ISSN 1070-4280, Russian Journal of Organic Chemistry, 2018, Vol. 54, No. 5, pp. 742–746. © Pleiades Publishing, Ltd., 2018.
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Synthesis of 2-Methyl-7-phenyl-5,8-dihydro-4*H*-pyrzylo-[5,1-*d*][1,2,5]triazepin-4-one

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Received June 19, 2017

Abstract—An approach is developed to the synthesis of 2-methyl-7-phenyl-5,8-dihydro-4*H*-pyrazolo[5,1-*d*]-[1,2,5]triazepin-4-one, based on the recyclization of 2-methyl-6-phenyl-4*H*-pyrazolo[5,1-*c*][1,4]oxazin-4-one with hydrazine.

DOI: 10.1134/S1070428018050111

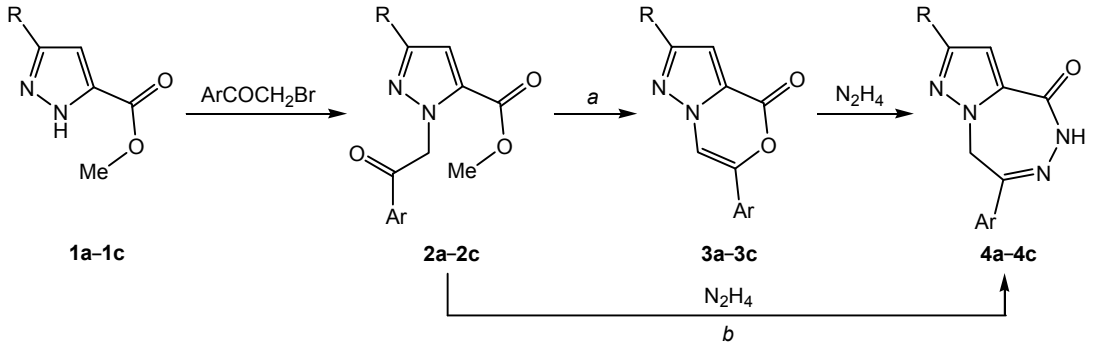
A bicyclic heterocyclic system with a pyrazolo[5,1-*d*][1,2,5]triazepinone scaffold is a rarity. The first representative of this series, 2,7-diphenyl-5,8-dihydro-4*H*-pyrazolo[5,1-*d*][1,2,5]triazepin-4-one **4a** (Scheme 1) was obtained in [1]. Later, 4-oxo-7-phenyl-5,8-dihydro-4*H*-pyrazolo[5,1-*d*][1,2,5]triazepine-2-carbohydrazide **4b** [2] and 2-*t*-butyl-7-phenyl-5,8-dihydro-4*H*-pyrazolo[5,1-*d*][1,2,5]triazepin-4-one **4c** [3] were prepared. A preliminary biological evaluation [1] showed that triazepinone **4a** inhibits apoptosis of vascular endothelial cells at low concentration. Therefore, the development of a strategy for building such structures is an urgent task.

The key compounds for the preparation of triazepinons **4a**–**4c** are esters of 3-R-1-(2-oxo-2-phenyl-ethyl)-1*H*-pyrazole-5-carboxylic acids **2a**–**2c**. Two methods for the synthesis of pyrazolotriazepinones **4a**–**4c** (Scheme 1) are described: the transformation of keto acids **2a** and **2b** into 2-R-6-phenyl-4*H*-pyrazolo[5,1-*c*][1,4]oxazin-4-ones **3a** and **3b**, which then are treated with hydrazine hydrate [1, 2] (pathway *a*), or by the reaction of keto-esters **2a** and **2c** with hydrazine [3] (pathway *b*).

In order to select an optimal method for the synthesis of triazepinones **4** let us analyze these two approaches. Route *a* is a two-stage synthesis from pyrazole **2**. The yield of triazepinone **4a** is 68–82% [1], **4b**, 57% [2].

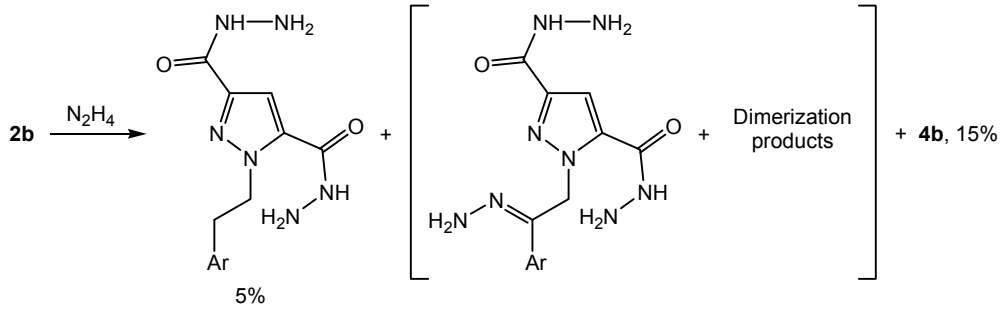
The route *b* is a one-stage synthesis. The yield of triazepinones **4a** and **4c** is 61 and 73% [3], however, the ^{1}H NMR spectrum of triazepinone **4c** given in this paper contradicts the assumed structure, and the ^{1}H NMR spectrum of triazepinone **4a** does not coincide with the previously described spectrum of this compound [1]. In addition, it was shown in [1] that when treating a keto ester **2a** with 1 equiv or an excess of hydrazine hydrate in ethanol for 12 hours triazepinone **4a** did not

Scheme 1.

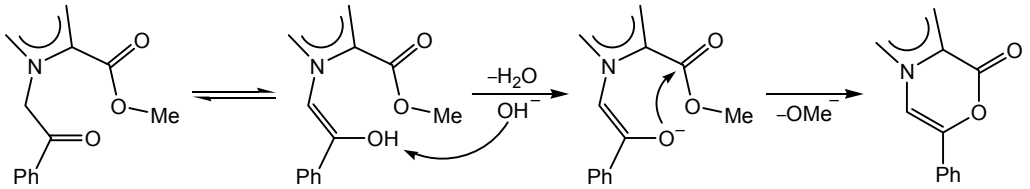


1, R = Ar (**a**), COMe (**b**), *t*-Bu (**c**); **4**, R = Ar (**a**), $CONHNH_2$ (**b**), *t*-Bu (**c**).

Scheme 2.



Scheme 3.



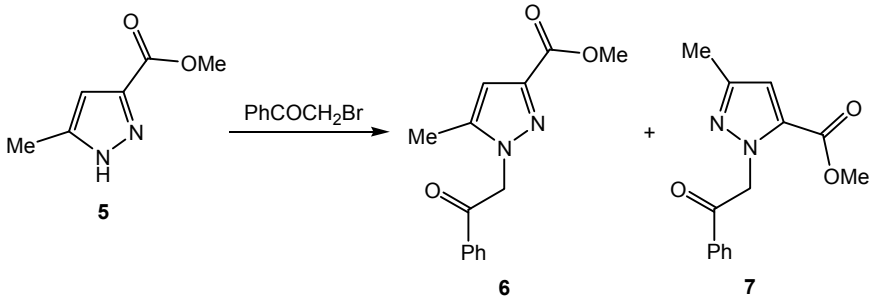
form due to competitive reactions. Zeng et al. [1] did not study the composition of the products of these reactions.

To understand the discrepancies in the results of [1, 3] we attempted to reproduce the path *b* with pyrazole **2b** (Scheme 2). The treatment of pyrazole **2b** with hydrazine hydrate in 2-propanol gave a mixture of compounds with a content of triazepinone **4b** of ~15%. Taking into account that the keto group of pyrazole **2b** is prone to reduction by Kizhner-Wolff reaction [2], esters of organic acids are easily transformed with hydrazine into hydrazides of these acids, and ketones into hydrazones, the possible composition of the products of pyrazole **2b** reaction with hydrazine along the route *b* is presented in Scheme 2.

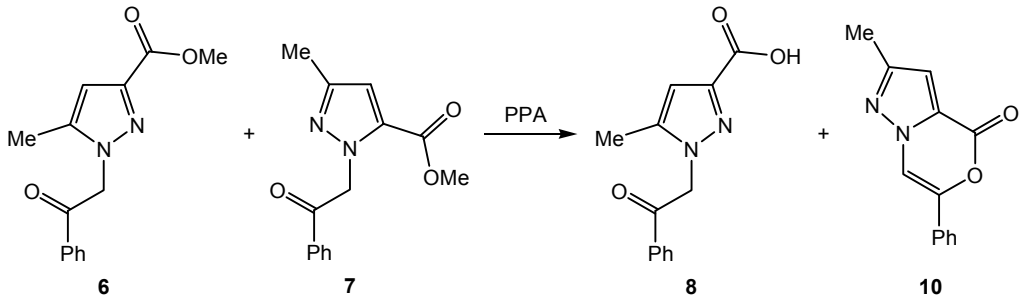
Thus, the competition of various reactions of keto ester **2b** with hydrazine gives the spectrum of products and leads to a decrease in the yield of triazepinone **4b**, therefore the route *a* seems more rational in the targeted synthesis of triazepinone **4b** than route *b*. Triazepinone **4b** along pathway *b* appears to be formed from pyrone **3b**, which is generated *in situ* in basic medium in the same manner as isocoumarin by cyclization of ethyl ether of 2-methoxy-6-acetonylbenzoic acid in basic media [4]. Here hydrazine is the base. The probable mechanism of the formation of pyrone 3 from pyrazole **2** is shown in Scheme 3.

An important feature of pyrazoles **1a–1c** is the high regioselectivity of their *N*-alkylation with γ-bromoacetophenone: the alkylation product is formed only at the nitrogen atom adjacent to the COOMe group. However, it is known [5] that the alkylation of the ester of 3-methyl-1*H*-pyrazole-5-carboxylic acid **5** results in two isomeric *N*-alkyl products. Apparently, due to steric effects, the bulky substituents (phenyl and *tert*-butyl) direct the attack of the alkylating agent on the nitrogen atom located closer to the carboxy group. The decrease in steric factors at the transition to the methyl derivative makes both nitrogen atoms in the pyrazole ring available for alkylation. In the case of pyrazole **1b** only one isomer **2b** is obtained because of the symmetry of the original pyrazole.

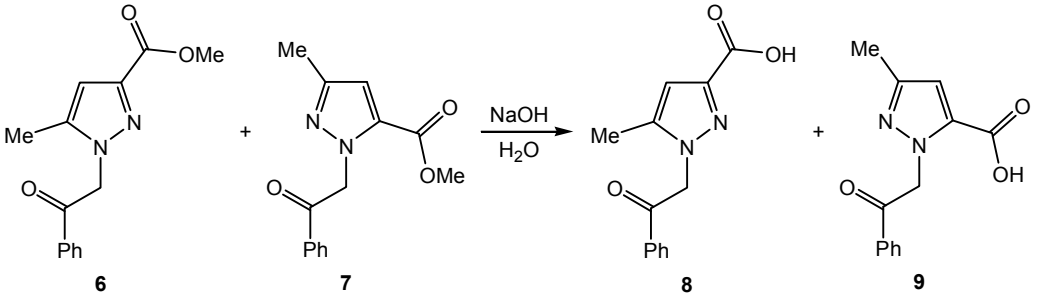
Scheme 4.



Scheme 5.



Scheme 6.



This paper presents the approach along the path *a* to the synthesis of a new specimen among pyrazolotriazepinones, 2-methyl-7-phenyl-5,8-dihydro-4*H*-pyrazolo[5,1-*d*][1,2,5]triazepin-4-one **12** using 3-methyl-1*H*-pyrazole-5-carboxylic acid as the initial reagent and without separating the N-alkylation products.

The initial 3-methyl-1*H*-pyrazole-5-carboxylic acid was obtained by oxidation of 3,5-dimethylpyrazole followed by esterification [2]. After alkylating the obtained ester **5** with γ-bromoacetophenone in acetonitrile a semicrystalline brown mass was extracted and recrystallized from diethyl ether. According to ^{1}H NMR, the reaction product was one of the isomeric alkylation products (Scheme 4). After removing diethyl ether from the mother liquor a dark viscous mass remained. According to ^{1}H NMR, this is a mixture of two isomeric N-alkylation products **6** and **7** in approximately equal amounts (57 and 43%) and a small amount of impurity, apparently, of crotonic condensation products.

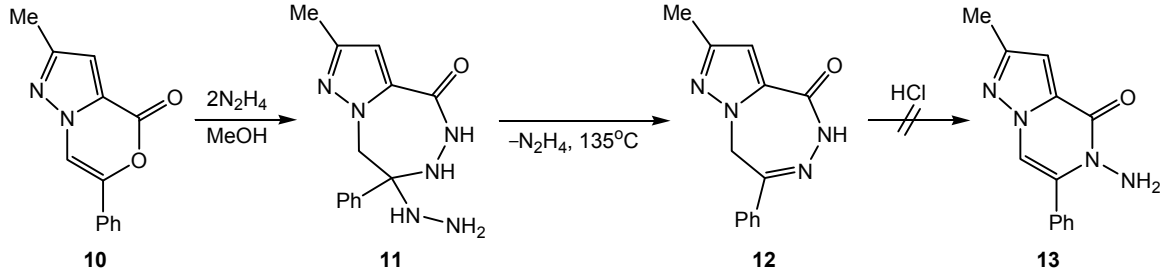
Attempting to perform the cyclization of the mixture of isomers **6** and **7** in polyphosphoric acid at 170°C, we isolated in a low yield a mixture of pyrazolecarboxylic acid **8** and pyrazoloxazinone **10**, 3 : 1 (Scheme 5).

The cyclization under the same condition of the alkylated isomer first isolated by recrystallization from diethyl ether provided keto acid **8**. Hence, the previously isolated isomer is the product of alkylation at the nitrogen atom adjacent to the methyl group.

In the hydrolysis of a mixture of isomers **6** and **7** under alkaline conditions (Scheme 6), a crystalline mixture of acids **8** and **9** was isolated in the ratio 3 : 7 according to ^{1}H NMR.

Cyclization of a mixture of acids **8** and **9** in acetic anhydride leads to the formation of lactone **10**, which

Scheme 7



is isolated from the reaction mass as fine needle crystals in pure form. Apparently, the isomeric acid **8** gives under these conditions a mixed anhydride, which is readily soluble in acetic anhydride, in contrast to the poorly soluble lactone **10**.

The recyclization of lactone **10** into triazepinone was carried out under mild conditions by boiling with an excess of hydrazine hydrate in methanol (Scheme 7) to avoid the Kizhner-Wolff side reaction [2]. The product of lactone recycling with the attached second molecule of hydrazine **11** was isolated. Formation of the latter indirectly confirms the mechanism of the formation of the pyrazolotriazepinone cycle [2].

Boiling of compound **11** in ethyl cellosolve for 1 hour results in the elimination of hydrazine and the formation of pyrazolotriazepinone **12**.

In the ^{1}H NMR spectra of the pyrazole derivatives **6–11**, the protons of the phenyl ring appear as two triplets and a doublet in the aromatic region with the coupling constant 7.2–7.6 Hz. Pyrazolotriazepinone **12** is an exception. In the ^{1}H NMR spectrum, the *para*- and *meta*-protons of the phenyl ring are seen as a narrow multiplet in the region of 7.47–7.55 ppm, and *ortho*-protons, in the form of two superimposed doublets in the region of 7.87 ppm with the coupling constant 5.6 Hz. A similar picture was observed in [1] for pyrazolotriazepinone **1a**. This result suggests that at room temperature in the solution of compound **12** the rotation of the phenyl substituent at the C^7-Ph bond is impeded.

As is known, the triazepinone ring in 4-methyl-2,3-dihydro-1*H*-pyrrolo[2,1-*d*][1,2,5]triazepin-1-one at room temperature underwent contraction even by traces of acid present in the chloroform [6]. However, the triazepinone ring in pyrazolotriazepinone **12** is resistant to acids: even prolonged boiling of pyrazolotriazepinone **12** with hydrochloric acid does not result in the contraction of the triazepinone ring into pyrazolopyrasinone **13**. The stability of the triazepinone ring **12** may be due to the protonation at the nitrogen atom of the pyrazole ring. This prevents further protonation of the molecule at the oxygen atom of the carbonyl group, which is necessary for the contraction of the triazepinone ring, as is shown in [6].

Thus, in this paper we have developed an approach to the synthesis of a new member of the family of pyrazolotriazepinones, 2-methyl-7-phenyl-5,8-dihydro-4*H*-pyrazolo[5,1-*d*][1,2,5]triazepin-4-one. A two-step process for the preparation of pyrazolotriazepinones, which involves the preliminary synthesis of 2-R-6-phenyl-4*H*-pyrazolo[5,1-*c*][1,4]oxazin-4-one from esters of pyrazole-5-carboxylic acids and its subsequent treatment with hydrazine provides a higher yield of the desired product than a one-pot synthesis without prior isolation of pyrazolopyrone.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance^{II} instrument (400 and 100 MHz, respectively) in DMSO-d_6, the internal reference was TMS. The IR spectra were taken on a spectrophotometer Specord 75IR from KBr pellets. The melting points of synthesized compounds were determined on a Boëtius heating apparatus and were not corrected.

Methyl 5-methyl-1-(2-oxo-2-phenyl)-1*H*-pyrazole-3-carboxylate (6). A mixture of 13 g (93 mmol) of compound **5**, 19 g (96 mmol) of γ-bromoacetophenone, and 25 g (181 mmol) of fine powder of potassium carbonate in 50 mL of acetonitrile was stirred for 6 hours at 80°C, cooled, and poured into 200 mL of water. A precipitated dark oily substance gradually crystallized. The precipitate was filtered off, washed with water, and dried in air. To the crystalline mass 80 mL of diethyl ether was added, the mass was stirred for 30 minutes and was kept for 4 hours. The precipitate was filtered off and washed with a small amount of ether. Yield 9.1 g (38%), colorless crystals, mp 92–93°C. IR spectrum, ν, cm^{-1}: 1720 (CO), 1680 (CO), 1600 (Ph). ^{1}H NMR spectrum, δ, ppm: 2.22 s (3H, CH_3), 3.80 s (3H, CH_3), 5.87 s (2H, CH_2), 6.55 s (1H, CH), 7.56 t (2H, Ph, *J* 7.6 Hz), 7.68 t (1H, Ph, *J* 7.2 Hz), 8.06 d (2H, Ph, *J* 7.6 Hz). ^{13}C NMR spectrum, δ, ppm: 11.9 (CH_3), 52.3 (CH_3), 58.3 (CH_2), 110.7 (CH), 129.3 (Ph), 129.9 (Ph), 130.9 (Ph), 131.4 (Ph), 136.2, 143.6, 164.0 (COO), 194.1 (CO). Found, %: C 65.09; H 5.49; N 10.84. $C_{14}H_{14}N_2O_3$. Calculated, %: C 65.11; H 5.46; N 10.85.

5-Methyl-1-(2-oxo-2-phenyl)-1*H*-pyrazole-3-carboxylic acid (8) and 3-methyl-1-(2-oxo-2-phenyl)-1*H*-pyrazole-5-carboxylic acid (9). The ether mother liquor from the synthesis of compound **6** was evaporated, to 6 g of a resinous residue were added 20 mL of water and 3.72 g (9.3 mmol) of NaOH. The mixture was refluxed for 4 hours, 2 g of activated carbon was added and then it was boiled for 15 minutes. A hot solution was filtered, carbon was washed with 20 mL

of hot water, 7 mL of acetic acid was added to the filtrate. The separated viscous dark-yellow mass was decanted, and 10 g of NaCl was added to the solution. After 1 day from the solution fine light yellow crystals weighing 1.52 g precipitated. According to ^{1}H NMR, the mixture contains substances **8** and **9** in the ratio 3 : 7. ^{1}H NMR spectrum, δ, ppm, **8**: 2.21 s (3H, CH_3), 5.85 s (2H, CH_2), 6.51 s (1H, CH), 7.55 t (2H, Ph, *J* 7.6 Hz), 7.65 t (1H, Ph, *J* 7.2 Hz), 8.06 d (2H, Ph, *J* 7.6 Hz); **9**: 2.24 s (3H, CH_3), 5.94 s (2H, CH_2), 6.62 s (1H, CH), 7.55 t (2H, Ph, *J* 7.6 Hz), 7.65 t (1H, Ph, *J* 7.2 Hz), 8.02 d (2H, Ph, *J* 7.6 Hz).

2-Methyl-6-phenyl-4*H*-pyrazolo[5,1-*c*][1,4]oxazin-4-one (10). To 1.2 g of a mixture of acids **8** and **9** obtained in the previous synthesis 5 mL of acetic anhydride was added, the mixture was stirred for 4 hours at boiling and left overnight. The precipitated crystals in the form of fine colorless needles were filtered off and washed with acetic acid. Yield 452 mg (41%), mp 144–145°C. The acetic anhydride contained in the mother liquor was hydrolyzed with water. The precipitated crystals were filtered off, washed with water and after drying recrystallized from methanol. Additionally, 101 mg of the reaction product were obtained, total yield 50%. IR spectrum, ν, cm^{-1}: 1730 (CO), 1630 (Ph). ^{1}H NMR spectrum, δ, ppm: 2.41 s (3H, CH_3), 6.97 s (1H, CH), 7.41 t (1H, Ph, *J* 7.2 Hz), 7.45 t (2H, Ph, *J* 7.2 Hz), 7.82 d (2H, Ph, *J* 7.6 Hz), 8.50 s (1H,CH). ^{13}C NMR spectrum, δ, ppm: 15.3 (CH_3), 109.1 (CH), 109.5 (CH), 126.1 (Ph), 128.8, 130.6 (Ph), 131.2 (Ph), 131.7 (Ph), 143.6, 152.9, 154.8 (CO). Found, %: C 64.98; H 4.48; N 12.40. $C_{13}H_{10}N_2O_2$. Calculated, %: C 65.02; H 4.46; N 12.38.

7-Hydrazino-2-methyl-7-phenyl-5,6,7,8-tetrahydro-4*H*-pyrazolo[5,1-*d*][1,2,5]triazepin-4-one (11). A mixture of 480 mg (1.8 mmol) of compound **10** and 0.2 mL (4 mmol) of hydrazine hydrate were boiled for 3 hours in 0.5 mL of methanol. After cooling, a small cheesy precipitate fell out. On the next day the precipitate was filtered off and washed with a small amount of methanol. Yield 310 mg (53%), mp 142–143°C. ^{1}H NMR spectrum, δ, ppm: 2.16 s (3H, CH_3), 4.46 br.s (2H, NH_2), 5.61 s (2H, CH_2), 6.55 s (1H, CH), 7.09 br.s (1H, NH), 7.18 t (1H, Ph, *J* 7.2 Hz), 7.26 t (2H, Ph, *J* 7.6 Hz), 7.74 d (2H, Ph, *J* 7.6 Hz), 9.84 br.s (1H, NH). Found, %: C 57.30; H 5.93; N 30.89. $C_{13}H_{16}N_6O$. Calculated, %: C 57.34; H 5.92; N 30.86.

2-Methyl-7-phenyl-5,8-dihydro-4*H*-pyrazolo[5,1-d][1,2,5]triazepin-4-one (12). A mixture of 250 mg (0.92 mmol) of hydrazine **11** and 0.5 mL of ethyl cellosolve was boiled for 1 hour, cooled and 0.5 mL of water was added. The precipitated crystals were filtered off and washed with water. Yield 185 mg (84%), fine colorless crystals, mp 205–206°C. IR spectrum, ν, cm^{-1}: 3160, 3080, 2900, 1660 (CO), 1600 (Ph). ^{1}H NMR spectrum, δ, ppm: 2.22 s (3H, CH_3), 5.36 s (2H, CH_2), 6.59 s (2H, CH), 7.47–7.55 m (3H, Ph), 7.86 d (1H, Ph, *J* 5.6 Hz), 7.87 d (1H, Ph, *J* 5.6 Hz), 11.27 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 12.9 (CH_3), 47.9 (CH_2), 108.9 (CH), 126.5 (Ph), 128.4 (Ph), 130.1 (Ph), 134.3 (Ph), 136.1, 147.1, 154.4, 157.6 (CO). Found, %: C 64.94; H 5.06; N 23.35. $C_{13}H_{12}N_4O$. Calculated, %: C 64.99; H 5.03; N 23.32.

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