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A facile and effective synthesis of 2-azetidinones via phosphonitrilic chloride

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ABSTRACT

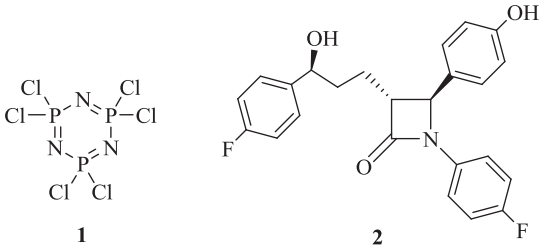
The Staudinger reaction of imines to β-lactams was successfully achieved with substituted acetic acid and phosphonitrilic chloride in one-pot under mild conditions. Several types of β-lactams, especially 3-electron-withdrawing group β-lactams, can be synthesized by this versatile and efficient method in good to excellent yields. This method is simple, clean, and the by-products were removed by simple aqueous work-up. The effects of solvents, molar ratio of reagent, and the temperature were considered.

1. Introduction

Phosphonitrilic chloride **1** (1,3,5-triaza-2,4,6-triphosphorin-2,2,4,4,6,6-hexachloride) is a precursor to poly(dichlorophosphazene) or inorganic rubber[1] and is used for the synthesis of dandelion dendrimers.[2] It has been widely used in organic reactions,[3] such as the conversion of aldoximes to nitriles,[4] the Beckmann rearrangement of ketoximes to lactams,[5] and the conversion of sulfonic acids into the corresponding sulfonyl chlorides.[6] Also, phosphonitrilic chloride has been used as activator of carboxylic acids to formation of amides and hydrazides.[7] This compound can be prepared by reaction of PCl_5 and NH_4Cl, although it is commercially available.[8]

β-Lactams (2-azetidinones) have served humanity for several decades in its war against the infections caused by bacteria and are responsible for saving millions of lives.[9] Ezetimibe **2** is a new drug as cholesterol absorption inhibitor for clinical use that it has 2-azetidinone ring in its structure.[10] Literature survey reveals that 2-azetidinones shown to possess other relevant biological activities,[11] which include human cytomegalovirus (HCMV) inhibitor,[12] human leukocyte elastase (HLE) inhibitor,[13] thrombin inhibitor,[14] porcine pancreatic elastase (PPE) inhibitor,[15] HIV-1 protease inhibitor,[16] cysteine protease inhibitor,[17] anticancer,[18] antifungal,[19] potential antimalarials,[20] anti-influenzavirus,[21] antihyperglycemic,[22] central nervous system (CNS) active agents,[23] combatant of neurological diseases,[24] antiproliferative activities,[25] antitubercular,[26] anti-oxidant,[27] and insecticidal activities.[28]

Furthermore, β-lactams have received wide use as key synthons for many classes of compounds in organic synthesis,[29] especially in the semisynthesis of Taxol derivatives.[30]



1 **2**

Many synthetic methods have been developed for the formation of the β-lactam ring because of tremendous important of β-lactams and several review for this subject has been published.[31] Mostly, synthesis of β-lactams through [2+2] cycloaddition reaction of ketenes with imines (Staudinger reaction)[32] is applied.[33] Reaction of acyl halides with tertiary amines remains the most useful approach for generation of ketenes.[34] But use of acyl chloride has some drawbacks. The preparation, isolation, and handling of acid chlorides are difficult, their stability is low and some of acid halides are not commercially available. Scientists have reported carboxylic acid activators to solve this problem.[35] Some of these acid activators

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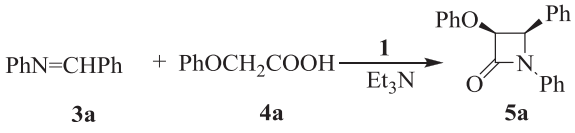
require low or high temperatures, inconvenient reaction conditions for their execution, and are often accompanied by painful chromatographic separations to remove by-products from desired products.

To the best of our knowledge, there have been no reports employing phosphonitrilic chloride as a reagent for the activation of carboxylic acids in the synthesis of 2-azetidinones. Hence, based on the aforementioned, phosphonitrilic chloride was utilized as activating agent for carboxylic acids to afford 2-azetidinones.

2. Results and discussion

As a model substrate to determine the best reaction conditions, a set of experiments using *N*-benzylideneaniline **3a** and phenoxyacetic acid **4a** in the presence of Et_3N were performed to examine the effects of solvents, temperature, and different amount of phosphonitrilic chloride in the synthesis of 2-azetidinone **5a**. As it is shown in Table 1, dry dichloromethane was the best solvent for this reaction. For optimization of amount of phenoxyacetic acid, 3 equiv of phenoxyacetic acid relative to the equivalent phosphonitrilic chloride were used. According to Table 1, the highest yield was obtained when 1.5 mmol phenoxyacetic acid and 0.5 mmol phosphonitrilic chloride were reacted with 1.0 mmol of imine **3a** (Table 1, entry 7). An increase in the amount of phosphonitrilic chloride to 0.6 equiv did not improve the yield (entry 8). Cold media poorly decreased the yield of β-lactam **5a** (entry 9). Then reaction of 1.0 mmol imine, 1.5 mmol acid, and 0.5 mmol phosphonitrilic chloride in the presence of triethylamine in dry dichloromethane at room temperature is the best condition.

Table 1
Reaction condition in the synthesis of 2-azetidinone **5a**



3a **4a** **5a**

Entry	Solvent	Temp	Phosphonitrilic chloride (mmol)	Yield (%)
1	Toluene	rt	0.3	57
2	CH_2Cl_2	rt	0.3	73
3	THF	rt	0.3	51
4	DMF	rt	0.3	48
5	CH_3CN	rt	0.3	29
6	CH_2Cl_2	rt	0.4	82
7	CH_2Cl_2	rt	0.5	95
8	CH_2Cl_2	rt	0.6	92
9	CH_2Cl_2	0 °C	0.5	90

With the best conditions in hands, the scope of the reaction was extended to a diverse range of 2-azetidinones. As can be seen from Table 2, a wide range of carboxylic acids and imines containing aromatic and aliphatic substituents can all be converted into the corresponding 2-azetidinones in excellent yields and with high purity.

The 2-azteidinones **5a**–**u** were synthesized by treatment of 1.0 mmol of imines **3**, 1.5 mmol of substituted acetic acids **4**, and 0.5 mmol of phosphonitrilic chloride **1** in the presence of triethylamine in dry dichloromethane at room temperature (Scheme 1, Table 2). The purification of 2-azteidinones **5a**–**u** was performed by crystallization from EtOAc after simple aqueous work-up. All products were characterized by their spectral data and elemental analyses. The stereochemistry of them were assigned by the comparison of the coupling constant H-3 and H-4 ($J_{3,4}$>4.0 Hz) for the *cis* stereoisomer and ($J_{3,4}\leq$3.0 Hz) for the *trans* stereoisomer.[31e]

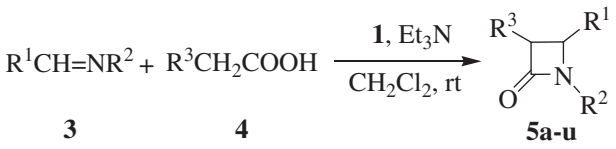
Phosphonitrilic chloride **1** was successfully employed for the synthesis of 3-allyloxy β-lactams **7a**–**c**. The treatment of (prop-2-enyloxy)acetic acid (allyloxyacetic acid) **6**, prepared from allyl alcohol and chloroacetic acid by a reported procedure,[36] with various Schiff bases and phosphonitrilic chloride in the presence of triethylamine afforded *cis* 2-azetidinones **7a**–**c** after crystallization from EtOAc (Scheme 2).

L-Menthoxyacetic acid (2-((1*S*,2*S*,5*S*)-2-isopropyl-5-methylcyclohexyloxy)acetic acid) **8** was prepared from L-menthol and chloroacetic acid by a procedure described in the literature.[37] The reaction of L-menthoxyacetic acid **8** and the corresponding imines in the presence of phosphonitrilic chloride yielded the *cis* 2-azetidinones **9a**–**c** in good yields (Scheme 2).

Benzothiazoles and their derivatives have recently received interest in the field of physiologically and pharmacologically activities.[38] Previously Bahekar and co-workers synthesized 1-benzothiazol-2-yl azetidin-2-ones and the anti-inflammatory activity of these compounds has been investigated.[39] β-Lactams **11a**–**c** were also easily obtained from various Schiff bases **10** derived from 2-aminobenzothiazole by this method and purified by crystallization from EtOAc (Scheme 2).

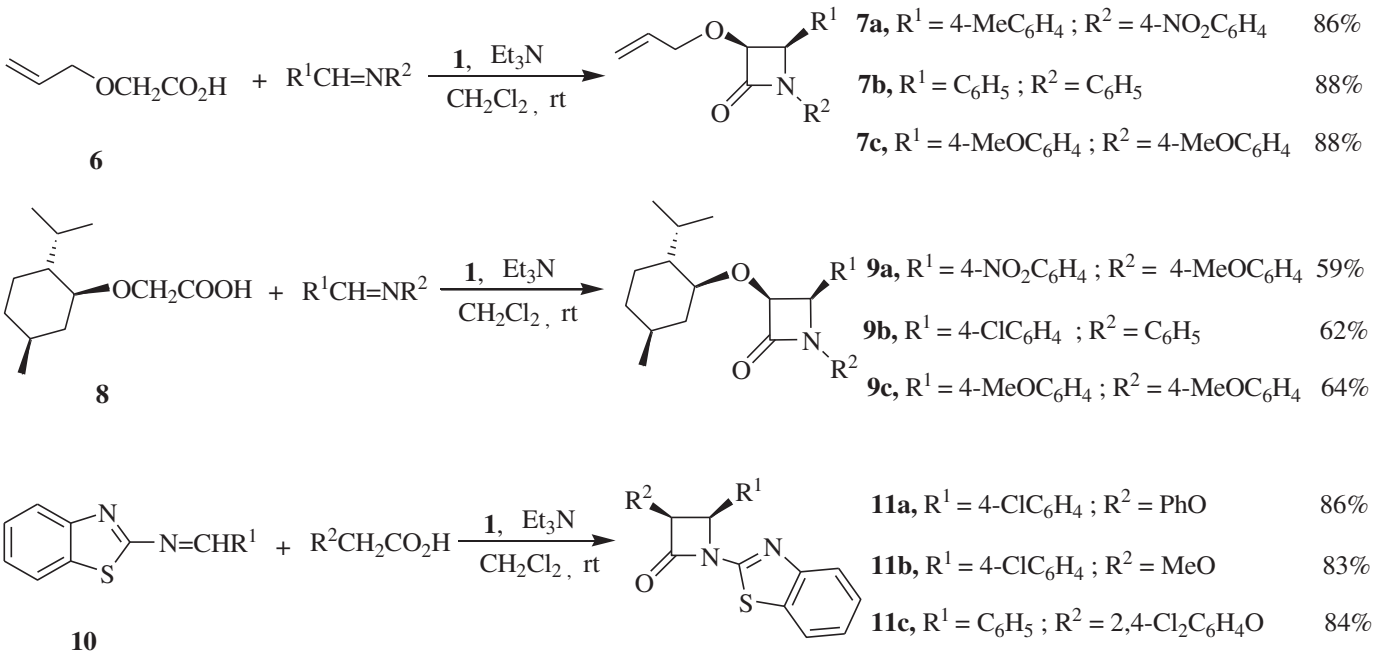
Table 2
Synthesis of 2-azetidinones **5a**–**u** using phosphonitrilic chloride

Entry	R^1	R^2	R^3	*cis*/*trans*	Product	Isolated yield (%)
1	C_6H_5	C_6H_5	PhO	*cis*	**5a**	95
2	4-ClC_6H_4	4-$EtOC_6H_4$	PhO	*cis*	**5b**	92
3	4-$MeOC_6H_4$	4-$MeOC_6H_4$	PhO	*cis*	**5c**	94
4	CH=CHPh	4-$EtOC_6H_4$	PhO	*cis*	**5d**	88
5	CH=CHPh	4-$EtOC_6H_4$	PhthN	*cis*	**5e**	83
6	4-ClC_6H_4	4-$MeOC_6H_4$	PhthN	*trans*	**5f**	81
7	4-$NO_2C_6H_4$	4-$MeOC_6H_4CH_2$	PhthN	*trans*	**5g**	86
8	4-$MeOC_6H_4$	4-$EtOC_6H_4$	PhthN	*trans*	**5h**	85
9	4-$NO_2C_6H_4$	C_6H_5	2-NaphthO	*cis*	**5i**	90
10	4-$MeOC_6H_4$	4-$MeOC_6H_4$	2-NaphthO	*cis*	**5j**	92
11	4-$NO_2C_6H_4$	$C_6H_5CH_2$	2-NaphthO	*cis*	**5k**	89
12	4-ClC_6H_4	4-$EtOC_6H_4$	2,4-$Cl_2C_6H_3O$	*cis*	**5l**	92
13	4-$NO_2C_6H_4$	4-$MeOC_6H_4CH_2$	2,4-$Cl_2C_6H_3O$	*cis*	**5m**	93
14	4-MeC_6H_4	4-$MeOC_6H_4$	MeO	*cis*	**5n**	89
15	4-ClC_6H_4	4-MeO-naphthyl	MeO	*cis*	**5o**	90
16	4-$MeOC_6H_4$	Me	MeS	*cis*	**5p**	77
17	$C_6H_5CH_2$	4-ClC_6H_4	MeS	*cis*	**5q**	86
18	4-$MeOC_6H_4$	4-$MeOC_6H_4$	PhS	*cis*	**5r**	91
19	4-$NO_2C_6H_4$	3,4-$(MeO)_2C_6H_3CH_2$	PhO	*cis*	**5s**	93
20	4-ClC_6H_4	3,4-$(MeO)_2C_6H_3CH_2$	MeO	*cis*	**5t**	90
21	4-$NO_2C_6H_4$	3,4-$(MeO)_2C_6H_3CH_2$	MeS	*cis*	**5u**	84

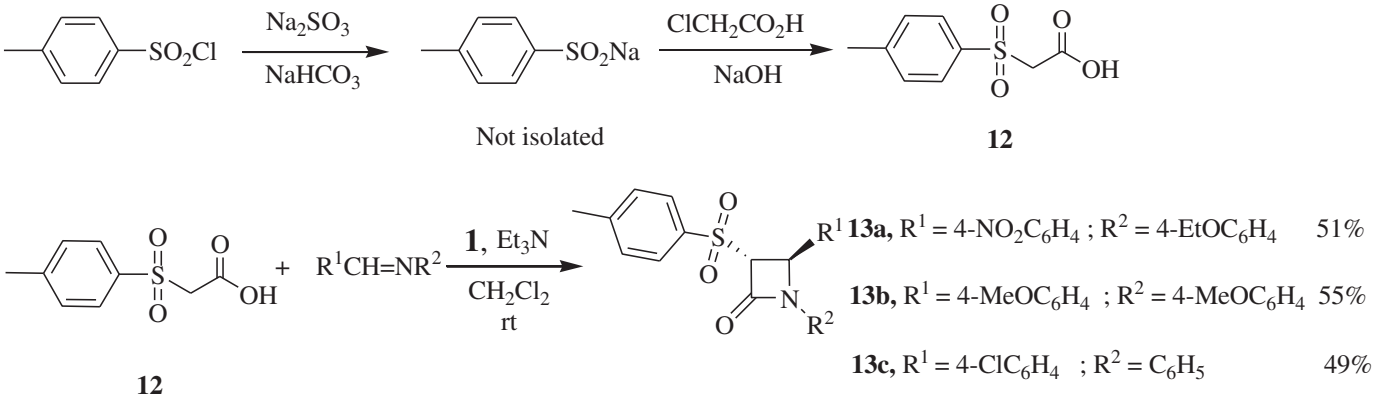


Scheme 1.

temperature gave *trans* 2-azetidinones **13a**–**c**, which were purified by short column chromatography on silica gel (Scheme 3). Previously the synthesis and antimicrobial activity of *cis* 3-(methylsulfonyl) β-lactams using 3-methylthio β-lactams and *m*-CPBA have been reported.[41] Steric hindrance of sulfonyl group on ketene mediates to synthesis of *trans* 2-azetidinones **13a**–**c** from 2-tosylacetic acid (Scheme 3). Phosphonitrilic chloride **1** was also successfully employed for the synthesis of 3-acetyl-β-lactams **15a**–**c**. The



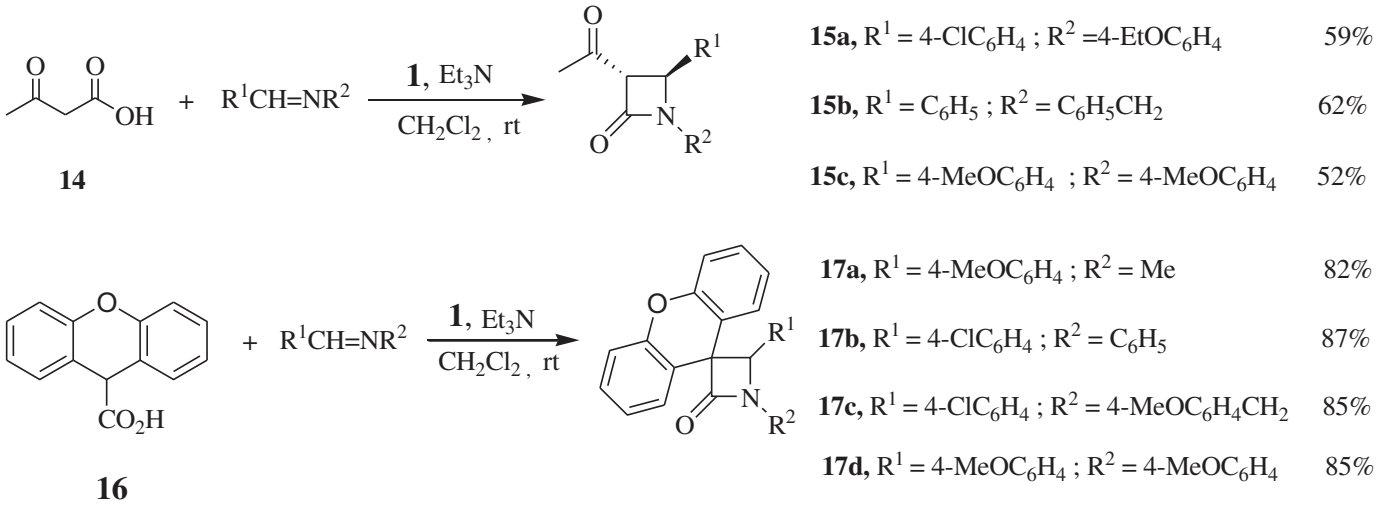
Scheme 2.



Scheme 3.

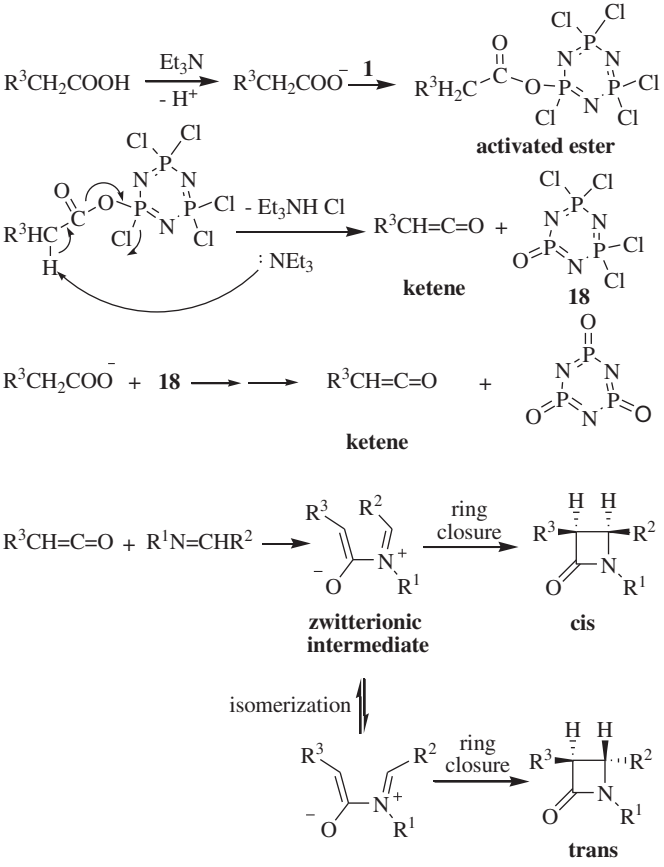
The synthesis of 3-electron-withdrawing 2-azetidinones by the [2+2] cycloaddition reaction of ketene–imine using α-electron-withdrawing substituted carboxylic acids is one of the main problems in the synthesis of 2-azetidinones. To check the generality of this method, the synthesis of 3-electron-withdrawing 2-azetidinones also were investigated. Firstly, 2-tosylacetic acid **12** was synthesized from *p*-toluenesulfonyl chloride in two stage as described in Scheme 5.[40] Treatment of 2-tosylacetic acid **12** with various imines in the presence of phosphonitrilic chloride at room temperature gave *trans* 2-azetidinones **13a**–**c**, which were purified by short column chromatography on silica gel (Scheme 3). Previously the synthesis and antimicrobial activity of *cis* 3-(methylsulfonyl) β-lactams using 3-methylthio β-lactams and *m*-CPBA have been reported.[41] Steric hindrance of sulfonyl group on ketene mediates to synthesis of *trans* 2-azetidinones **13a**–**c** from 2-tosylacetic acid (Scheme 3). Phosphonitrilic chloride **1** was also successfully employed for the synthesis of 3-acetyl-β-lactams **15a**–**c**. The treatment of acetoacetic acid **14** with the corresponding imines in the presence of phosphonitrilic chloride and triethylamine afforded pure 3-acetyl-β-lactams **15a**–**c** after purification by short column chromatography on silica gel (Scheme 4).

This method was successfully extended to the synthesis of C-3 spiro-β-lactams. The reaction of xanthene-9-carboxylic acid **16** with various imines in the presence of phosphonitrilic chloride and triethylamine afforded spiro-β-lactams **17a**–**d**, which were purified by crystallization from EtOAc (Scheme 4).



Scheme 4.

Temperature, solvent, electronic effects, and the steric hindrance of the ketene and imine substituents affect the stereochemistry of β-lactams in the Staudinger reaction. According to a reported mechanism for the Staudinger reaction[42] and for OH activation using phosphonitrilic chloride,[3f] it is suggested that the reaction performed via formation of an activated ester (Scheme 5). One mol phosphonitrilic chloride can activate three moles of acid to generate in situ three moles of ketene. Then ketene reacts with imines to form a zwitterionic intermediate, which undergoes a conrotatory ring closure to produce the β-lactam. The relative (*cis*/*trans*) stereoselectivity is generated as a result of the competition between the direct ring closure and the isomerization of the imine moiety in the zwitterionic intermediate. Ketenes derived from phthalimidoacetic acid (β-lactams **5f**–**h**), tosylacetic acid **12**, and acetoacetic acid **14** have more steric hindrance than other ketenes, and then lead to *trans* isomer. *Cis* β-lactam **5e** have obtained from phthalimidoketene because styryl group on C-4 of β-lactam ring prepare enough space to stability of zwitterionic intermediate and then direct ring closure to form *cis* β-lactam **5e**.



Scheme 5.

3. Conclusion

In summary, an evaluation of the cycloaddition reaction between carboxylic acids and imines using phosphonitrilic chloride demonstrated that this method has high efficiency and was thus used to prepare a series of β-lactams. This method provides a new methodology allowing for a wide functional group tolerance and monocyclic, spirocyclic, *N*-alkyl, and 3-electron-withdrawing group β-lactams are obtained in good to excellent yields. This reaction is clean and the by-products were removed by simple aqueous work-up.

4. Experimental section

4.1. Chemical reagents

All required chemicals were purchased from Merck, Fluka or Acros chemical companies. The melting points were determined on a Buchi 535 apparatus and are uncorrected. IR spectra were measured on a galaxy series FT-IR 5000 spectrometer. NMR spectra were recorded in $CDCl_3$ using a Bruker spectrophotometer (^{1}H NMR 300 MHz, ^{13}C NMR 75 MHz) using tetramethylsilane as an internal standard and coupling constants were given in cycles per second (Hertz). Elemental analyses were run on a Vario EL III elemental analyzer. Thin-layer chromatography was carried out on silica gel 254 analytical sheets obtained from Fluka. Column chromatography was performed on silica gel 60 (Merck, 70–230 mesh). Spectral data for **5a**–**e**, **5h**–**j**, **5l**, **5n**, **5p**–**r**, **7a**, **15c**, and **17d** have been previously reported.[35b,35d,35f,41,42b,43]

4.2. General procedure for the synthesis of 2-azetidinones

A phosphonitrilic chloride (0.5 mmol) was added to a solution of the substituted acetic acid (1.5 mmol), the Schiff base (1.0 mmol), and Et_3N (5.0 mmol) in dry CH_2Cl_2 (15 mL) at room temperature and the mixture was stirred overnight. The mixture was washed

successively with saturated $NaHCO_3$ (15 mL) and brine (15 mL). The organic layer was dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure to give the crude products. β-Lactams **5a**–**u**, **7a**–**d**, **11a**–**c**, **17a**–**d** were purified by crystallization from ethyl acetate, β-lactams **9a**–**c** were purified by crystallization from 96% ethanol, β-lactams **13a**–**c** by short column chromatography (hexane/EtOAc 7:3), and β-lactams **15a**–**c** by short column chromatography (hexane/EtOAc 9:1).

*4.2.1. 2-(2-(4-Chlorophenyl)-1-(4-methoxyphenyl)-4-oxoazetidin-3-yl)isoindoline-1,3-dione (**5f**).* White solid. Mp: 228–230 °C. IR (KBr) cm^{-1}: 1726, 1753 (CO, phth), 1780 (CO, β-lactam); ^1H NMR δ 3.61 (OMe, s, 3H), 5.17 (H-4, d, 1H, J=2.3), 5.39 (H-3, d, 1H, J=2.3), 6.71–7.90 (ArH, m, 12H); ^{13}C NMR δ 56.3 (OMe), 64.9 (C-4), 66.3 (C-3), 113.7, 117.5, 120.3, 121.1, 124.6, 125.0, 129.2, 136.8, 139.4, 143.8, 157.3 (aromatic carbons), 162.7 (CO, phth), 165.9 (CO, β-lactam); Anal. Calcd for $C_{24}H_{17}ClN_2O_4$: C, 66.59; H, 3.96; N, 6.47. Found: C, 66.68; H, 4.11; N, 6.53.

*4.2.2. 2-(1-(4-Methoxybenzyl)-2-(4-chlorophenyl)-4-oxoazetidin-3-yl)isoindoline-1,3-dione (**5g**).* White solid. Mp: 110–112 °C. IR (KBr) cm^{-1}: 1739, 1777 (CO, phth), 1783 (CO, β-lactam); ^1H NMR δ 3.68 (OMe, s, 3H), 3.83, 4.87 (CH_2-benzyl, 2d, 2H, J=14.4), 5.35 (H-4, d, 1H, J=2.5), 5.60 (H-3, d, 1H, J=2.5), 6.83–7.81 (ArH, m, 12H); ^{13}C NMR δ 43.7 (CH_2), 55.4 (OMe), 61.8 (C-4), 63.5 (C-3), 113.5, 116.2, 121.4, 126.9, 128.6, 129.2, 134.7, 142.2, 144.5, 147.3, 151.8 (aromatic carbons), 160.3 (CO, phth), 162.9 (CO, β-lactam); Anal. Calcd for $C_{25}H_{19}ClN_2O_4$: C, 67.19; H, 4.29; N, 6.27. Found: C, 67.26; H, 4.39; N, 6.21.

*4.2.3. 1-Benzyl-3-(naphthalen-2-yloxy)-4-(4-nitrophenyl)-azetidin-2-one (**5k**).* White solid. Mp: 141–143 °C. IR (KBr) cm^{-1}: 1347, 1539 (NO_2), 1748 (CO, β-lactam); ^1H NMR δ 3.93, 4.86 (CH_2-benzyl, 2d, 2H, J=15.0), 4.75 (H-4, d, 1H, J=4.8), 5.51 (H-3, d, 1H, J=4.8), 6.63–8.08 (ArH, m, 16H); ^{13}C NMR δ 43.7 (CH_2), 61.9 (C-3), 81.6 (C-4), 108.6, 109.7, 114.1, 118.5, 118.8, 120.3, 122.7, 124.8, 125.2, 128.6, 129.4, 129.8, 131.0, 135.3, 138.6, 144.9, 151.7, 155.9 (aromatic carbons), 163.6 (CO, β-lactam); Anal. Calcd for $C_{26}H_{20}N_2O_4$: C, 73.57; H, 4.75; N, 6.60. Found: C, 73.68; H, 4.88; N, 6.67.

*4.2.4. 3-(2,4-Dichlorophenoxy)-1-(4-methoxybenzyl)-4-(4-nitrophenyl)azetidin-2-one (**5l**).* Light-yellow solid. Mp: 84–86 °C. IR (KBr) cm^{-1}: 1344, 1557 (NO_2), 1751 (CO, β-lactam); ^1H NMR δ 3.60 (OMe, s, 3H), 3.81, 4.75 (CH_2-benzyl, 2d, 2H, J=14.7), 4.93 (H-4, d, 1H, J=5.0), 5.45 (H-3, d, 1H, J=5.0), 6.77–8.08 (ArH, m, 11H); ^{13}C NMR δ 45.9 (CH_2), 55.6 (OMe), 63.1 (C-3), 82.7 (C-4), 113.5, 114.6, 116.0, 117.2, 119.5, 120.3, 125.8, 126.2, 128.0, 128.9, 133.6, 147.5, 152.1, 155.8 (aromatic carbons), 163.6 (CO, β-lactam); Anal. Calcd for $C_{23}H_{18}Cl_2N_2O_5$: C, 58.37; H, 3.83; N, 5.92. Found: C, 58.49; H, 3.97; N, 5.98.

*4.2.5. 1-(3,4-Dimethoxybenzyl)-4-(4-chlorophenyl)-3-methoxyazetidin-2-one (**5t**).* White solid. Mp: 77–79 °C. IR (KBr) cm^{-1}: 1755 (CO, β-lactam); ^1H NMR δ 3.22, 3.68, 3.72 (3OMe, 3s, 9H), 4.03, 4.79 (CH_2-benzyl, 2d, 2H, J=14.5), 4.65 (H-4, d, 1H, J=4.5), 5.47 (H-3, d, 1H, J=4.5), 6.86–7.84 (ArH, m, 7H); ^{13}C NMR δ 40.9 (CH_2), 55.1, 56.0, 56.7 (3OMe), 63.2 (C-3), 84.4 (C-4), 114.7, 118.3, 121.9, 123.5, 129.1, 129.8, 132.7, 137.4, 142.8, 151.4 (aromatic carbons), 163.2 (CO, β-lactam); Anal. Calcd for $C_{19}H_{20}ClNO_4$: C, 63.07; H, 5.57; N, 3.87. Found: C, 63.16; H, 5.70; N, 3.94.

*4.2.6. 1-(3,4-Dimethoxybenzyl)-3-(methylthio)-4-(4-nitrophenyl)-azetidin-2-one (**5u**).* White solid. Mp: 55–57 °C. IR (KBr) cm^{-1}: 1338, 1550 (NO_2), 1747 (CO, β-lactam); ^1H NMR δ 2.18 (SMe, s, 3H), 3.53, 3.61 (2OMe, 2s, 6H), 4.00, 4.68 (CH_2-benzyl, 2d, 2H, J=14.7), 4.54 (H-4, d, 1H, J=4.4), 5.52 (H-3, d, 1H, J=4.4), 6.92–7.96 (ArH, m, 7H); ^{13}C NMR δ 15.7 (SMe), 41.5 (CH_2), 56.3, 57.0 (2OMe), 62.4 (C-3), 82.8 (C-4), 111.9, 116.3, 122.7, 123.3, 125.2, 127.5, 135.8, 136.4, 146.2, 152.1 (aromatic carbons), 162.5 (CO, β-lactam); Anal. Calcd for $C_{19}H_{20}N_2O_5S$: C, 58.75; H, 5.19; N, 7.21. Found: C, 58.68; H, 5.31; N, 7.26.

*4.2.7. 3-(Allyloxy)-1,4-diphenylazetidin-2-one (**7b**).* White solid. Mp: 85–87 °C. IR (KBr) cm^{-1}: 1756 (CO, β-lactam); ^1H NMR δ 4.40–4.49 (CH_2O-allyl, m, 2H), 5.17–5.29 (vinilic H, m, 2H), 5.43 (H-4, d, 1H, J=4.8), 5.58 (H-3, d, 1H, J=4.8), 5.79–5.88 (vinilic H, m, 1H), 6.86–7.75 (ArH, m, 10H); ^{13}C NMR δ 55.1 (CH_2O-allyl), 63.7 (C-4), 83.0 (C-3), 107.5, 111.4, 115.9, 123.4, 123.8, 126.0, 129.3, 130.1, 144.6, 155.8 (C=C, aromatic carbons), 162.7 (CO, β-lactam); Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.42; H, 6.13; N, 5.01. Found: C, 77.48; H, 6.25; N, 5.07.

*4.2.8. 3-(Allyloxy)-1,4-bis(4-methoxyphenyl)azetidin-2-one (**7c**).* White solid. Mp: 91–93 °C. IR (KBr) cm^{-1}: 1752 (CO, β-lactam); ^1H NMR δ 3.57, 3.67 (2OMe, 2s, 6H), 4.47–4.55 (CH_2O-allyl, m, 2H), 5.09–5.17 (vinilic H, m, 2H), 5.50 (H-4, d, 1H, J=4.8), 5.49 (H-3, d, 1H, J=4.8), 5.84–5.92 (vinilic H, m, 1H), 6.75–7.91 (ArH, m, 8H); ^{13}C NMR δ 54.5 (CH_2O-allyl), 55.7, 56.3 (2OMe), 61.6 (C-4), 81.4 (C-3), 110.3, 112.8, 114.3, 125.2, 125.8, 127.1, 131.9, 133.5, 149.6, 157.0 (C=C, aromatic carbons), 161.9 (CO, β-lactam); Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.86; H, 6.34; N, 4.06.

*4.2.9. 3-Menthoxy-1-(4-methoxyphenyl)-4-(4-nitrophenyl)-azetidin-2-one (**9a**).* White solid. Mp: 181–183 °C. IR (KBr) cm^{-1}: 1332, 1554 (NO_2), 1744 (CO, β-lactam); ^1H NMR δ 0.29–2.08 (H menthoxy, m, 18H), 3.11 (CH–O menthoxy, m, 1H), 3.59 (OMe, s, 3H), 4.83 (H-4, d, 1H, J=4.6), 5.21 (H-3, d, 1H, J=4.6), 6.82–8.12 (ArH, m, 8H); ^{13}C NMR δ 16.4, 21.2, 22.5, 23.9, 26.4, 31.3, 35.3, 41.1, 47.7 (menthoxy carbons), 56.4 (OMe), 63.6 (C-4), 81.7 (CH–O, menthoxy), 83.1 (C-3), 112.8, 122.5, 123.2, 126.8, 133.1, 138.4, 146.0, 155.7 (aromatic carbons), 163.9 (CO, β-lactam); Anal. Calcd for $C_{26}H_{32}N_2O_5$: C, 69.01; H, 7.13; N, 6.19. Found: C, 68.93; H, 7.25; N, 6.13.

*4.2.10. 4-(4-Chlorophenyl)-3-menthoxy-1-phenylazetidin-2-one (**9b**).* White solid. Mp: 188–190 °C. IR (KBr) cm^{-1}: 1741 (CO, β-lactam); ^1H NMR δ 0.24–2.13 (H menthoxy, m, 18H), 3.16 (CH–O menthoxy, m, 1H), 4.75 (H-4, d, 1H, J=4.8), 5.32 (H-3, d, 1H, J=4.8), 6.87–7.84 (ArH, m, 9H); ^{13}C NMR δ 15.9, 20.6, 22.7, 23.4, 27.1, 30.7, 37.0, 42.3, 46.8 (menthoxy carbons), 64.4 (C-4), 82.1 (CH–O, menthoxy), 84.9 (C-3), 114.0, 120.9, 122.4, 125.6, 133.8, 136.3, 145.7, 153.9 (aromatic carbons), 164.2 (CO, β-lactam); Anal. Calcd for $C_{25}H_{30}ClNO_2$: C, 72.89; H, 7.34; N, 3.40. Found: C, 72.99; H, 7.47; N, 3.48.

*4.2.11. 3-Menthoxy-1,4-bis(4-methoxyphenyl)azetidin-2-one (**9c**).* White solid. Mp: 181–183 °C. IR (KBr) cm^{-1}: 1746 (CO, β-lactam); ^1H NMR δ 0.33–2.21 (H menthoxy, m, 18H), 3.20 (CH–O menthoxy, m, 1H), 3.63, 3.69 (2OMe, 2s, 6H), 4.77 (H-4, d, 1H, J=5.0), 5.29 (H-3, d, 1H, J=5.0), 6.76–8.06 (ArH, m, 8H); ^{13}C NMR δ 16.7, 21.4, 23.7, 24.5, 28.1, 32.6, 37.8, 40.3, 46.8 (menthoxy carbons), 55.4, 56.2 (2OMe), 62.9 (C-4), 81.4 (CH–O, menthoxy), 83.5 (C-3), 110.7, 121.5, 122.9, 124.7, 134.4, 137.1, 146.7, 156.3 (aromatic carbons), 163.4 (CO, β-lactam); Anal. Calcd $C_{27}H_{35}NO_4$: C, 74.11; H, 8.06; N, 3.20. Found: C, 74.03; H, 8.15; N, 3.15.

*4.2.12. 1-(Benzo[d]thiazol-2-yl)-4-(4-chlorophenyl)-3-phenoxyazetidin-2-one (**11a**).* Pale yellowish solid. Mp: 171–173 °C. IR (KBr) cm^{-1}: 1638 (C=N), 1755 (CO, β-lactam); ^1H NMR δ 4.53 (H-4, d, 1H, J=5.1), 5.37 (H-3, d, 1H, J=5.1), 6.81–8.26 (ArH, m, 13H); ^{13}C NMR δ 61.5 (C-3), 83.8 (C-4), 114.3, 119.5, 120.1, 120.3, 123.2, 123.5, 127.2, 127.7, 128.9, 129.2, 129.6, 130.4, 131.0, 148.4 (aromatic carbons), 163.9 (C=N), 164.5 (CO, β-lactam); Anal. Calcd for $C_{22}H_{15}ClN_2O_2S$: C, 64.94; H, 3.72; N, 6.88. Found: C, 65.03; H, 3.84; N, 6.95.

*4.2.13. 1-(Benzo[d]thiazol-2-yl)-4-(4-chlorophenyl)-3-methoxyazetidin-2-one (**11b**).* White solid. Mp: 145–147 °C. IR (KBr) cm^{-1}: 1641

(C=N), 1749 (CO, β-lactam); ^{1}H NMR δ 3.27 (OMe, s, 3H), 4.46 (H-4, d, 1H, *J*=4.8), 5.30 (H-3, d, 1H, *J*=4.8), 6.73–8.20 (ArH, m, 8H); ^{13}C NMR δ 55.4 (OMe), 62.2 (C-3), 84.6 (C-4), 118.3, 119.0, 121.5, 121.8, 124.9, 125.4, 128.2, 128.7, 139.5, 146.1 (aromatic carbons), 163.3 (C=N), 164.0 (CO, β-lactam); Anal. Calcd for $C_{17}H_{13}ClN_2O_2S$: C, 59.21; H, 3.80; N, 8.12. Found: C, 59.31; H, 3.94; N, 8.07.

*4.2.14. 1-(Benzo[d]thiazol-2-yl)-3-(naphthalen-2-yloxy)-4-phenylazetidin-2-one (**11c**).* Pale yellowish solid. Mp: 190–192 °C. IR (KBr) cm^{-1}: 1644 (C=N), 1743 (CO, β-lactam); ^{1}H NMR δ 4.71 (H-4, d, 1H, *J*=4.6), 5.45 (H-3, d, 1H, *J*=4.6), 6.93–8.31 (ArH, m, 16H); ^{13}C NMR δ 60.9 (C-3), 83.4 (C-4), 108.3, 110.5, 113.9, 115.4, 119.0, 119.7, 122.8, 123.3, 126.5, 127.2, 127.9, 128.4, 129.7, 130.2, 132.8, 134.1, 135.0, 145.2, 148.7, 157.4 (aromatic carbons), 162.8 (C=N), 164.2 (CO, β-lactam); Anal. Calcd for $C_{26}H_{18}N_2O_2S$: C, 73.91; H, 4.29; N, 6.63. Found: C, 73.88; H, 4.39; N, 6.55.

*4.2.15. 1-(4-Ethoxyphenyl)-4-(4-nitrophenyl)-3-tosylazetidin-2-one (**13a**).* White solid. Mp: 166–168 °C. IR (KBr) cm^{-1}: 1149, 1322 (SO_2), 1337, 1551 (NO_2), 1747 (CO, β-lactam); ^{1}H NMR δ 1.34 (Me, t, 3H, *J*=7.0), 2.21 (Me, s, 3H), 3.96 (OCH_2, q, 2H, *J*=7.0), 4.48 (H-4, d, 1H, *J*=2.4), 5.46 (H-3, d, 1H, *J*=2.4), 6.86–8.10 (ArH, m, 12H); ^{13}C NMR δ 14.1, 23.7 (2Me), 61.4 (OCH_2), 62.1 (C-4), 81.9 (C-3), 113.1, 118.4, 122.5, 122.8, 123.0, 128.6, 129.2, 134.8, 137.2, 141.0, 146.4, 157.1 (aromatic carbons), 162.8 (CO, β-lactam); Anal. Calcd for $C_{24}H_{22}N_2O_6S$: 61.79; H, 4.75, N, 6.00. Found: C, 61.86; H, 4.85; N, 6.06.

*4.2.16. 1,4-Bis(4-methoxyphenyl)-3-tosylazetidin-2-one (**13b**).* White solid. Mp: 173–175 °C. IR (KBr) cm^{-1}: 1155, 1319 (SO_2), 1744 (CO, β-lactam); ^{1}H NMR δ 2.16 (Me, s, 3H), 3.59, 3.63 (2OMe, 2s, 6H), 4.43 (H-4, d, 1H, *J*=2.5), 5.55 (H-3, d, 1H, *J*=2.5), 6.79–7.85 (ArH, m, 12H); ^{13}C NMR δ 22.4 (Me), 55.4, 56.0 (2OMe), 62.7 (C-4), 83.3 (C-3), 112.4, 115.7, 120.0, 121.5, 121.7, 125.4, 126.1, 131.9, 132.5, 138.3, 148.7, 153.4 (aromatic carbons), 161.6 (CO, β-lactam); Anal. Calcd for $C_{24}H_{23}NO_5S$: C, 65.89; H, 5.30; N, 3.20. Found: C, 65.83; H, 5.39; N, 3.15.

*4.2.17. 4-(4-Chlorophenyl)-1-phenyl-3-tosylazetidin-2-one (**13c**).* White solid. Mp: 191–193 °C. IR (KBr) cm^{-1}: 1151, 1327 (SO_2), 1743 (CO, β-lactam); ^{1}H NMR δ 2.25 (Me, s, 3H), 4.39 (H-4, d, 1H, *J*=2.5), 5.52 (H-3, d, 1H, *J*=2.5), 6.90–7.74 (ArH, m, 13H); ^{13}C NMR δ 23.4 (Me), 61.5 (C-4), 82.6 (C-3), 114.5, 116.9, 123.1, 123.7, 124.2, 127.9, 128.3, 131.7, 134.2, 142.6, 144.5, 150.7 (aromatic carbons), 162.1 (CO, β-lactam); Anal. Calcd for $C_{22}H_{18}ClNO_3S$: C, 64.15; H, 4.40; N, 3.40. Found: C, 64.22; H, 4.51; N, 3.44.

*4.2.18. 3-Acetyl-4-(4-chlorophenyl)-1-(4-ethoxyphenyl)azetidin-2-one (**15a**).* White solid. Mp: 57–59 °C. IR (KBr) cm^{-1}: 1712 (CO, ketone), 1747 (CO, β-lactam); ^{1}H NMR δ 1.28 (Me, t, 3H, *J*=6.9), 2.35 (MeCO, s, 3H), 3.86 (H-3, d, 1H, *J*=2.4), 3.91 (OCH_2, q, 2H, *J*=6.9), 4.63 (H-4, d, 1H, *J*=2.4), 6.74–7.69 (ArH, m, 8H); ^{13}C NMR δ 14.5, 25.3 (2Me), 60.9 (OCH_2), 62.2 (C-3), 67.5 (C-4), 113.0, 116.3, 121.7, 125.5, 130.4, 142.9, 144.5, 152.1 (aromatic carbons), 161.8 (CO, β-lactam), 197.4 (CO, ketone); Anal. Calcd for $C_{19}H_{18}ClNO_3$: C, 66.38; H, 5.28; N, 4.07. Found: C, 66.45; H, 5.40; N, 4.12.

*4.2.19. 3-Acetyl-1-benzyl-4-phenylazetidin-2-one (**15b**).* White solid. Mp: 41–43 °C. IR (KBr) cm^{-1}: 1709 (CO, ketone), 1751 (CO, β-lactam); ^{1}H NMR δ 2.33 (MeCO, s, 3H), 3.80 (H-3, d, 1H, *J*=2.5), 3.91, 4.77 (CH_2-benzyl, 2d, 2H, *J*=14.7), 4.56 (H-4, d, 1H, *J*=2.5), 6.84–7.48 (ArH, m, 8H); ^{13}C NMR δ 24.1 (Me), 43.9 (CH_2), 62.5 (C-3), 66.7 (C-4), 115.6, 121.9, 126.3, 129.4, 130.8, 144.1, 147.3, 148.5 (aromatic carbons), 164.7 (CO, β-lactam), 199.1 (CO, ketone); Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.49; H, 6.27; N, 4.94.

*4.2.20. 2-(4-Methoxyphenyl)-1-methylspiro[azetidine-3,9′-xanthen]-4-one (**17a**).* Milky-color solid. Mp: 135–137 °C. IR (KBr) cm^{-1}: 1750 (CO, β-lactam); ^{1}H NMR δ 2.85 (Me-N, s, 3H), 3.66 (OMe, s, 3H), 5.12 (H-4, s, 1H), 6.72–7.85 (ArH, m, 12H); ^{13}C NMR δ 28.3 (Me-N), 55.9 (OMe), 61.4 (C-4), 73.0 (C-3), 113.7, 119.2, 121.8, 122.2, 122.8, 129.5, 134.7, 150.9, 153.1, 155.4 (aromatic carbons), 164.6 (CO, β-lactam); Anal. Calcd for $C_{23}H_{19}NO_3$: C, 77.29; H, 5.36; N, 3.92. Found: C, 77.22; H, 5.47; N, 3.86.

*4.2.21. 2-(4-Chlorophenyl)-1-phenylspiro[azetidine-3,9′-xanthen]-4-one (**17b**).* White solid. Mp: 207–209 °C. IR (KBr) cm^{-1}: 1748 (CO, β-lactam); ^{1}H NMR δ 5.12 (H-4, s, 1H), 6.84–7.82 (ArH, m, 17H); ^{13}C NMR δ 61.9 (C-4), 75.0 (C-3), 111.9, 117.3, 119.9, 123.1, 123.7, 125.0, 126.2, 129.1, 129.6, 131.6, 142.0, 146.8, 147.4, 152.7 (aromatic carbons), 163.6 (CO, β-lactam); Anal. Calcd for $C_{27}H_{18}ClNO_2$: C, 76.50; H, 4.28; N, 3.30. Found: C, 76.59; H, 4.41; N, 3.36.

*4.2.22. 2-(4-Chlorophenyl)-1-(methoxybenzyl)spiro-[azetidine-3,9′-xanthen]-4-one (**17c**).* White solid. Mp: 157–159 °C. IR (KBr) cm^{-1}: 1743 (CO, β-lactam); ^{1}H NMR δ 3.71 (OMe, s, 3H), 3.90, 4.73 (CH_2-benzyl, 2d, 2H, *J*=14.5), 5.25 (H-4, s, 1H), 6.74–7.92 (ArH, m, 16H); ^{13}C NMR δ 42.6 (CH_2), 56.3 (OMe), 62.7 (C-4), 74.0 (C-3), 108.1, 114.7, 117.3, 117.9, 118.3, 121.5, 123.7, 126.0, 126.6, 128.1, 128.7, 132.0, 146.2, 154.5 (aromatic carbons), 163.1 (CO, β-lactam); Anal. Calcd for $C_{29}H_{22}ClNO_3$: C, 74.43; H, 4.74; N, 2.99. Found: C, 74.51; H, 4.87; N, 3.05.

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