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Enantiotropic Transformation of Carbethoxyhydrazones of Acetophenones

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Abstract—Hydrazinecarboxylates have been synthesized by reacting substituted acetophenones with carbethoxyhydrazine. One of product is formed as a mixture of *E*- and *Z*-isomers. In the process of measuring the melting point of the resulting hydrazinecarboxylates, a transition of one crystalline form to another has been detected. That process has been recorded on video in “time-laps” mode for one of the substances.

Keywords: hydrazinecarboxylates, enantiotropic conversion, acetophenone

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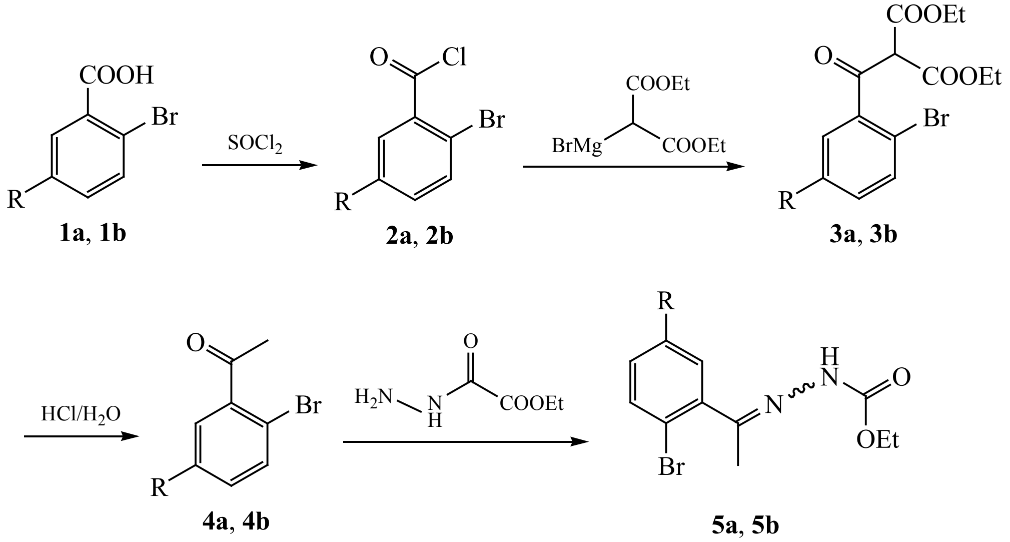
Carbethoxyhydrazones are well known for a variety of biological activities that stimulate synthesis of their derivatives [1, 2]. The specific tendency of carbethoxyhydrazones to isomerism with respect to the C=N bond, results in different physical and chemical properties of the isomers [3, 4]. Herein, we present synthesis of two new representatives of this class of compounds.

RESULTS AND DISCUSSION

The disubstituted benzoic acids **1a** and **1b** were introduced into the reaction with thionyl chloride according to the procedure described in [5] to form the corresponding acid chlorides **2a**, **2b** (Scheme 1) with the yields of 88 and 94%, respectively. The intermediates **2a**, **2b** were converted into the corresponding esters **2a**, **3d** in their reaction with a Grignard reagent derived from diethyl malonate [yield 56% (**3a**), yield 65% (**3b**)] [6]. The following refluxing of compounds **3a**, **3b** for 6 h in the presence of hydrochloric acid gave acetophenones **4a** (73%) or **4b** (81%), respectively [6]. The reaction of intermediates **4a**, **4b** with carbethoxyhydrazine in toluene medium in the presence of *p*-toluene sulfonic acid led to hydrazinecarboxylates **5a**, **5b** (Scheme 1). The product **5b** was isolated as a mixture of *E*- and *Z*-isomers.

Scheme 1.



R = CH_3 (**a**), OCH_3 (**b**).

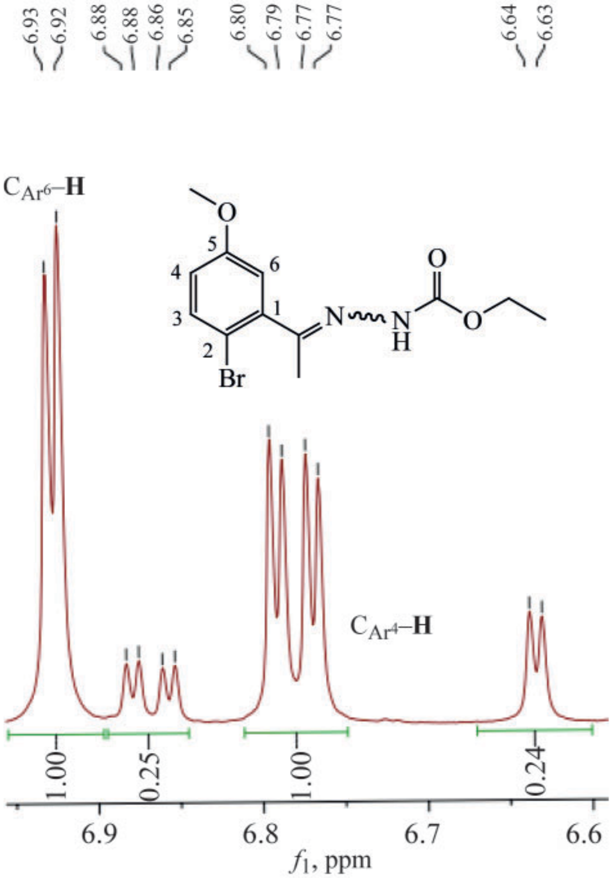


Fig. 1. Fragment of ^{1}H NMR spectrum of compound **5b** that demonstrates signals of C_{Ar^4}–**H** and C_{Ar^6}–**H**.

In ^{1}H NMR spectrum of compound **5b** (Fig. 1), doubling of signals of the aromatic and NH groups which indicated the presence of two geometric isomers was detected. The ratio of geometric isomers of compound **5b** was 4 : 1 (Fig. 1). In the course of measuring melting point of compound **5b** in the range of 81–83°C partial fusion of the sample and its recrystallization at 110°C were observed (Fig. 2). The second melting point was recorded in the range of 122–124°C. In the process of melting the compound **5a**, a similar effect was observed, but the first melting point was measured at higher temperature. A significant difference between the gaps of melting points of two enantiomers of the products were determined to be Δ = 12 (**5a**) and 46°C (**5b**). The link to the video of melting **5b** is shown in Fig. 3.

The process observed in the course of melting of carbethoxyhydrazones **5a**, **5b**, attributed initially to the thermal cis/trans isomerization, appeared to be the conversion of one polymorphic form into another. This conclusion was based on the following facts: (1) Even after melting and re-crystallization of compounds, the pattern of the crystals melting did not change. (2) The ratio of *E*/*Z*-isomers in the NMR spectra of **5b** ($CDCl_3$ solution) after isolation from reaction mixture and after melting procedure remained the same. The similar phenomenon was observed for carbethoxyhydrazone **5a**, characterized by a single geometric isomer according to ^{1}H NMR spectra. It exhibited the melting pattern similar to that of **5b**. In addition, this phenomenon could not be attributed to degradation of a molecular complex of the substance with the solvent. Recrystallization of carbethoxyhydrazones from ethyl alcohol after isolation of those from deuterated chloroform solutions did not influence upon the behavior of the compounds in the course of their melting.

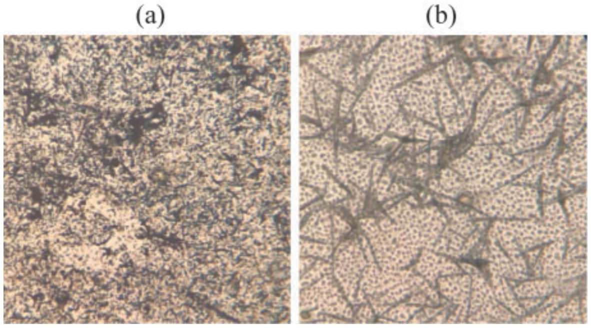


Fig. 2. (a) Initial sample **5b** before melting, (b) crystallization from the melt after the first step.

Based on the above, the enantiotropic nature of compounds **5a**, **5b** was established.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were measured on a Bruker DPX-400 spectrometer at 400.13 and 100.16 MHz, respectively. The signals of residual ^{1}H and ^{13}C of deuterated chloroform were used as internal standards. Melting points were measured on a Boetius Cofler instrument.

In a 50 mL round bottom flask equipped with magnetic stirrer, a Dean-Stark nozzle and condenser, the mixture of a ketone **4a**, **4b** (17.6 mmol) with carbethoxyhydrazine (1.98 g, 19.0 mmol), *p*-toluene sulfonic acid (0.17 g, 1.0 mmol) and 30 mL of toluene was refluxed for 8 h. Then the solvent was evaporated under reduced pressure. The precipitated crystals were stirred with cold ethanol, filtered off and air dried. The corresponding products **5a**, **5b** were recrystallized from ethanol.

Ethyl-2-[1-(2-bromo-5-methylphenyl)ethylidene]-hydrazine-1-carboxylate (5a). Yield 78.4%. T^1_{melt} = 110–111°C, T^2_{melt} = 122–123°C. Spectral data are pre-

Fig. 3. Reference to the melting video of sample **5b**: https://www.youtube.com/watch?v=rFz5GzfQp_I.

sented for the dominant form. ^{1}H NMR spectrum, δ, ppm: 1.35 t (3H, CH_3CH_2, *J* = 7.2 Hz), 2.22 s (3H, CH_3C=N), 2.30 s (3H, CH_3), 4.33 q (2H, CH_3CH_2, *J* = = 7.2 Hz), 7.19 s (1H, $H^6{}_{Ph}$), 7.01 d 1H, $H^4{}_{Ph}$, *J* = 8.0 Hz), 7.42 d (1H, $H^3{}_{Ph}$, *J* = 8.0 Hz), 8.04 br.s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 14.6 (CH_3CH_2), 17.2 (CH_3C=N), 20.8 (CH_3), 62.1 (CH_3CH_2), 118.0 ($C^2{}_{Ph}$), 130.8 ($C^6{}_{Ph}$), 131.3 ($C^4{}_{Ph}$), 132.6 ($C^3{}_{Ph}$), 137.5 ($C^1{}_{Ph}$), 140.4 ($C^5{}_{Ph}$), 150.8 (CH_3C=N), 154.0 (C=O). HRMS-EI, *m/z*: 299.0390 $[M + H]^+$. $C_{12}H_{15}BrN_2O_2$.

Ethyl-2-[1-(2-bromo-5-methoxyphenyl)ethylidene]-hydrazine-1-carboxylate (5b). White crystals, yield 41.5%. T^1_{melt} = 81–83°C, T^2_{melt} = 128–129°C. ^{1}H NMR spectrum, δ, ppm: 1.36 t (3H, CH_3CH_2, *J* = 7.1, Hz), 2.23 s (3H, CH_3C=N), 3.81 s (3H, OCH_3), 4.34 q (2H, CH_3CH_2, *J* = 7.1 Hz), 6.78 d.d (1H, $H^4{}_{Ph}$, ^3J = 3.2 Hz, ^2J = 8.8 Hz), 6.93 d (1H, $H^6{}_{Ph}$, ^3J = 3.2 Hz), 7.43 d (1H, $H^3{}_{Ph}$, ^2J = 8.8 Hz), 7.86 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 14.6 (CH_3CH_2), 17.0 (CH_3C=N), 55.6 (OCH_3), 62.1 (CH_3CH_2O), 111.8 ($C^2{}_{Ph}$), 115.7 ($C^6{}_{Ph}$), 116.3 ($C^4{}_{Ph}$), 133.6 ($C^3{}_{Ph}$), 134.5 ($C^1{}_{Ph}$), 141.5 (CH_3C=N), 158.9 ($C^5{}_{Ph}$), 159.7 ($C^5{}_{Ph}$). HRMS-EI, *m/z*: 314.0266 $[M]^+$. $C_{12}H_{15}BrN_2O_3$.

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CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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