_4$), 3.10–3.45 m and 3.57–3.70 m (8H, NCH_2CH_2O), 3.85 d (1H, 4-H, J = 12 Hz), 4.96 d (1H, 3-H, J = 12 Hz), 6.98 d and 7.25 d (2H each, $CH_3C_6\mathbf{H}_4$, J = 8 Hz), 7.27–7.38 m (5H, C_6H_5). Found, %: C 71.36; H 6.80. $C_{25}H_{28}N_2O_4$. Calculated, %: C 71.41; H 6.71.

4-(3-Bromophenyl)-5,5-dimethyl-1-(4-methylphenyl)-2,6-dioxopiperidine-3-carboxylic acid morpholide (IXb). Yield 51%, mp 214–215°C. ^{1}H NMR spectrum, δ, ppm: 1.04 s and 1.26 s (3H, 5-CH_3), 2.36 s (3H, $C\mathbf{H}_3C_6H_4$), 3.12–3.45 m and 3.53–3.69 m (8H, NCH_2CH_2O), 3.80 d (1H, 4-H, J = 12 Hz), 4.91 d (1H, 3-H, J = 12 Hz), 6.91 d and 7.29 d (2H each, $CH_3C_6\mathbf{H}_4$, J = 8 Hz), 7.30–7.41 m (4H, 3-BrC_6H_4, J = 8 Hz). Found, %: C 60.21; H 5.52; N 5.72. $C_{25}H_{27}BrN_2O_4$. Calculated, %: C 60.13; H 5.45; N 5.61.

4-(4-Dimethylaminophenyl)-5,5-dimethyl-1-(4-methylphenyl)-2,6-dioxopiperidine-3-carboxylic acid morpholide (IXc). Yield 60%, mp 215–216°C. ^{1}H NMR spectrum, δ, ppm: 1.03 s and 1.25 s (3H each, 5-CH_3), 2.34 s (3H, $C\mathbf{H}_3C_6H_4$), 2.88 s (6H, NCH_3), 3.18–3.40 m and 3.57–3.66 m (8H, NCH_2CH_2O), 3.71 d (1H, 4-H, J = 12 Hz), 4.75 d (1H, 3-H, J = 12 Hz), 6.91 d and 7.25 d (2H each, $CH_3C_6\mathbf{H}_4$, J = 8 Hz), 6.67 d and 7.08 d (4H, 4-$Me_2NC_6\mathbf{H}_4$, J = 8 Hz). Found, %: C 70.04; H 7.10. $C_{27}H_{33}N_3O_4$. Calculated, %: C 69.96; H 7.18.

5,5-Dimethyl-1-(4-methylphenyl)-2,6-dioxo-4-phenylpiperidine-3-carboxylic acid *N′*-phenylhydrazide (Xa). Yield 56%, mp 225–226°C. ^{1}H NMR spectrum, δ, ppm: 1.07 s and 1.23 s (3H each, 5-CH_3); 2.36 s (3H, $C\mathbf{H}_3C_6H_4$); 3.86 d (1H, 4-H, J = 12 Hz); 4.47 d (1H, 3-H, J = 12 Hz); 6.20 d, 6.57 d, and 6.87 d (5H, $NHC_6\mathbf{H}_5$); 7.03 d and 7.27 d (2H each, $CH_3C_6\mathbf{H}_4$, J = 8 Hz); 7.42–7.50 m (5H, 4-C_6H_5); 7.68 s (1H, $N\mathbf{H}C_6H_5$); 9.71 s (1H, CONH). Found, %: C 73.37; H 6.25. $C_{27}H_{27}N_3O_3$. Calculated, %: C 73.45; H 6.16.

4-(4-Dimethylaminophenyl)-5,5-dimethyl-1-(4-methylphenyl)-2,6-dioxopiperidine-3-carboxylic acid *N′*-phenylhydrazide (Xb). Yield 63%, mp 234–235°C. ^{1}H NMR spectrum, δ, ppm: 1.04 s and 1.19 s

(3H, 5-CH_3); 2.31 s (3H, C**H**$_3C_6H_4$); 2.80 s (6H, NCH_3); 3.82 d (1H, 4-H, J = 12 Hz); 4.41 d (1H, 3-H, J = 12 Hz); 6.19 d, 6.61 d, and 6.90 d (5H, NHC_6**H**$_5$); 7.00 d and 7.25 d (2H each, CH_3C_6**H**$_4$, J = 8 Hz); 7.42–7.51 m (4H, 4-Me_2NC_6**H**$_4$); 7.65 s (1H, N**H**C_6H_5); 9.69 s (1H, CONH). Found, %: C 71.80; H 6.73. $C_{29}H_{32}N_4O_3$. Calculated, %: C 71.88; H 6.66.

This study was performed under financial support by the Russian Foundation for Basic Research (project nos. 04-03-96036 and 04-03-97505).

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