REACTIONS OF 3-BUTINE-2-METHYL-2-OL WITH ISOTHIOCYANATES*

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3-Butine-2-methyl-2-ol reacts with isothiocyanates in the presence of sodium hydride in dimethylformamide to give various products depending on structure of the isothiocyanate residue. Isothiocyanates with the NCS group bound to sp^2 carbon atom (phenyl, 4-bromophenyl, and styryl isothiocyanates) give the respective 1,3-oxazolidine derivatives. If the NCS group is bound to an sp^3-hybridized carbon atom (ethyl and benzyl isothiocyanates), derivatives of 1,3-oxathiolane are formed. Acyl isothiocyanates (benzoyl and 3-phenylpropenoyl isothiocyanates) give products of substitution of the NCS group, *viz.* 1-butine-3-methyl-3-yl benzoate and 3-phenylpropenoic anhydride.

Intramolecular nucleophilic addition reactions at the triple bond of compounds containing 2-propinyl residue represent a frequently used method of synthesis of heterocyclic compounds[1]. This approach is predominantly used for five-membered heterocycles with two heteroatoms which are interesting with respect to their biological activity and, recently, also as substances possessing antiradiation effects[2]. The starting substances for the cyclization are most often obtained by the alkylation of suitable substrates with acetylenic halogeno derivatives or by addition of acetylenic nucleophilic reagents to heterocumulenes[3]. Whereas the reactions of isothiocyanates with β-acetylenic amines were studied in detail[4,5], less attention was paid to applications of β-acetylenic alcohols. Only described are the reactions with primary β-acetylenic alcohols involving cyclization of the intermediate esters of monothiocarbamic acid — preferently *via* the sulphur atom. The reaction of 2-propin-1-ol with phenyl isothiocyanate in the presence of catalytic amount of sodium methoxide proceeds slowly and gives a mixture of isomeric derivatives of 1,3-oxathiolane (46%) and 1,3-oxazolidine (16%) (ref.[6]). The main product of the reaction of methoxycarbonyl isothiocyanate with 2-propin-1-ol also is the corresponding 1,3-oxathiolane (55% yield), whereas formation of the respective 1,3-oxazolidine was not observed[7].

In the present paper we want to deal with the results of a study of reactions of 3-butine-2-methyl-2-ol with alkyl, aryl, and acyl isothiocyanates. At the conditions at which primary and secondary alcohols react with isothiocyanates, tertiary alcohols are unreactive. Therefore, for a verification of possible application of the reaction studied to syntheses of five-membered heterocycles, we chose a tertiary β-acetylenic

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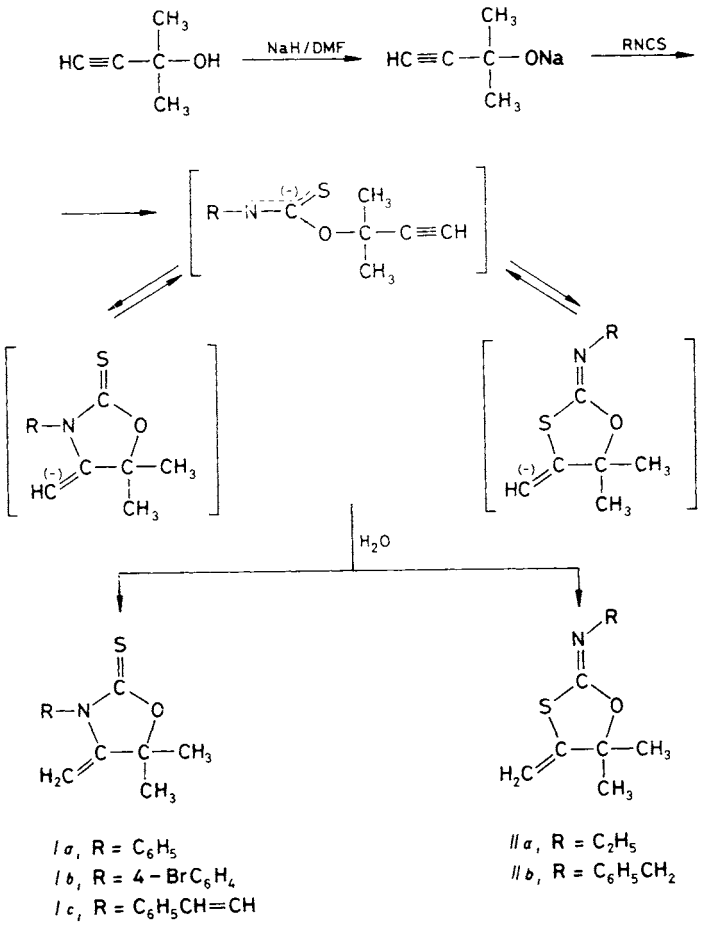
alcohol with decreased reactivity. It was found that 3-butine-2-methyl-2-ol reacts with isothiocyanates only in the form of the corresponding alkoxide ion. As it turned out, it is advantageous to generate the alkoxide anion *in situ* by action of sodium hydride on 3-butine-2-methyl-2-ol in absolute dimethylformamide[8]. After addition of isothiocyanate to the reagent prepared in this way the reaction is over within 40 min at room temperature, and the product is isolated after pouring the reaction mixture onto water. If the reaction was carried out with various isothiocyanates, the structure of product depended dramatically on the nature of the isothiocyanate residue.

The isothiocyanates having NCS group at an sp^2 carbon atom react with formation of 3-substituted 4-methylidene-5,5-dimethyl-1,3-oxazolidine-2-thiones (*I*, Scheme 1).



I a, R = C_6H_5
I b, R = 4-BrC_6H_4
I c, R = $C_6H_5CH{=}CH$

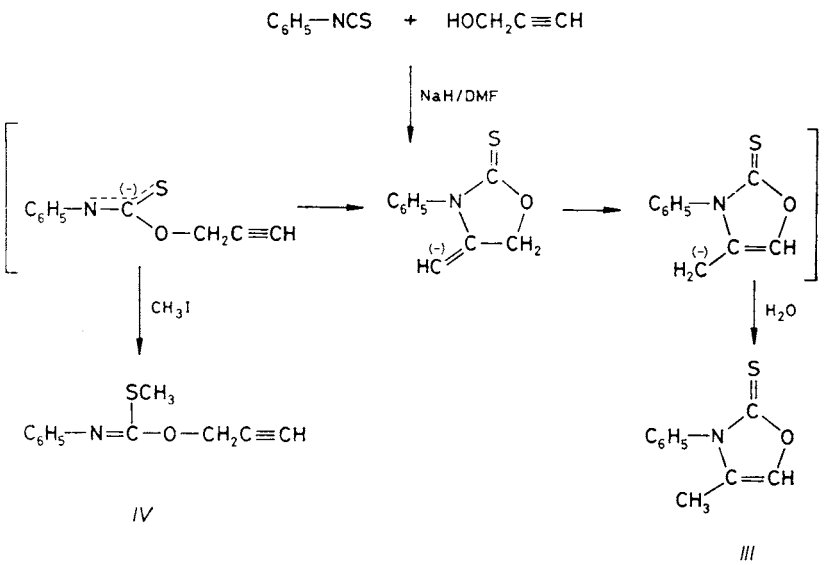
II a, R = C_2H_5
II b, R = $C_6H_5CH_2$

SCHEME 1

Their structure was derived from spectral data. The ^{13}C NMR spectra exhibit a signal of thiocarbonyl carbon atom at $\delta = 185$ ppm, the ^{1}H NMR spectra contain two doublets of the methylene protons at $\delta = 4{\cdot}00$ and $4{\cdot}20$ ppm with the coupling constant $J = 3$ Hz.

The isothiocyanates having NCS group at an sp^3 carbon atom undergo a cyclization *via* the sulphur atom. The ^{13}C NMR spectra of the 2-alkylimino-4-methylidene--5,5-dimethyl-1,3-oxathiolanes (*II*) formed contain signals of the double bond C=N in the region of $\delta = 156$ ppm. The ^{1}H NMR spectra exhibit doublets of the protons of methylene group at $\delta = 5{\cdot}10$ ppm. In the IR spectra there are absorption bands of valence vibrations ν(C=N) at 1 660 cm^{-1}. The compounds *IIa* and *IIb* are instable and are decomposed into a mixture of products (which we could not identify) on standing or during isolation. The samples used for the spectral measurements were purified by column chromatography and subsequent distillation, and their purity checked by gas chromatography was 93% (*IIa*) and 91% (*IIb*).

The different reaction course with alkyl and aryl isothiocyanates can be explained by different stabilization of negative charge in the transition ambident anion of N-substituted O-(2-propinyl) ester of monothiocarbamic acid due to the R substituent. In the case of aryl isothiocyanates the negative charge is stabilized by delocalization to the arylamino residue, which favours the formation of oxazolidine derivatives. With alkyl isothiocyanates such stabilization is impossible, and the cyclization gives 1,3-oxathiolane derivatives because of higher nucleophilicity of the sulphur atom.



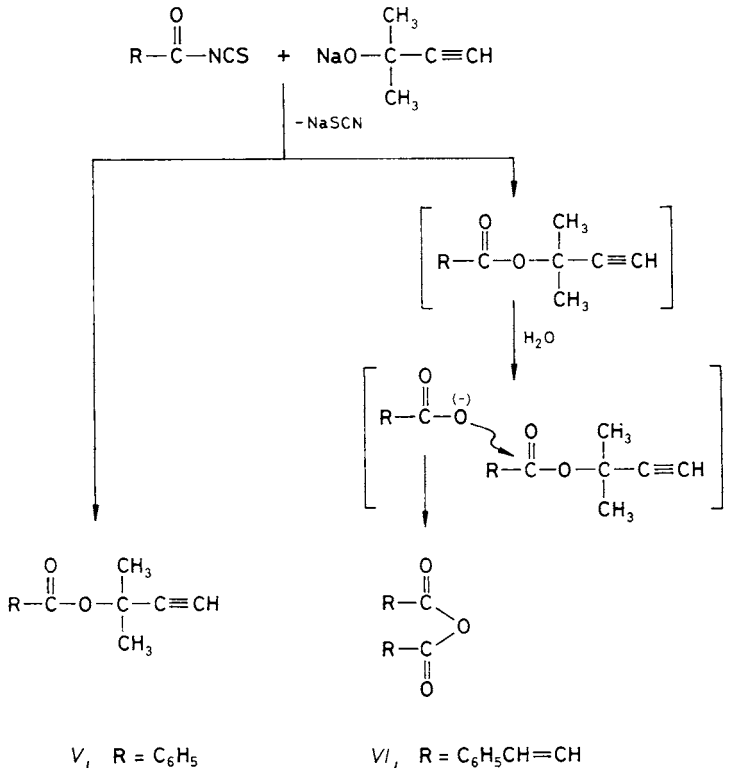
SCHEME 2

These presumptions are confirmed by the reaction of 2-propin-1-ol with phenyl isothiocyanate which gives 1,3-oxazoline (*III*, Scheme 2) in the yield of 80% under these conditions. The migration of α hydrogen atom at these conditions results in formation of the isomer with endocyclic C=C bond.

The formation of another product as in ref.[6] (see above) can be explained by different reaction conditions. In the work quoted the reaction was catalyzed with sodium methoxide (5 mol %), so that the reaction mixture always contained free 2-propin-1-ol which can transfer the proton to the transient sodium salt of the monothiocarbamate ester. The neutral ester thus formed is cyclized preferently through the sulphur atom to give the oxathiolane derivative as the main product. In accordance therewith it was found that the unstable thioureas prepared by the addition of primary β-acetylenic amines to isothiocyanates are cyclized to thiazolidine derivatives in neutral medium, whereas imidazolidine derivatives are formed in basic medium[4]. In our case, obviously, the proton migration is connected with production of a high concentration of the anionic intermediates which cannot be reached in the presence of 2-propin-1-ol as the proton donor. The authors of ref.[6], however, mentioned that they had observed an admixture exhibiting little intensive ^{1}H NMR signals in the region of methyl protons which they assigned to the isomers with endocyclic C=C bond.

If the reaction is carried out in the presence of methyl iodide, the transient sodium salt of N-phenyl-O-(2-propinyl) ester of monothiocarbamic acid undergoes S--methylation to give N-phenyl-O-(2-propinyl)-S-methyl iminomonothiocarbonate (*IV*). 1,3-Oxazoline *III* was isolated from the reaction mixture as a side product due to incomplete methylation.

The reaction of acyl isothiocyanates with sodium salt of 3-butine-2-methyl-2-ol differs from those of alkyl and aryl isothiocyanates. Acyl isothiocyanates contain two electrophilic centres, *viz.* the carbon atom of carbonyl group and that of NCS group. The tertiary alkoxide anion used (as a strong base) reacts preferentially with the carbonyl carbon atom to give products of substitution of NCS group. In the case of benzoyl isothiocyanate the ester V formed is stable, whereas with 3-phenylpropenoyl isothiocyanate the ester undergoes hydrolysis during processing of the reaction mixture. The carboxylate anion formed probably reacts with the not yet hydrolyzed ester to give 3-phenylpropenoic anhydride (*VI*, Scheme 3) as the only product isolated. The same product was also obtained from the reaction with another strong base – sodium amide – and 3-phenylpropenoyl isothiocyanate. Structures of compounds *V* and *VI* were confirmed by IR spectra. The ester *V* exhibits the absorption bands ν(C=O) at 1 720 cm^{-1} and ν(C—O) at 1 110 and 1 270 cm^{-1}. The spectrum of 3-phenylpropenoic anhydride (*VI*) contains characteristical bands of the CO—O—CO grouping at 1 770 and 1 705 cm^{-1}. The different reaction course with benzoyl and 3-phenylpropenoyl isothiocyanates agrees with the findings concerning hydrolysis of these compounds. Whereas the main hydrolysis product of



SCHEME 3

benzoyl isothiocyanate is benzamide[9], the hydrolysis of 3-phenylpropenoyl isothiocyanate produces 3-phenylpropenoic acid[10].

EXPERIMENTAL

3-Butine-2-methyl-2-ol[11], benzyl isothiocyanate[12], 2-phenylvinyl isothiocyanate[13], and 3-phenylpropenoyl isothiocyanate[14] were prepared according to the literature data. Ethyl isothiocyanate (Koch and Light), phenyl isothiocyanate (Lachema, Brno), benzoyl isothiocyanate (Fluka), and 2-propin-1-ol (Aldrich) were commerical products and were distilled before use. The infrared absorption spectra were measured with an IR-75 apparatus (Zeiss, Jena). The ^{1}H NMR spectra (80 MHz) and ^{13}C NMR spectra (25·15 MHz) were measured with a Tesla BS 487 A and a Tesla BS 567 apparatus, respectively, using tetramethylsilane as the internal standard. The gas chromatography analyses were carried out with a Fractovap apparatus (Carlo Erba, Milano).

3-*Substituted* 4-*Methylidene*-5,5-*dimethyl*-1,3-*oxazolidine*-2-*thiones* (I)

A solution of 1·35 g (1·56 ml; 16 mmol) 3-butine-2-methyl-2-ol in 5 ml absolute dimethylformamide was added drop by drop to a suspension of 0·23 g (18 mmol) sodium hydride in 20 ml

absolute dimethylformamide with stirring and cooling (ice and salt) during 20 min, whereafter the stirring and cooling was continued for another 20 min. Then a solution of the respective isothiocyanate (16 mmol) in 5 ml dimethylformamide was added drop by drop during 10 min, and stirring was continued at room temperature 40 min. The reaction mixture was poured onto 800 ml cold water. The separated solid (*Ia, Ib*) was collected by suction and recrystallized from a suitable solvent. The product *Ic* was extracted with 5 × 100 ml eter, the extract was dried with magnesium sulphate, and the ether was evaporated. The evaporation residue was submitted to chromatography on 300 g silica gel 100/250 μ, using benzene–acetone (7 : 1) as the eluent.

3-*Phenyl*-4-*methylidene*-5,5-*dimethyl*-1,3-*oxazolidine*-2-*thione* (Ia)

Yield 68%, m.p. 117–119°C (n-hexane). For $C_{12}H_{13}NOS$ (219·3) calculated: 65·72% C, 5·97% H, 6·39% N; found: 65·60% C, 6·07% H, 6·51% N. IR spectrum ($CHCl_3$): ν(C=C) 1 648 cm^{-1}, ^1H NMR spectrum (C^2HCl_3): 1·68 (s, CH_3—), 4·00 and 4·13 (d, d, =CH_2, J = 3 Hz), 7·42 (m, C_6H_5—). ^{13}C NMR spectrum (C^2HCl_3): 28·00 (q, CH_3—), 84·14 (t, =CH_2), 88·02 (s, >C<), 128·11, 129·30, 129·75, 135·50 (d, d, d, s, C_6H_5—), 153·12 (s, =C<), 186·41 (s, C=S).

3-(4-*Bromophenyl*)-4-*methylidene*-5,5-*dimethyl*-1,3-*oxazolidine*-2-*thione* (Ib)

Yield 50%, m.p. 191–192°C (methanol). For $C_{12}H_{12}BrNOS$ (298·2) calculated: 48·33% C, 4·05% H, 4·69% N; found: 48·47% C, 4·25% H, 4·88% N. IR spectrum ($CHCl_3$): ν(C=C) 1 655 cm^{-1}. ^1H NMR spectrum (C^2HCl_3): 1·66 (s, CH_3—), 3·98 and 4·12 (d, d, =CH_2, J = 3 Hz), 7·18 and 7·63 (d, d, 4-Br—C_6H_4—, J = 8 Hz). ^{13}C NMR spectrum (C^2HCl_3): 28·00 (q, CH_3—), 84·14 (t, =CH_2), 88·22 (s, >C<), 123·37, 129·90, 133·15, and 134·53 (s, d, d, s, 4-Br—C_6H_4—), 152·86 (s, =C<), 186·28 (s, C=S).

3-(2-*Phenylvinyl*)-4-*methylidene*-5,5-*dimethyl*-1,3-*oxazolidine*-2-*thione* (Ic)

Yield 55%, m.p. 71–73°C (n-hexane). For $C_{14}H_{15}NOS$ (254·3) calculated: 58·77% C, 6·12% H, 5·71% N; found: 58·57% C, 6·20% H, 5·46% N. IR spectrum ($CHCl_3$): ν(C=C) 1 652 and 1 635 cm^{-1}. ^1H NMR spectrum (C^2HCl_3): 1·60 (s, CH_3—), 4·35 and 4·80 (d, d, =CH_2, J = 3 Hz), 6·83 and 7·20 (d, d, —CH=CH—, J = 16 Hz), 7·35 (m, C_6H_5—). ^{13}C NMR spectrum (C^2HCl_3): 27·93 (q, CH_3—), 85·65 (t, =CH_2), 87·64 (s, >C<), 122·58 and 126·24 (d, d, —CH=CH—), 126·39, 128·33, 128·85, and 134·53 (d, d, d, s, C_6H_5—), 149·83 (s, =C<), 185·29 (s, C=S).

2-*Substituted Imino*-4-*methylidene*-5,5-*dimethyl*-1,3-*oxathiolanes* (II)

The procedure was the same as that for compound *Ic*. Ether–petroleum ether (1 : 7) was used as the eluent in the column chromatography on silica gel (100/250 μ, 150 g per 1 g raw product). After evaporation of the solvent from the eluate, the compounds *IIa, IIb* were distilled under reduced pressure.

2-*Ethylimino*-4-*methylidene*-5,5-*dimethyl*-1,3-*oxathiolane* (IIa)

The gas chromatography analysis of the product (3% FFAP on chromosorb W) showed 93% purity of the substance. Yield 55%, b.p. 101–103°C/2 135 Pa. IR spectrum ($CHCl_3$): ν(C=N) 1 670 cm^{-1}, ν(C=C) 1 630 cm^{-1}. ^1H NMR spectrum (C^2HCl_3): 1·20 (t, CH_3—), 1·55 (s, CH_3—), 3·10 (q, —CH_2—), 5·07 and 5·12 (d, d, =CH_2, J = 3 Hz). ^{13}C NMR (C^2HCl_3): 15·90

(q, CH_3—), 27·55 (q, CH_3—), 47·93 (t, —CH_2—), 87·27 (s, >C<), 103·77 (t, =CH_2), 148·86 (s, =C<), 156·47 (s, C=N).

2-*Benzylimino*-4-*methylidene*-5,5-*dimethyl*-1,3-*oxathiolane* (IIb)

The gas chromatography analysis of the product (3% OV-1 on chromosorb W) showed 91% purity of the substance. Yield 51%, b.p. 154—156°C/933 Pa. IR spectrum ($CHCl_3$): ν(C=N) 1 660 cm^{-1}, ν(C=C) 1 625 cm^{-1}. ^{1}H NMR spectrum (C^2HCl_3): 1·55 (s, CH_3—), 4·29 (s, —CH_2—), 5·05 and 5·13 (d, d, =CH_2, J = 3 Hz), 7·23 (m, C_6H_5—). ^{13}C NMR spectrum (C^2HCl_3): 27·55 (q, CH_3—), 57·11 (t, —CH_2—), 87·97 (s, >C<), 104·14 (t, =CH_2), 127·00, 127·51, 128·63, and 139·16 (d, d, d, s, C_6H_5—), 148·41 (s, =C<), 158·27 (s, C=N).

3-*Phenyl*-4-*methyl*-1,3-*oxazoline*-2-*thione* (III)

The procedure was the same as that for compound *Ic*. The product was isolated by column chromatography (silica gel, benzene–acetone 19 : 1). Yield 80%, m.p. 95—97°C (ether–petroleum ether at −10°C). For $C_{10}H_9NOS$ (191·3) calculated: 62·78% C, 4·74% H, 7·32% N; found: 62·61% C, 4·90% H, 7·48% N. IR spectrum ($CHCl_3$): ν(C=C) 1 645 cm^{-1}. ^{1}H NMR spectrum (C^2HCl_3): 1·65 (s, CH_3—), 7·35 (m, =CH— and C_6H_5—). ^{13}C NMR spectrum (C^2HCl_3): 9·18 (q, CH_3—), 126·41 (s, =C<), 129·82 (d, =CH—), 127·66, 129·82, 131·99, and 134·60 (d, d, d, s, C_6H_5—), 179·47 (s, C=S).

N-*Phenyl*-O-(2-*propinyl*)-S-*methyl Iminomonothiocarbonate* (IV)

A solution of 1·35 g (1·44 ml; 24 mmol) 2-propin-1-ol in 8 ml dimethylformamide was added drop by drop to a suspension of 0·43 g (27 mmol) sodium hydride in 20 ml absolute dimethylformamide with stirring and cooling (ice and salt) during 20 min, and the stirring and cooling was continued for another 20 min. Then a solution of 3·42 g (2·88 ml; 24 mmol) phenyl isothiocyanate in 8 ml dimethylformamide was added drop by drop within 5 min, and stirring was continued at room temperature 20 min. Thereafter, 4·26 g (1·92 ml; 30 mmol) methyl iodide was added, the mixture was stirred 40 min, and then it was poured onto 1 000 ml cold water. The product was extracted with 4 × 200 ml ether, the extract was dried with magnesium sulphate, and the solvent was evaporated. The oily residue was dissolved in 10 ml chloroform, and petroleum ether was added until turbidity. The compound *III* (0·7 g) separated on standing. The solvent was evaporated, and the residue was purified by chromatography on 250 g silica gel 100/250 μ with benzene as the eluent. In this way, further portion (0·5 g) of the oxazoline *III* was obtained along with 1·2 g (21%) and 2 g (42%) ester *IV*, b.p. 138—140°C/2 399 Pa. For $C_{11}H_{11}NOS$ (205·3) calculated: 64·35% C, 5·40% H, 6·82% N; found: 64·49% C, 5·19% H, 6·90% N. ^{1}H NMR spectrum (C^2HCl_3): 2·36 (s, CH_3S—), 2·51 (t, HC≡, J = 3 Hz), 4·97 (d, —CH_2—, J = 3 Hz), 7·80 (m, C_6H_5—).

1-*Butine*-3-*methyl*-3-*yl Benzoate* (V)

The procedure was the same as that for compound *IIa*. For the chromatography, benzene was used as the eluent. Yield 61%, b.p. 74—76°C/665 Pa. For $C_{12}H_{12}O_2$ (168·2) calculated: 73·88% C, 7·19% H; found: 73·65% C, 7·31% H. IR spectrum ($CHCl_3$): ν(≡C—H) 3 308 cm^{-1}, ν(C=O) 1 720 cm^{-1}, ν(C—O) 1 270 cm^{-1} and 1 109 cm^{-1}. ^{1}H NMR spectrum (C^2HCl_3): 1·55 (s, CH_3—), 2·57 (s, ≡CH), 7·45 and 8·00 (m, m, C_6H_5—). ^{13}C NMR spectrum (C^2HCl_3): 29·04 (q, CH_3—), 72·19 (s, >C<), 72·56 (d, ≡CH), 84·66 (d, ≡C—), 128·26, 129·60, 130·79, and 132·81 (d, d, s, d, C_6H_5—), 164·70 (s, C=O).

3-*Phenylpropenoic Anhydride* (*VI*)

a) The same procedure as that for compound *Ic*. Yield 52%. *b*) 3-Phenylpropenoyl isothiocyanate (0·47 g; 2·5 mmol) was added to a suspension of 0·14 g (3·7 mmol) sodium amide in 6 ml dimethylformamide within 10 min, and the mixture was stirred at room temperature 45 min. The solid separated on addition of 10 ml water was collected by filtration. Yield 0·32 g (91%). The compounds obtained by both the procedures (*a*) and (*b*) are identical with the authentic sample[15].

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