

Synthesis and Reactions of 5-Methoxycarbonyl-2-furylisocyanate

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The synthesis of furo[3,2-*e*]pyrimidine-4-thione is described starting from 5-methoxy-2-furylisocyanate. The starting material is converted to substituted ureas by reaction with secondary amines. Chlorination of a urea affords chloroformamidine, which in turn cyclizes with potassium thiocyanate to give the target furopyrimidinethione.

The 2-methoxycarbonyl-3-thienylisocyanate, accessible by treatment with phosgene of methyl 3-amino-2-thienylcarboxylate in dry toluene, affords the corresponding ureas and chloroformamidines [1]. Also, preparation of thieno[2,3-*d*]pyrimidines by reaction of the above chloroformamidines with *N*-nucleophiles has been described [2]. In addition, reactions of the ethyl ester of 5-amino-2-furylcarboxylic acid with aldehydes [3], as well as with carbonylisocyanates have been described. The products of the latter reaction could be cyclized to furo[2,3-*d*]thiazoles [4].

We describe a modified preparation procedure [5], as applied for 5-ethoxy- and 5-methoxycarbonyl-2-furylisocyanate (*Ia* and *Ib*). Thus the starting ester of 5-amino-2-furylcarboxylic acid was treated with phosgene in dichloromethane or tetrachloromethane in the presence of triethylamine in a glass autoclave at 60 °C. Although isocyanates were formed in good yields, their lower stability led to frequent formation of dimers. The dimers, 1,3-bis(5-methoxycarbonyl-2-furyl)-1,3-diazetidene-2,4-dione (*IIa*) and 1,3-bis(5-ethoxycarbonyl-2-furyl)-1,3-diazetidene-2,4-dione (*IIb*) could be separated from isocyanates based on their low solubility in tetrachloromethane. Crude dimers were crystallized from dimethyl sulfoxide.

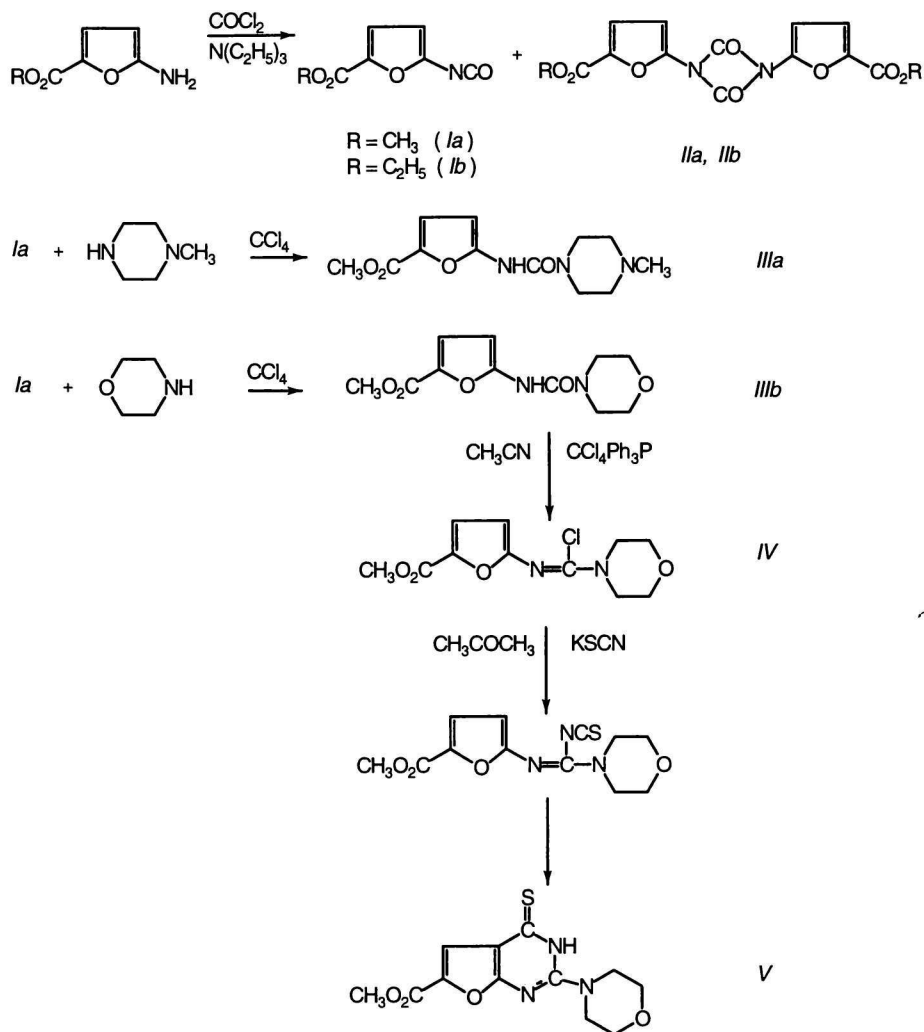
The isocyanate *Ib* was converted to the *N',N'*-disubstituted ureas (*IIIa* in 47 % and *IIIb* in 64 % yield) by treatment with morpholine and *N*-methylpiperazine, respectively. Their purification was done by crystallization from ethanol (*IIIb*) or chromatography on a silica gel column (*IIIa*). Several chlorination procedures of *N*-(5-methoxycarbonyl-2-furyl)-*N',N'*-[1,5-(3-oxapentanediy)]urea (*IIIb*) were tested, such as the use of thionyl chloride in the presence of triethylamine or 1-phenoxy-2,3-epoxypropane. Best results were achieved with triphenylphosphine/tetrachloromethane in dry acetonitrile under argon atmosphere. The work-up of the reaction mixture posed some problems with separation of the imidoyl chloride (*IV*) from triphenylphosphine and triphenylphosphine ox-

ide. The purification was effected by fractional crystallization from diethyl ether. The subsequent reaction of imidoyl chloride *IV* with potassium thiocyanate afforded, instead of the expected formamidinoyl isothiocyanate, a product of cyclization, namely the 6-methoxycarbonyl-2-(*N*-morpholinyl)-3,4-dihydrofuro[3,2-*e*]pyrimidine-4-thione (*V*). The whole reaction sequence is shown in Scheme 1. The last reaction was carried out in acetone at -5 to 5 °C. The structures of obtained compounds were deduced from their IR, UV, ¹H NMR, and mass spectra.

The UV spectra of compounds *IIa*, *IIb*, *IIIa*, and *IIIb* display only one major maximum at $\lambda = 301\text{--}313$ nm ($\log \{\epsilon\} = 4.38\text{--}5.32$). The UV spectrum of compound *V* features two bands at 287 nm ($\log \{\epsilon\} = 4.05$) and 365 nm ($\log \{\epsilon\} = 3.83$). Mass spectra of compounds *IIb*, *IIIa*, *IIIb*, and *V* were taken and analyzed. Whilst compounds *IIIa*, *IIIb*, and *V* afford molecular ion peaks, dimer *IIb* fails to give M^{+} , the base peak being that at $m/z = 181$, corresponding to the monomer. The monomer loses the C_2H_4COO and ethylene fragments, respectively as confirmed by two metastable ions at $m/z = 65$ and $m/z = 129$ (Scheme 2). Compounds *IIIa* and *IIIb* both lose in mass spectrometer the secondary amine with the concomitant hydrogen shift, giving rise to the ion at $m/z = 167$. This in turn splits off $CH_3O\cdot$ radical and generates a metastable ion at $m/z = 111$. Peaks at $M^{+} - 31$ testify to the presence of methyl ester structural unit in the molecule. The mass spectrum of *IIIb* displays a very intense peak at $m/z = 114$, from which a molecule of ethylene oxide is split off, hence a metastable peak at $m/z = 43$ (Scheme 3).

The fragmentation in the mass spectrum of compound *V* follows two paths, namely that of the pyrimidinethione skeleton and cleavage of the 4-cyanomorpholine fragment ($M^{+} - 112$). Metastable ion at $m/z = 236$ testifies to the loss of methoxy radical from the molecular ion (Scheme 2).

Strong maxima at $\tilde{\nu} = 1699\text{--}1724$ cm^{-1} (C=O)



Scheme 1

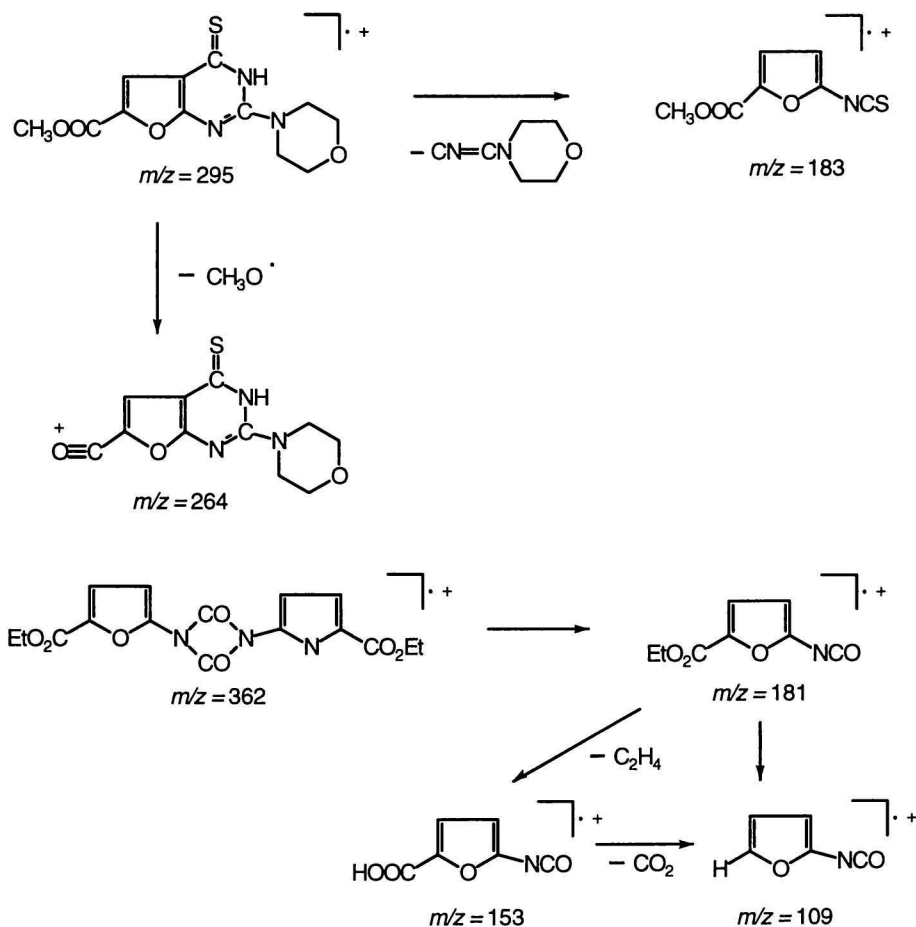
dominate the IR spectra. The NH maxima in the spectra of *IIIa* and *IIIb* can be seen at $\tilde{\nu} = 3412\text{--}3432\text{ cm}^{-1}$. In the spectrum of *V* the band at $\tilde{\nu} = 3212\text{ cm}^{-1}$, belonging to the vibration of an NH group indicates the presence of a thione structure. While the spectrum of *Ia* shows a heterocumulene band at $\tilde{\nu} = 2206\text{ cm}^{-1}$, in the spectra of *IIa* and *IIb* there is no such band.

All the ^1H NMR spectra show a sharp singlet of the methoxy group at $\delta = 3.80\text{--}3.91$, the highest downfield shift belonging to compound *Ia*. Furthermore, all compounds with the exception of *V*, display characteristic AX doublets of furan protons with $J_{\text{AX}} = 3.6\text{ Hz}$. The H-4 of the furan ring is found at $\delta = 7.12\text{--}7.16$, largely unaffected by substituents at furan. In contrast, H-3 is much more sensitive to substitution pattern and its signals are found at $\delta = 5.95\text{--}6.31$. Compound *V* displays a sharp singlet of the furan proton at $\delta = 7.44$, and the morpholine multiplet at $\delta = 3.67\text{--}3.75$.

For compound *IIb* the structure elucidation required the measurement of ^{13}C NMR spectra, in which the carbon atom of the 1,3-diazetidone-2,4-dione skeleton had the signal at $\delta = 135.8$. Isocyanates are known to possess signals of the NCO carbon at $\delta = 120\text{--}125$, the formation of a dimer accounts for the difference of ≈ 10 [6].

EXPERIMENTAL

Melting points were determined on the Kofler hot stage. Infrared spectra were measured with Zeiss spectrophotometer, model IR 71, UV spectra on the model Specord UV VIS. Mass spectra were taken with MS 902 S (AEI Manchester, $100\text{ }\mu\text{A}$, 70 eV). ^{13}C and ^1H NMR spectra were taken with the FX-100 (60 MHz) Jeol spectrometer using tetramethylsilane as internal reference.



Scheme 2

5-Methoxycarbonyl-2-furylisocyanate (*Ia*)

To the solution of 1 g (7 mmol) of methyl ester of 5-amino-2-furylcarboxylic acid dissolved in 70 cm³ of dry dichloromethane and 2 cm³ of triethylamine the solution of phosgene in benzene (12 mmol in 4 cm³ of benzene) was added. The mixture was heated in a pressure tube at 60°C for 12 h. Then the solvent was removed *in vacuo* and the residue extracted with carbon tetrachloride. The solution of crude isocyanate was used directly in subsequent reaction to avoid its dimerization on standing. This procedure was used also for preparation of 5-ethoxycarbonyl-2-furylisocyanate (*Ib*). When left to stand for 24 h at room temperature, the carbon tetrachloride solutions of isocyanates contained precipitates of dimers, 1,3-bis(5-methoxycarbonyl-2-furyl)-1,3-diazetidene-2,4-dione (*IIa*) and 1,3-bis(5-ethoxycarbonyl-2-furyl)-1,3-diazetidene-2,4-dione (*IIb*), respectively. Crude dimers were obtained in 95% (*IIa*) and 96% (*IIb*) yields, respectively. Dimers were purified by crystallization from dimethyl sulfoxide.

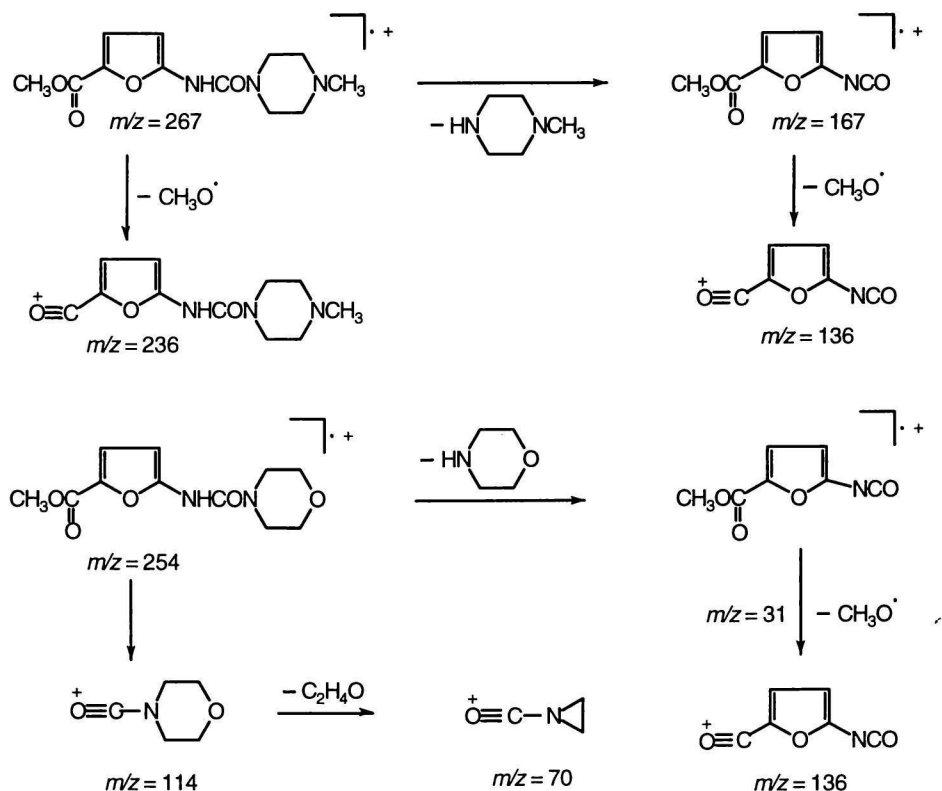
Ia: IR spectrum (CCl₄), $\bar{\nu}/\text{cm}^{-1}$: 2206, 1726, 1628, 1542, 1434, 1402, 1140, 1017, 713, 678. ¹H NMR spec-

trum (CDCl₃), δ : 3.91 (s, 3H, CH₃), 5.99 (d, 1H, *J* = 3.5 Hz, H-3), 7.12 (d, 1H, H-4).

Ib: IR spectrum (CCl₄), $\bar{\nu}/\text{cm}^{-1}$: 2206, 1720, 1629, 1547, 1434, 1405, 1141, 1017, 720, 685. ¹H NMR spectrum (CDCl₃), δ : 1.28 (t, 3H, CH₃), 4.27 (q, 2H, CH₂), 6.01 (d, 1H, *J* = 3.5 Hz, H-3), 7.12 (d, 1H, H-4).

IIa: M.p. = 235–237°C. For C₁₄H₁₀N₂O₈ (*M_r* = 334.14) *w_i*(calc.): 50.30% C, 2.99% H, 8.38% N; *w_i*(found): 50.73% C, 3.40% H, 8.01% N. IR spectrum (KBr), $\bar{\nu}/\text{cm}^{-1}$: 3052, 1714, 1670, 1655, 1620, 1431, 1312, 1192, 1137, 1018, 788, 742. UV spectrum (dioxane), $\lambda_{\text{max}}/\text{nm}$ (log{ ϵ }): 301 (5.32). ¹H NMR spectrum (DMSO-*d*₆), δ : 3.81 (s, 6H, 2 × CH₃), 6.27 (d, 2H, *J* = 3.6 Hz, H-3, H-3'), 7.16 (d, 2H, H-4, H-4').

IIb: M.p. = 248–250°C. For C₁₆H₁₄N₂O₈ (*M_r* = 362.16), *w_i*(calc.): 53.04% C, 3.86% H, 7.74% N; *w_i*(found): 52.73% C, 3.79% H, 7.9% N. IR spectrum (KBr), $\bar{\nu}/\text{cm}^{-1}$: 3072, 1714, 1677, 1560, 1536, 1409, 1249, 1172, 1150, 1110, 760. UV spectrum (dioxane), $\lambda_{\text{max}}/\text{nm}$ (log{ ϵ }): 313 (4.57). ¹H NMR spectrum (DMSO-*d*₆), δ : 1.29 (t, 6H, 2 × CH₃), 4.27 (q, 4H, 2 × CH₂), 5.95 (d, 2H, *J* = 3.5 Hz, H-3, H-3'), 7.29 (d, 2H, H-4, H-4'). ¹³C NMR spectrum (DMSO-*d*₆), δ : 14.29 (CH₃), 60.23 (CH₂), 94.66 (CH), 121.3



(CH), 135.79 (NCON), 148.53 (C-5 furan), 50.61 (C-2 furan), 157.68 (CO₂).

***N*-(5-Methoxycarbonyl-2-furyl)-*N*',*N*'-[1,5-(3-methylazapentanediy)]urea (*IIIa*)**

To the solution of 1 g (7 mmol) of *Ia* in carbon tetrachloride 0.7 g (7 mmol) of *N*-methylpiperazine was added and the reaction mixture was heated to 40–50 °C for 30 min. Then the solvent was evaporated and the oily residue purified by thin-layer chromatography (silica gel LS 5-40, eluant benzene—ether ($\varphi_r = 1:1$)) to obtain 0.9 g of *IIIa*, yield = 47.4 %, m.p. = 120–122 °C (ethanol). For C₁₃H₁₇N₃O₄ ($M_r = 267.12$) w_i (calc.): 53.92 % C, 6.37 % H, 15.73 % N; w_i (found): 54.20 % C, 6.63 % H, 15.60 % N. IR spectrum (KBr), $\tilde{\nu}/\text{cm}^{-1}$: 3412, 3002, 2790, 1715, 1665, 1534, 1397, 1317, 1252, 1133, 990, 756. UV spectrum (methanol), $\lambda_{\text{max}}/\text{nm}$ ($\log\{\epsilon\}$): 303 (4.53). ¹H NMR spectrum (acetone-*d*₆), δ : 2.25 (s, 3H, NCH₃), 2.40 (t, 4H, 2 × CH₂), 3.60 (t, 4H, 2 × CH₂), 3.80 (s, 3H, CH₃), 6.31 (d, 1H, $J = 4$ Hz, H-3 furan), 7.17 (d, 1H, H-4 furan). Mass spectrum, m/z : ($M^{+\bullet}$) 267.

***N*-(5-Methoxycarbonyl-2-furyl)-*N*',*N*'-[1,5-(3-oxapentanediy)]urea (*IIIb*)**

To 1 g (7 mmol) of *Ia* dissolved in CCl₄ 0.65 g

(7 mmol) of morpholine was added and the reaction mixture warmed up by the addition of morpholine was heated to 40–45 °C for another 30 min. After cooling 1.3 g of crude product was separated. Subsequent recrystallization from ethanol gave crystalline urea *IIIb*, m.p. = 154–156 °C. For C₁₁H₁₄N₂O₅ ($M_r = 254.11$) w_i (calc.): 51.97 % C, 5.54 % H, 11.02 % N; w_i (found): 51.72 % C, 5.67 % H, 11.39 % N. IR spectrum (CHCl₃), $\tilde{\nu}/\text{cm}^{-1}$: 3432, 2970, 2850, 1720, 1690, 1545, 1447, 1430, 1420, 1260, 1156, 1132, 1030, 885. UV spectrum (methanol), $\lambda_{\text{max}}/\text{nm}$ ($\log\{\epsilon\}$): 301 (4.38). ¹H NMR spectrum (CDCl₃), δ : 3.85 (s, 3H, CH₃), 3.61 (s, 4H, 2 × CH₂), 3.69 (s, 4H, 2 × CH₂), 6.25 (d, 1H, $J = 3.9$ Hz, H-3 furan), 7.13 (d, 1H, H-4 furan), 8.04 (s, 1H, NH). Mass spectrum, m/z : ($M^{+\bullet}$) 254.

***N*-(5-Methoxycarbonyl-2-furyl)-4-morpholinecarboximidoyl Chloride (*IV*)**

To a stirred mixture of 1 g (3.9 mmol) of *IIIb* and 1.5 g (5.8 mmol) of triphenylphosphine in 10 cm³ of absolute acetonitrile 0.89 g (5.8 mmol) of carbon tetrachloride was added dropwise under argon atmosphere. The originally limpid reaction mixture was stirred until clear (about 1 h). Solvents were then evaporated at max. 40 °C and the oily residue was extracted with dry ether (3 × 10 cm³). Concentration of extracts af-

forded 0.8 g (76 %) of crude imidoyl chloride *IV*. IR spectrum (CHCl_3), $\tilde{\nu}/\text{cm}^{-1}$: 2937, 1719, 1650, 1532, 1437, 1312, 1113, 723, 703.

6-[Methoxycarbonyl-2-(*N*-morpholinyl)]-3,4-dihydrofuro[3,2-*e*]pyrimidine-4-thione (*V*)

To a stirred solution of 0.3 g (3 mmol) of potassium thiocyanate in 10 cm^3 of absolute acetone, cooled to -5°C an acetone solution of 1 g (3.9 mmol) of imidoyl chloride *IV* was dropwise added so that the temperature remained within -5°C to 5°C . After addition the mixture was stirred for another 30 min at $0-5^\circ\text{C}$. Then the mixture was concentrated, the residue extracted with hot acetonitrile to give compound *V*, yield = 0.2 g (17 %), m.p. = $217-220^\circ\text{C}$ (CH_3CN).

For $\text{C}_{12}\text{H}_{13}\text{N}_3\text{O}_4\text{S}$ ($M_r = 295.18$) $w_i(\text{calc.})$: 48.81 % C, 4.41 % H, 14.24 % N, 10.85 % S; $w_i(\text{found})$: 48.55 % C, 4.50 % H, 13.68 % N, 10.79 % S. IR spectrum (KBr), $\tilde{\nu}/\text{cm}^{-1}$: 3212, 2950, 1744, 1601, 1574, 1452,

1362, 1325, 1277, 1175, 1118, 983, 870, 755, 713. UV spectrum (methanol), $\lambda_{\text{max}}/\text{nm}$ ($\log\{\epsilon\}$): 287 (4.05), 365 (3.83). ^1H NMR spectrum ($\text{DMSO}-d_6$), δ : 3.55—3.67 (m, 8H, morpholine), 3.84 (s, 3H, OCH_3), 7.44 (s, 1H, H furan). Mass spectrum, m/z ($\text{M}^{+\cdot}$) 295.

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