ISSN 1070-4280, Russian Journal of Organic Chemistry, 2006, Vol. 42, No. 7, pp. 1031–1035. © Pleiades Publishing, Inc., 2006.
Original Russian Text © V.M. Tormyshev, T.V. Mikhalina, O.Yu. Rogozhnikova, T.I. Troitskaya, D.V. Trukhin, 2006, published in Zhurnal Organicheskoi Khimii, 2006, Vol. 42, No. 7, pp. 1049–1053.

A Combinatorially Convenient Version of Synthesis of 5-Substituted Oxazole-4-carboxylic Acid Ethyl Esters

V. M. Tormyshev, T. V. Mikhalina, O. Yu. Rogozhnikova, T. I. Troitskaya, and D. V. Trukhin

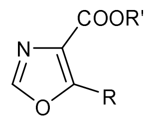
Vorozhtsov Novosibirsk Institute of Organic Chemistry, Siberian Division, Russian Academy of Sciences,
pr. Akademika Lavrent'eva 9, Novosibirsk, 630090 Russia
e-mail: torm@nioch.nsc.ru

Received May 14, 2005

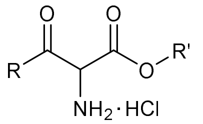
Abstract—Reaction of ethyl isocyanoacetic acid with sodium hydride in anhydrous benzene, followed by treatment with carboxylic acid chlorides or *N*-(acyloxy)pyrrolidine-2,5-diones, gives 5-substituted oxazole-4-carboxylic acid esters. The procedure is applicable to derivatives of various carboxylic acids, including saturated aliphatic, α,β-unsaturated, alicyclic, aromatic, heterocyclic, and *N*-Boc-protected amino acids.

DOI: 10.1134/S1070428006070177

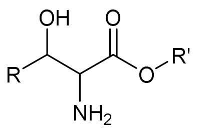
5-Substituted oxazole-4-carboxylic acid esters (**I**) are valuable intermediate products which are used in the synthesis of numerous biologically active compounds. Apart from their direct application as pharmacophoric reagents (e.g., in the preparation of prostacyclin mimetics [1] possessing pronounced antithrombotic activity), 5-substituted oxazole-4-carboxylates may be used as precursors of a number of polyfunctionalized amines (e.g., compounds **II–IV**) which are intermediate products in the synthesis of antifungal, anticarcinogenic [2], cytotoxic [3], gastroprotecting [4], and neurotrophic agents [5].



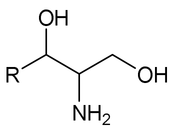
I



II



III

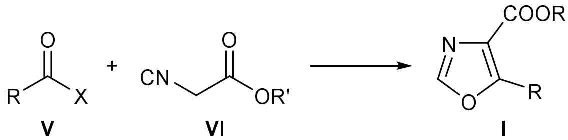


IV

R = Alk, Ar, Ht, 1-NH_2Alk; R' = Me, Et.

In the framework of our research program oriented at synthesizing oxazoles **I** having various substituents in the 5-position, we thought it to be reasonable to involve procedures typical of combinatorial chemistry. Analysis of published data showed that a universal and quite convenient method for the preparation of target oxazole derivatives is based on the reaction of carboxylic acids and their derivatives, such as anhydrides, esters, and acid chlorides **V**, with isocyanoacetates **VI** in the presence of bases [1–4, 6–15] and activating agents [2, 4, 6] provided that carboxylic acid itself is used (Scheme 1).

Scheme 1.



R = Alk, Ar, Ht, 1-NH_2Alk; R' = Me, Et; X = OH, OR, O(CO)R, Cl.

The range of reagents and reaction conditions is fairly broad and is determined primarily by the nature of the R and X substituents in the substrate. For example, various carboxylic acids, including aromatic, aliphatic, alicyclic, and *N*-protected amino acids, in the presence of bases (potassium carbonate, triethylamine, or ethyldiisopropylamine) are successfully involved in the heterocyclization process as mixed anhydrides (which are activated to nucleophilic substitution) generated *in situ* by the action of diethoxyphosphoryl isocyanate [DEPC, $(EtO)_2P(O)NCO$] or diphenoxyphosphoryl azide [DPPA, $(PhO)_2P(O)N_3$] [2, 4, 6]. Esters, anhydrides, and chlorides derived from aromatic carboxylic acids (including pyridinecarboxylic acids) give rise to oxazoles **I** in good yields in the presence of various basic reagents, e.g., potassium *tert*-

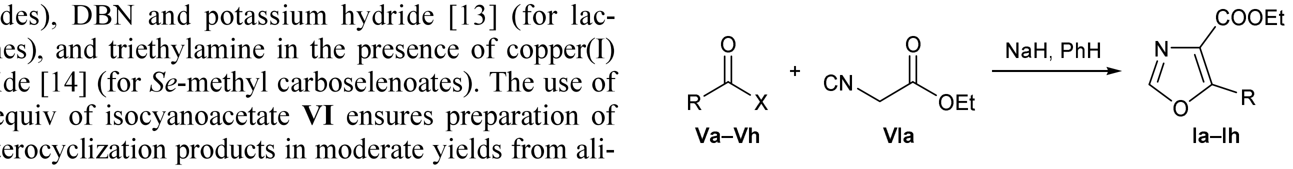
butoxide [7], *n*-butyllithium [7], triethylamine [3, 8, 9], lithium hexamethyldisilylazide [1], 2,8,9-trimethyl-2,5,8,9-tetraaza-1-phosphabicyclo[3.3.3]undecane [10], 1,5-diazabicyclo[4.3.0]non-7-ene (DBN) [1], and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) [1, 11]. However, in going to aliphatic and alicyclic carboxylic acid derivatives, the number of suitable basic reagents considerably decreases: DBU [11, 12] (for anhydrides), DBN and potassium hydride [13] (for lactones), and triethylamine in the presence of copper(I) oxide [14] (for *Se*-methyl carboselenoates). The use of 2 equiv of isocyanoacetate **VI** ensures preparation of heterocyclization products in moderate yields from aliphatic carboxylic acid anhydrides, chlorides, and esters in the presence of butyllithium or potassium *tert*-butoxide [7, 15].

It is seen that direct implementation of the existing procedures in a combinatorial version of synthesis should involve considerable difficulties. In fact, combinatorial syntheses of libraries of organic compounds are based on those reactions (or reaction sequences) which meet at least two requirements: (1) these procedures should be universal and applicable to a maximally broad range of structurally diverse substrates; and (2) all operations should be simple and (in the ideal case) reproducible on a large scale [16].

Among the procedures described previously, only a group of methods based on activation of carboxylic acids with DEPC or DPPA completely meets the first requirement. However, the second condition is difficult to satisfy due to some experimental specificity, in particular the necessity of using extraction procedure for isolation of products from aqueous–organic mixtures, which is undesirable for combinatorial chemistry. The above stated prompted us to search for alternative versions of carrying out heterocyclization process with the emphasis made on the use of readily accessible reagents.

As model substrate we selected isobutyryl chloride (**Va**) (Scheme 2); it is a typical representative of aliphatic carboxylic acid derivatives which, in keeping with published data, is the most sensitive to the nature of base and solvent. Systematic testing of various solvents (diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, hexane, toluene, benzene) and bases (triethylamine, ethyldiisopropylamine, pyridine, butyllithium, phenyllithium, potassium *tert*-butoxide, sodium hydride) showed that only the combination NaH–benzene ensures almost quantitative conversion of isocyanide **VIa** in the reaction with an equimolar amount of acid chloride **Va** with formation of the target oxazole. In the other cases, nearly complete consumption of isocyanide **VIa** but poor yield of the target oxazole (in the systems NaH–THF and *t*-BuOK–THF) or its absence in the reaction mixture (in the presence of triethylamine in various solvents) were observed.

Scheme 2.



V, X = Cl, R = *i*-Pr (**a**), Me (**b**), *cyclo*-C_6H_{11} (**c**), (*E*)-2-(2-thienyl)ethenyl (**d**), Ph (**e**); X = 2,5-dioxopyrrolidin-1-yloxy, R = pyridin-3-yl (**f**), $BocNHCH_2$ (**g**), $BocNHCMe_2$ (**h**); Boc = *tert*-butyloxycarbonyl.

While optimizing the reaction conditions we found that a slight excess of acid chloride (10–15 mol %) is desirable. The procedure is quite simple, and it implies preliminary transformation of initial isocyanoacetate **VIa** into sodium derivative, followed by reaction with acid chloride **Va**. Chromatographic separation of the reaction mixture which contained 81% of the target oxazole (according to the ^1H NMR data) gave product **Ia** in 69% yield (see Experimental). Interestingly, replacement of benzene by toluene did not ensure complete conversion of the substrate even at elevated temperature and prolonged reaction. In this series of experiments, the yield of oxazole **Ia** was considerably lower, 23 to 48%.

The optimal conditions thus determined were applied to structurally different acyl-containing reagents, namely, acid chlorides **Vb**–**Ve** and *N*-acyloxypyrrolidine-2,5-diones **Vf**–**Vh**. Like isobutyryl chloride (**Va**), acetyl chloride and cyclohexanecarbonyl chloride reacted with ethyl isocyanoacetate (**VIa**) to give ethyl 5-methyloxazole-4-carboxylate (**Ib**) and ethyl 5-cyclohexyloxazole-4-carboxylate (**Ic**) in satisfactory yields (56 and 66%, respectively), the conversion of isocyanide **VIa** being nearly quantitative. The proposed conditions turned out to be applicable in the reaction with α,β-unsaturated acid chloride **Vd**: the yield of 5-vinyl-substituted oxazole **Id** was 59%.

Aromatic acid chlorides are the least sensitive to the reaction conditions, and they undergo heterocyclization in the presence of various bases [1, 3, 7–11]. Therefore, it was not surprising that the reaction of benzoyl chloride with sodium derivative of isocyanide **VIa** gave oxazole **Ie** in a fairly high yield (83%). The reaction can be performed in THF in the presence of NaH, triethylamine, or ethyldiisopropylamine with equal success. Nicotinic acid was brought into the heterocyclization in the form of *N*-(pyridin-3-ylcarbonyloxy)pyrrolidine-2,5-dione (**Vf**). When the reaction was performed under the conditions proposed previously (stirring for 24 h at room temperature), oxazole **If** was isolated in a very poor yield 6%, and most initial isocyanide **VIa** was recovered from the reaction mixture. It seemed quite probable that the process is hampered due to low solubility of the reactants, both ester compound **Vf** and ethyl isocyanoacetate sodium salt. Taking into account that prolonged reaction (72 h) did not result in appreciable increase of the product yield, we resorted to an alternative version implying enhanced solubility of isocyanide **VIa** sodium salt in the presence of a phase-transfer catalyst. The best result was obtained with the use of benzyl(triethyl)ammonium chloride (BTEAC, 25 mol %): the yield of target oxazole **If** attained an acceptable level of 59%. The effects of the concentration and nature of phase-transfer catalyst were not examined in detail. We can only note that reduction of the BTEAC concentration to 5 or 10 mol % or replacement of BTEAC by 15-crown-5 led to considerable decrease in the yield. In the reactions with acid chlorides **Va**–**Ve**, addition of BTEAC almost did not affect the product yield.

In the recent years, specific attention is given to peptidomimetics which are structural analogs of polycyclic and acyclic peptides based on unnatural amino acids, including difunctional oxazoles with exocyclic amino and carboxy groups [17]. In order to synthesize such oxazole derivatives we used *N*-(aminoacetyloxy)- and *N*-(2-amino-2-methylpropanoyloxy)pyrrolidine-2,5-diones **Vg** and **Vh** in which the primary amino groups were protected with a *tert*-butyloxycarbonyl group (Boc). No heterocyclization products were obtained from these substrates in the absence of phase-transfer catalyst, while addition of BTEAC resulted in formation of oxazoles **Ig** and **Ih** in good yields (68 and 67%, respectively).

We can conclude that the procedure proposed for the synthesis of 5-substituted oxazole-4-carboxylic acid esters is applicable to derivatives of various carboxylic acids, including saturated aliphatic, α,β-unsaturated, alicyclic, aromatic, heterocyclic, and *N*-Boc-protected amino acids. The procedure is simple (treatment of ethyl isocyanoacetate with sodium hydride in anhydrous benzene, followed by addition of acid chloride or *N*-acyloxy-pyrrolidine-2,5-dione) and is promising for combinatorial chemistry.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded from solutions in $CDCl_3$ or DMSO-d_6 (5 wt %) on Bruker AC-200 (200.13 MHz for ^{1}H and 50.32 MHz for ^{13}C) and Bruker AM 400 spectrometers (400.13 MHz for ^{1}H and 100.61 MHz for ^{13}C); the chemical shifts were referenced to the solvent signals [^{1}H: $CHCl_3$, δ 7.24 ppm; $(CHD_2)_2SO$, δ 2.50 ppm; ^{13}C: $CDCl_3$, δ_C 77.00 ppm]. The high-resolution mass spectra (electron impact, 70 eV) were measured on a Finnigan MAT-8200 mass spectrometer (vaporizer temperature 200–270°C). The melting points were determined on a Boetius melting point apparatus and are uncorrected.

Compounds **Vf**–**Vh** were synthesized according to the procedure described in [18].

1-(Pyridine-3-carbonyloxy)-pyrrolidine-2,5-dione (Vf). Yield 91%, mp 125–127°C (from EtOH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.88 s (4H, $2CH_2$), 7.44 d.d (1H, CH, J = 8.0, 4.8 Hz), 8.35 d.d.d (1H, CH, J = 8.0, 1.8, 1.8 Hz), 8.85 d.d (1H, CH, J = 4.8, 1.8 Hz), 9.28 d (1H, CH, J = 1.8 Hz).

***tert*-Butyl [2-(2,5-dioxopyrrolidin-1-yloxy)-2-oxoethyl]carbamate (Vg).** Yield 86%, mp 162–166°C (from EtOH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.39 s (9H, $3CH_3$), 2.81 s (4H, $2CH_2$), 4.08 d (2H, CH_2, J = 6.2 Hz), 7.45 br.s (1H, NH).

***tert*-Butyl [2-(2,5-dioxopyrrolidin-1-yloxy)-1,1-dimethyl-2-oxoethyl]carbamate (Vh).** Yield 96%, mp 162–164°C (from EtOH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.45 s (9H, $3CH_3$), 1.64 s (6H, $2CH_3$), 2.80 s (4H, $2CH_2$), 4.90 br.s (1H, NH).

Ethyl 5-isopropyloxazole-4-carboxylate (Ia). A 5-ml Wheaton V-vial was charged with 0.042 g (1.04 mmol) of sodium hydride (a 60% suspension in mineral oil) and 1 ml of anhydrous benzene, a solution of 0.102 g (0.90 mmol) of ethyl isocyanoacetate (**VIa**) in 0.5 ml of anhydrous benzene was added, and the reaction vessel was capped (either not tightly or the septum was pierced with a syringe needle to allow liberated hydrogen to escape). The resulting suspension was stirred for 2 h at room temperature, a solution of 0.111 g (1.04 mmol) of isobutyryl chloride (**Va**) in 0.5 ml of anhydrous benzene was added, and the mixture was stirred for 24 h at room temperature and treated with 0.1 ml of ethanol to decompose excess sodium hydride. The mixture was passed through a column containing a small amount (1 cm^3) of silica gel, the column was washed with ethyl acetate (2× 0.5 ml), and the solvent was evaporated in a stream of nitrogen at room temperature. The crude product, 0.195 g, was purified by column chromatography on silica gel using hexane–chloroform (1 : 1) as eluent to isolate 0.114 g (69%) of oxazole **Ia** as a light yellow oily substance. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.26 d [6H, $CH(C\mathbf{H}_3)_2$, *J* = 6.8 Hz], 1.36 t (3H, $CH_2C\mathbf{H}_3$, *J* = 7.2 Hz), 3.77 sept [1H, $C\mathbf{H}(CH_3)_2$, *J* = 6.8 Hz], 4.34 q (2H, $C\mathbf{H}_2CH_3$, *J* = 7.2 Hz), 7.70 s (1H, CH); the spectrum coincided with that given in [15]. ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.02 ($CH_2\mathbf{C}H_3$), 20.22 [$CH(\mathbf{C}H_3)_2$], 25.75 [$\mathbf{C}H(CH_3)_2$], 60.62 ($\mathbf{C}H_2CH_3$), 125.13 (C^4), 148.42 (C^2), 161.85 (C^5), 164.05 (CO). Found: M^+ 183.0901. $C_9H_{13}NO_3$. Calculated: *M* 183.0895.

Oxazoles **Ib**–**Ie** were synthesized in a similar way.

Ethyl 5-methyloxazole-4-carboxylate (Ib). Yield 56%. Light yellow oily substance. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.34 t (3H, $CH_2C\mathbf{H}_3$, *J* = 7.2 Hz), 2.60 s (3H, CH_3), 4.34 q (2H, $C\mathbf{H}_2CH_3$, *J* = 7.2 Hz), 7.71 s (1H, CH) (cf. [14]). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 11.47 (CH_3), 13.92 ($CH_2\mathbf{C}H_3$), 60.52 ($\mathbf{C}H_2CH_3$), 126.98 (C^4), 148.50 (C^2), 155.98 (C^5), 161.73 (CO). Found: M^+ 155.0571. $C_7H_9NO_3$. Calculated: *M* 155.0582.

Ethyl 5-cyclohexyloxazole-4-carboxylate (Ic). Yield 66%. Light yellow oily substance. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.10–1.65 m (6H, $3CH_2$), 1.35 t (3H, $CH_2C\mathbf{H}_3$, *J* = 7.2 Hz), 1.65–1.90 m (4H, $2CH_2$), 3.40 m (1H, CH), 4.31 q (2H, $C\mathbf{H}_2CH_3$, *J* = 7.2 Hz), 7.67 s (1H, CH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.05 ($CH_2\mathbf{C}H_3$), 25.45 (CH_2), 25.75 (CH_2), 30.41 (CH_2), 35.30 (CH), 60.65 ($\mathbf{C}H_2CH_3$), 125.27 (C^4), 148.37 (C^2), 161.98 (C^5), 163.64 (CO). Found: M^+ 223.1215. $C_{12}H_{17}NO_3$. Calculated: *M* 223.1208.

Ethyl 5-[(*E*)-2-(2-thienyl)ethenyl]oxazole-4-carboxylate (Id). Yield 59%, mp 87–89°C (from toluene). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.40 t (3H, $CH_2C\mathbf{H}_3$, *J* = 7.2 Hz), 4.38 q (2H, $C\mathbf{H}_2CH_3$, *J* = 7.2 Hz), 6.99 d.d (1H, CH, *J* = 4.8, 3.4 Hz), 7.16 d.d (1H, CH, *J* = 3.4, 0.8 Hz), 7.30 d.d (1H, CH, *J* = 4.8, 0.8 Hz), 7.38 (2H, *AB* system, *J* = 16.0 Hz), 7.74 s (1H, CH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.11 ($CH_2\mathbf{C}H_3$), 60.98 ($\mathbf{C}H_2CH_3$), 112.17 (CH), 126.36 (CH), 126.41 (C^4), 126.96 (CH), 127.45 (CH), 127.95 (CH), 140.93 (C), 148.70 (C^2), 154.19 (C^5), 161.61 (CO). Found: M^+ 249.0457. $C_{12}H_{11}NO_3S$. Calculated: *M* 249.0460.

Ethyl 5-phenyloxazole-4-carboxylate (Ie). Yield 83%. Light yellow oily substance. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.33 t (3H, $CH_2C\mathbf{H}_3$, *J* = 7.2 Hz), 4.34 q (2H, $C\mathbf{H}_2CH_3$, *J* = 7.2 Hz), 7.39 m (3H), 7.85 s (1H, CH), 8.00 m (2H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 13.91 ($CH_2\mathbf{C}H_3$); 61.08 ($\mathbf{C}H_2CH_3$); 126.42 (C^4); 128.10, 128.17, 128.56, 130.16 (C_{arom}); 148.78 (C^2); 155.24 (C^5); 161.63 (CO) (cf. [19]). Found: M^+ 217.0745. $C_{12}H_{11}NO_3$. Calculated: *M* 217.0739.

Ethyl 5-(pyridin-3-yl)oxazole-4-carboxylate (If). A 5-ml Wheaton V-vial was charged with 0.042 g (1.04 mmol) of sodium hydride (a 60% suspension in mineral oil) and 1 ml of anhydrous benzene, and a solution of 0.102 g (0.90 mmol) of ethyl isocyanoacetate (**VIa**) in 0.5 ml of anhydrous benzene was added. The suspension was stirred for 2 h at room temperature, 0.229 g (1.04 mmol) of 1-(pyridin-3-ylcarbonyloxy)-pyrrolidine-2,5-dione (**Vf**), 0.051 g (0.225 mmol) of benzyl(triethyl)ammonium chloride, and 1 ml of anhydrous benzene were added, and the mixture was stirred for 72 h at room temperature and treated with 0.1 ml of ethanol to decompose excess sodium hydride. The mixture was passed through a column containing a small amount (1 cm^3) of silica gel, the column was washed with ethyl acetate (2 × 0.5 ml), and the solvent was evaporated in a stream of nitrogen at room temperature. The residue, 0.182 g, was purified by column chromatography on silica gel using hexane–chloroform (1 : 1) as eluent to isolate 0.116 g (59%) of oxazole **If** as a colorless crystalline substance with mp 66–68°C (from toluene). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.32 t (3H, $CH_2C\mathbf{H}_3$, *J* = 7.2 Hz), 4.32 q (2H, $C\mathbf{H}_2CH_3$, *J* = 7.2 Hz), 7.32 d.d.d (1H, CH, *J* = 8.2, 4.8, 0.8 Hz), 7.92 s (1H, CH), 8.38 d.d.d (1H, CH, *J* = 8.2, 2.2, 1.7 Hz), 8.57 d.d (1H, CH, *J* = 4.8, 1.7 Hz), 9.09 d.d (1H, CH, *J* = 2.2, 0.8 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 13.86 ($CH_2\mathbf{C}H_3$), 61.34 ($\mathbf{C}H_2CH_3$), 122.81 (CH), 122.82 (C), 127.82 (C^4), 135.48 (CH), 148.73 (C^2), 149.51 (CH), 150.62 (CH), 152.42 (C^5), 161.27 (CO). Found: M^+ 218.0689. $C_{11}H_{10}N_2O_3$. Calculated: *M* 218.0691.

Oxazoles **Ig** and **Ih** were synthesized in a similar way.

Ethyl 5-(*tert*-butoxycarbonylaminomethyl)oxazole-4-carboxylate (Ig). Yield 68%, mp 57–60°C (from toluene). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.29 t (3H, $CH_2C\mathbf{H}_3$, *J* = 7.2 Hz), 1.32 s [9H, $C(CH_3)_3$], 4.28 q (2H, $C\mathbf{H}_2CH_3$, *J* = 7.2 Hz), 4.56 d (2H, CH_2, *J* = 6.2 Hz), 5.32 m (1H, NH), 7.72 s (1H, CH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 13.93 (CH_2CH_3), 27.98 [$C(\mathbf{C}H_3)_3$], 35.35 ($NHCH_2$), 61.05 ($\mathbf{C}H_2CH_3$), 79.75 [$\mathbf{C}(CH_3)_3$], 127.83 (C^4), 149.22 (C^2), 155.24 (C^5), 155.81 (CONH), 161.43 (CO). Found, %:

C 53.64; H 6.81; N 10.39. $C_{12}H_{18}N_2O_5$. Calculated, %: C 53.33; H 6.71; N 10.36.

Ethyl 5-(1-*tert*-butoxycarbonylamino-1-methylethyl)oxazole-4-carboxylate (Ih). Yield 67%, mp 63–64°C (from toluene). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.28 s [9H, $C(CH_3)_3$], 1.36 t (3H, $CH_2C\mathbf{H}_3$, J = 7.2 Hz), 1.68 s [6H, $C(CH_3)_2$], 4.34 q (2H, $C\mathbf{H}_2CH_3$, J = 7.2 Hz), 5.61 br.s (1H, NH), 7.70 s (1H, CH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.13 ($CH_2\mathbf{C}H_3$), 25.48 [$C(\mathbf{C}H_3)_2$], 28.10 [$C(\mathbf{C}H_3)_3$], 51.34 [$\mathbf{C}(CH_3)_2$], 61.20 ($\mathbf{C}H_2CH_3$), 79.46 [$\mathbf{C}(CH_3)_3$], 125.66 (C^4), 147.43 (C^2), 154.83 (CONH), 161.75 (C^5), 163.30 (CO). Found, %: C 56.14; H 7.82; N 9.67. $C_{14}H_{22}N_2O_5$. Calculated, %: C 56.36; H 7.43; N 9.39.

REFERENCES

1. Meanwell, N.A., Romine, J.L., Rosenfeld, M.J., Martin, S.W., et al., *J. Med. Chem.*, 1993, vol. 36, p. 3884.
2. Hamada, Y. and Shioiri, T., *Tetrahedron Lett.* 1982, vol. 23, p. 1193; Omura, S., Katagiri, M., Atsumi, K., Hata, T., Jakubowski, A.A., Springs, E.B., and Tishler, M., *J. Chem. Soc., Perkin Trans. 1*, 1974, p. 1627; Okubo, S., Nakamura, N., Morimoto, M., Mineura, K., Marumo, H., and Omura, S., *J. Antibiot.*, 1980, vol. 33, p. 221.
3. Bosmans, J.-P., Van der Eycken, J., Vandewalle, M., Hulkenberg, A., Van Hes, R., and Veerman, W., *Tetrahedron Lett.*, 1989, vol. 30, p. 3877.
4. Kawai, A., Hara, O., Hamada, Y., and Shioiri, T., *Tetrahedron Lett.*, 1988, vol. 29, p. 6331.
5. Nagamitsu, T., Sunazuka, T., Tanaka, H., Omura, S., Sprengeler, P.A., and Smith, A.B., III, *J. Am. Chem. Soc.*, 1996, vol. 118, p. 3584.
6. Hamada, Y. and Shioiri, T., *Tetrahedron. Lett.*, 1982, vol. 23, p. 235; Hamada, Y., Morita, S., and Shioiri, T., *Heterocycles*, 1982, vol. 17, p. 321; Hamada, Y., Kawai, A., Matsui, T., Hara, O., and Shioiri, T., *Tetrahedron*, 1990, vol. 46, p. 4823.
7. von Schöllkopf, U. and Schröder, R., *Angew. Chem.*, 1971, vol. 83, p. 358.
8. Suzuki, M., Iwasaki, T., Miyoshi, M., Okumura, K., and Matsumoto, K., *J. Org. Chem.*, 1973, vol. 38, p. 3571.
9. Broom, N.J.P., Elder, J.S., Hannan, P.C.N., Pons, J.E., O'Hanlop, P.J., Walker, G., Wilson, J., and Woodall, P., *J. Antibiot.*, 1995, vol. 48, p. 1336; Fevig, J.M., Pinto, D.J., Han, Q., Quan, M.L., Pruitt, J.R., Jacobson, I.C., Galemmo, R.A., Wang, S., Orwat, M.J., Bostrom, L.L., Knabb, R.M., Wong, P.C., Lam, P.Y.S., and Wexler, R.R., *Bioorg. Med. Chem. Lett.*, 2001, vol. 11, p. 641.
10. Tang, J. and Verkade, J.G., *J. Org. Chem.*, 1994, vol. 59, p. 7793.
11. Suzuki, M., Nunami, K.-I., Matsumoto, K., Yoneda, N., and Miyoshi, M., *Synthesis*, 1978, p. 461; Nunami, K.-I., Suzuki, M., Matsumoto, K., Miyoshi, M., and Yoneda, N., *Chem. Pharm. Bull.*, 1979, vol. 27, p. 1373.
12. Makino, K., Okamoto, N., Hara, O., and Hamada, Y., *Tetrahedron: Asymmetry*, 2001, vol. 12, p. 1757.
13. Hall, R.H., Bischofberger, K., Eitelman, S.J., and Jordaan, A., *J. Chem. Soc., Perkin Trans. 1*, 1977, p. 2236; Eitelman, S.J., Hall, R.H., and Jordaan, A., *J. Chem. Soc., Chem. Commun.*, 1976, p. 923.
14. Kozikowski, A.P. and Ames, A., *Tetrahedron*, 1985, vol. 41, p. 4821; Kozikowski, A.P. and Ames, A., *J. Am. Chem. Soc.*, 1980, vol. 102, p. 860.
15. Henneke, K.W., von Schöllkopf, U., and Neudecker, N., *Justus Liebigs Ann. Chem.*, 1979, p. 1370; Schröder, R., von Schöllkopf, U., Blume, E., and Hoppe, I., *Justus Liebigs Ann. Chem.*, 1975, p. 533.
16. Balkenhohl, F., von dem Bussche-Hünnefeld, C., Lansky, A., and Zechel, C., *Angew. Chem., Int. Ed. Engl.*, 1996, vol. 35, p. 2289.
17. Li, P. and Roller, P.P., *Cur. Top. Med. Chem.*, 2002, vol. 2, p. 325; Cox, M.O. and Prager, R.H., *Aust. J. Chem.*, 2004, vol. 57, p. 593; Haberhauer, G. and Rominger, F., *Eur. J. Org. Chem.*, 2003, p. 3209.
18. Anderson, G.W., Zimmerman, J.E., and Callahan, F.M., *J. Am. Chem. Soc.*, 1964, vol. 86, p. 1839.
19. Couture, A., Grandclaudon, P., Hoarau, C., Cornet, J., Henichart, J.-P., and Houssin, R., *J. Org. Chem.*, 2002, vol. 67, p. 3601.