

Investigations for the Preparation of new Pyrazolo[4,3-d]isothiazole Derivatives

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Abstract

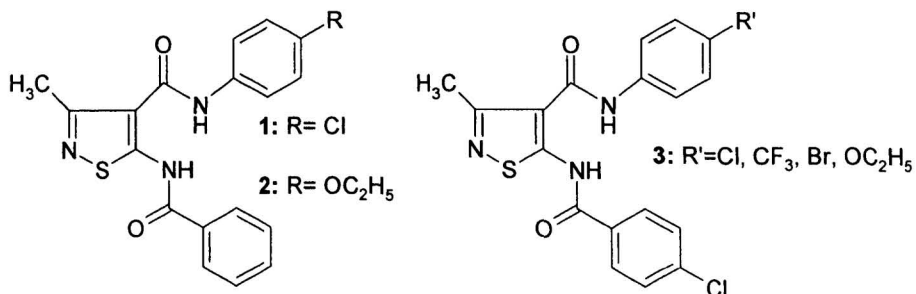
Synthesis of 5-acylhydrazine derivatives of ethyl 3-methyl-4-isothiazolo-carboxylate and their transformations under alcoxides influence have been described and presented.

Keywords

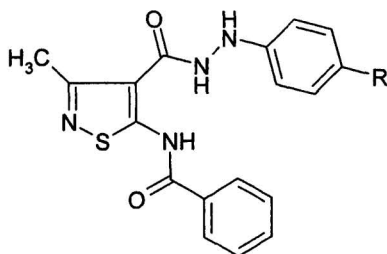
Isothiazole, pyrazolo[4,3-d]isothiazole.

Introduction

Vratizoline (Denotivir) **1** obtained by Machoń [1] is widespread used as a very effective antiviral drug against herpes viruses (Varicella zoster). Also, ITF (5-benzoylamino-N-(4-ethoxyphenyl)-3-methylisothiazole-4-carboxamide) **2** obtained by Machoń [2] and many diamides with general structure **3**, which have been synthesized by Regiec [3] show great anti-inflammatory activity. The compounds **3** also show immunosuppressive activity that is stronger than Cyclosporine A.



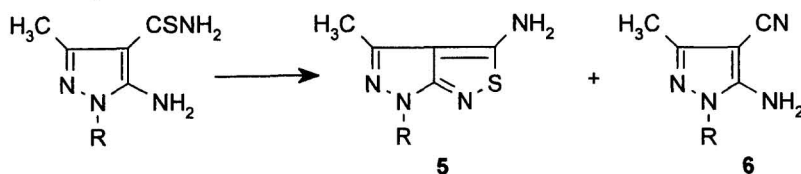
Hydrazide derivatives of 4-isothiazolecarboxylic acid **4** [4] described by us have immunosuppressive activity, too.



4 R= H, Cl

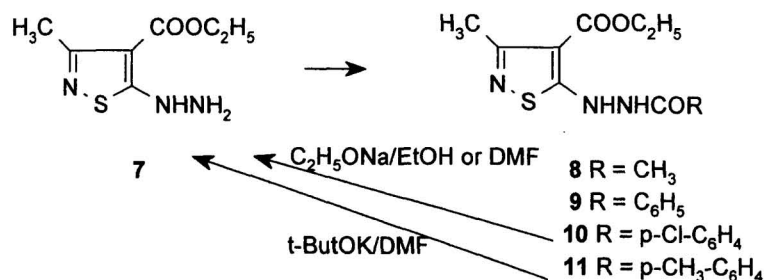
In 1974 Japanese authors presented the synthesis of pyrazolo[3,4-c]isothiazole [5].

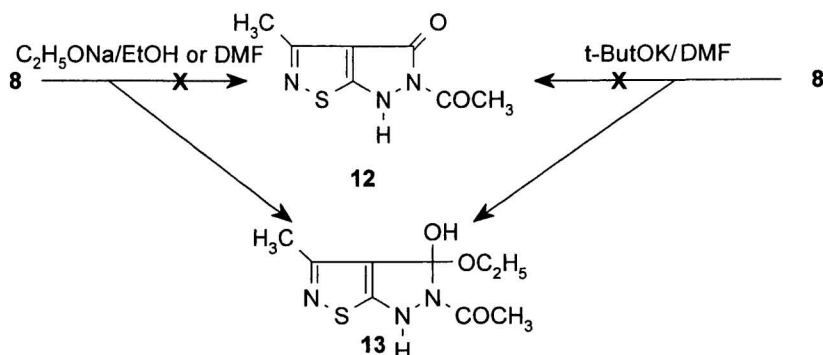
Vicentini and collaborators obtained derivatives of 4-aminopyrazolo[3,4-c] isothiazole **5** that showed antifungal activity [6].



The most active compounds (**5**) were with R = phenyl, o-chlorophenyl, p-nitrophenyl or p-tolyl. These data inclined us to try synthesizing new undescribed, up to date, ring system pyrazolo[4,3-d]isothiazole using as the starting material obtained earlier by us 5-hydrazino-3-methyl-isothiazolecarboxylic acid ethyl ester **7** [4,7].

The synthesis was conducted according to the following scheme 2.





The compound **7**, that has been treated with acetic anhydride or acid chlorides gives proper 5-*N*-acylhydrazine derivatives of 3-methyl-4-isothiazolecarboxylic acid ethyl ester **8-11**. These latter compounds have been reacted with sodium ethoxide and products of this reaction have been isolated. In this reaction the compound **8** gave unexpected, new undescribed compound **13**, containing stable hemiacetal moiety and being a pyrazolo[4,3-*d*]isothiazole derivative, instead of expected substance **12**. Similar reactions were conducted with the compounds **9-11** but in the case of 5-*N*-benzoyl derivative **9** the 10 hours heating with sodium ethoxide did not cause any change of the substrate. However, the compounds **10** and **11** under this reaction condition gave the same product **7** (see table 1).

Table 1. Investigation for cyclization of ethyl 5-(*N*-acyl)hydrazino-3-methylisothiazole-4-carboxylates (8-11**)**

Starting compound	Reagent	Reaction time, temp.	Solvent	Isolated compound	Mp °C
8	C ₂ H ₅ ONa t-ButOK	2 h, 80°C 1 h, 100°C	ethanol DMF	13	159-160.5
9	C ₂ H ₅ ONa t-ButOK	10h 1 h, 100°C	Ethanol DMF	9	112-114
10	C ₂ H ₅ ONa t-ButOK	5h 1 h, 100°C	Ethanol DMF	7	149-150
11	C ₂ H ₅ ONa t-ButOK	12 h 1 h, 100°C	Ethanol DMF	7	149-150

The above described ethoxolysis reaction occurred much quicker in the case of p-chorobenzoyl derivative **10** (5 h) than **11** (12 h).

The change of the solvent from protic ethanol to aprotic DMF did not affect the reaction proceeding. Also treating the compounds **8-11** with potassium t-butoxide in DMF did not make any change. The reaction occurrence was identical like in the ethanolic solution of sodium ethoxide.

Experimental Part

Melting point were determined on Büchi apparatus and are uncorrected. IR spectra: Pye-Unicam SP-1000 apparatus in KBr. ¹H-NMR spectra: Tesla BS 587 A, 80 MHz apparatus (TMS as internal reference).

Ethyl 5-hydrazino-3-methyl-4-isothiazolecarboxylate (7) was obtained according to [4,7].

Ethyl 5-N-acetylhydrazino-3-methyl-4-isothiazolecarboxylate (8).

The mixture of 70 ml of acetic anhydride, 14 ml of anhydrous pyridine and 7 g of hydrazinoester **7** has been heated at reflux, stirring, for 1 h. Next, the whole has been set for a night at room temperature and then poured on ice. A precipitate was filtered off and crystallized from ethanol giving 6.84 g (80%) of clean **8**, mp 93-94°C; IR (potassium bromide): 2944 (alkyl), 1722 (ester CO), 1698 (amide CO) cm⁻¹; ¹H-NMR (dimethyl sulfoxide-d₆): δ 1.19-1.37 (t, 3H, CH₃CH₂), 2.22 (s, 3H, CH₃CO), 2.41 (s, 3H, CH₃), 4.11-4.38 (q, 2H, CH₃CH₂). Anal. Calcd for C₉H₁₃N₃O₃S: C, 44.43; H, 5.39; N, 17.27. Found: C, 44.50; H, 5.43; N, 17.26.

General synthesis of ethyl 5-Aroylhydrazino-3-methylisothiazole-4-carboxylates 9-11.

To a cooled solution of 2 g (0.01m.) of compound **7** in anhydrous benzene (20 ml) anhydrous *N,N*-dimethylaniline (2 ml) was added and then a benzene solution of the proper acid chloride (0.011 m in 10 ml of benzene) was added dropwise. After 3 h. the solvent was evaporated to dryness under reduced pressure. A residue was treated

with 5% aqueous solution of sodium bicarbonate. The precipitated product was filtered off and washed with water to give the proper compounds **9**, **10** and **11** described below.

Ethyl 5-N-benzoylhydrazino-3-methyl-4-isothiazolecarboxylate (9).

The crude product was crystallized from ethanol to give 3 g (98%) of pure compound **9**, mp 112-114 °C; IR (potassium bromide): 3250 (NHNHCO), 1750 (ester CO), 1680 (amide CO) cm^{-1} . $^1\text{H-NMR}$ (dimethyl sulfoxide- d_6): δ 1.26-1.36 (t, 3H, CH_3CH_2), 2.06 (s, 3H, CH_3), 4.22-4.31 (q, 2H, CH_3CH_2), 7.3-7.8 (m, 5H, C_6H_5 -). Anal. Calcd. for $\text{C}_{14}\text{H}_{15}\text{N}_3\text{O}_3\text{S}$: C, 55.07; H, 4.95; N, 13.76. Found: C, 55.43; H, 4.83; N, 13.47.

Ethyl 5-N-(4-chlorobenzoyl)hydrazino-3-methyl-4-isothiazolecarboxylate (10).

The crude product was crystallized from ethanol to give 1.74 g (51%) of compound **10**, mp 190-192 °C what is consistent with [4] IR (potassium bromide): 3245 (NHNHCO), 1728 (ester CO), 1692 (amide CO) cm^{-1} ; $^1\text{H-NMR}$ (dimethyl sulfoxide- d_6): δ 1.20-1.40 (t, 3H, CH_3CH_2), 2.39 (s, 3H, CH_3), 3.43-3.55 (q, 2H, CH_3CH_2), 7.63-7.71 (d, 2H, C_6H_4 -), 7.8-7.9 (d, 2H, C_6H_4 -). Anal. Calcd. for $\text{C}_{14}\text{H}_{14}\text{N}_3\text{O}_3\text{Cl}$: C, 49.49; H, 4.15; N, 12.37. Found: C, 49.98; H, 4.50; N, 12.65

Ethyl 5-N-(4-methylbenzoyl)hydrazino-3-methyl-4-isothiazolecarboxylate (11).

The crude product was crystallized from ethanol to give 1.74 g (51%) of compound **11**, mp 142-144 °C; IR (potassium bromide): 3260 (NHNHCO), 1730 (ester CO), 1672 (amide CO) cm^{-1} ; $^1\text{H-NMR}$ (dimethyl sulfoxide- d_6): δ 1.30-1.45 (t, 3H, CH_3CH_2), 2.35 (s, 6H, 2x CH_3), 4.22-4.29 (q, 2H, CH_3CH_2), 7.24-7.83 (dd, 4H, C_6H_4). Anal. Calcd. for $\text{C}_{15}\text{H}_{17}\text{N}_3\text{O}_3\text{S}$: C, 56.41; H, 5.37; N, 13.16. Found: C, 56.63; H, 5.11; N, 13.38.

5-Acetyl-4-ethoxy-4-hydroxy-3-methyl-5,6-dihydro-4H-pyrazolo[4,3-d]isothiazole (13).

Method A. To the solution of 4.86 g (0.02 m) of **8** in anhydrous ethanol the sodium ethoxide solution in ethanol (0.48 g Na in 15 ml ethanol) was added. After refluxing for 2 h the reaction mixture was condensed to a half of its volume and poured into 500 ml of

cold water. Next 10% aqueous acetic acid solution was added to the mixture till pH=7. A precipitate was filtered off, washed with water and then crystallized from methanol to give 2.70 g (55%) white product **13**, mp 159-161 °C, IR (potassium bromide): 3300 (OH), 2912 (CH₃), 1672 (amide CO), 1076 (-O-C₂H₅) cm⁻¹; ¹H-NMR (dimethyl sulfoxide-d₆): δ 1.21-1.38 (t, 3H, CH₃CH₂), 1.91 (s, 3H, CH₃CO), 2.42 (s, 3H, CH₃), 4.17-4.40 (q, 2H, CH₃CH₂), 9.21 (s, 1H, OH), 10.45 (s, 1H, NH); ¹³C-NMR (dimethyl sulfoxide-d₆): δ 18.92 (CH₃CH₂), 34.31 (CH₃), 34.37 (CH₃CO), 65.14 (CH₃CH₂), 168.8 {C(OH)OC₂H₅}, 172.08 (C=C), 174.19 (CH₃CO), 188.39 (S-C-NH). MS: (70eV, electron impact) m/z 243 (molecular ion). Anal. Calcd. for C₉H₁₃N₃O₃S: C, 44.43; H, 5.39; N, 17.27. Found: C, 44.64; H, 5.31; N, 17.32. Use of anhydrous DMF instead of anhydrous ethanol did not affect the reaction course.

Method B. To cooled anhydrous DMF (25 ml), 2.25 g of potassium t-butoxide and 2 drops of water were added. After 10 minutes 0.6g (0.0025 m) of compound **8** in 30 ml of DMF has been added dropwise. After 60 minutes the solution was condensed under reduced pressure and to the residue 100 ml of water and 10 % aqueous acetic acid were added until pH=7. The precipitated product was filtered off, washed and crystallized from methanol to give 1.17 g (52%) of product **13**, mp 159-160.5°C which was identical with this one obtained by the method A.

The reactions of aroyl derivatives 9-11:

With sodium ethoxide in ethanol. To sodium ethoxide (0.005 m -120 mg Na in 20 ml of anhydrous ethanol) solution 0.005 m of proper derivative (**9-11**) was added and then the obtained mixture has been stirred and heated at reflux for 5-12 h (see table 1). Afterwards the whole mixture was condensed under reduced pressure and then 20 ml of water was added. The aqueous solution was treated with 10% aqueous acetic acid until pH=7. The precipitated compound was filtered off, washed with water and crystallized from ethanol to give the proper product **7** or **9** (see table 1). Use of anhydrous DMF instead of anhydrous ethanol did not affect the reaction occurring.

With potassium *t*-butoxide. To a cooled anhydrous DMF (25ml) 2.25 g (0.02 m) potassium *t*-butoxide and 2 drops of water were added. After 10 minutes 0.0025 m of the proper derivative (**9-11**) in a DMF solution (30 ml) was added slowly. The mixture has been heated and stirred in water bath for 60 min. Afterwards the whole mixture was condensed under reduced pressure. The dry residue was dissolved in 100 ml of water and then 10% acetic acid solution until pH=7 was added. The precipitated sediment was filtered off, washed with water and crystallized from ethanol to give the proper product **9** or **7** (see table 1) that were identical like in sodium ethoxide use case.

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