Tandem Palladium/Charcoal-Copper(I) Iodide (Pd/C-CuI) Catalyzed *Sonogashira* Coupling and Intramolecular Cyclization from 2-Bromonicotinic Acid (=2-Bromopyridine-3-carboxylic Acid) and Ethynylarenes to 4-Azaphthalides (= Furo[3,4-*b*]pyridin-5(7*H*)-ones) and 5-Azaisocoumarins (=5*H*-Pyrano[4,3-*b*]pyridin-5-ones)

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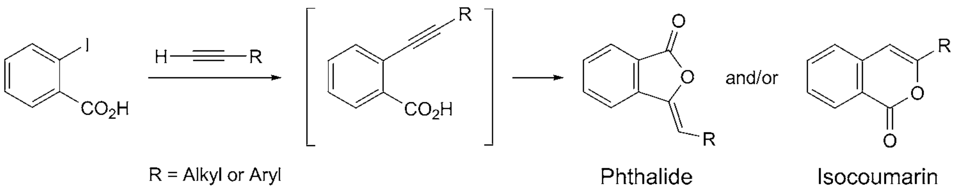
Several 4-azaphthalides (=furo[3,4-*b*]pyridin-5(7*H*)-ones) and 5-azaisocoumarins (=5*H*-pyrano[4,3-*b*]pyridin-5-ones) were prepared through a tandem heterogeneous Pd/C-mediated *Sonogashira* coupling and a 5-*exo-dig* or 6-*endo-dig* intramolecular cyclization of 2-bromonicotinic acid (=2-bromopyridine-3-carboxyclic acid) with various ethynylarenes or 3-ethynylthiophene. In the presence of Pd/C–Ph_3P–CuI and Et_3N in dry dioxane under Ar at 90°, a mixture of 4-azaphthalides (usually the major product) and 5-azaisocoumarins was obtained after 3.5 h under normal heating (*Schemes 3* and *4*; *Tables 1* and *2*). This mixture of compounds was also obtained with the same catalytic system under microwave (MW) irradiation in only 25 min (*Tables 3* and *4*). The 1-ethynyl-3-methoxybenzene gave on heating only the corresponding 4-azaphthalide (*Table 2*), while under MW irradiation, both the 5-*exo-dig* and the 6-*endo-dig* products were obtained (*Table 4*). For the 3-ethynylthiophene, the regioselectivity for the corresponding 4-azaphthalide was achieved with both methods (*Tables 2* and *4*). Although the yields and the regioselectivity of the reaction generally remained the same with both methods, the use of MW allowed us to obtain the corresponding products in a shorter reaction time. From 4-ethynyl-*N*,*N*-dimethylaniline (=4-ethynyl-*N*,*N*-dimethylbenzenamine), the corresponding 4-azaphthalide and 5-isocoumarin were only obtained under MW irradiation (*Tables 2* and *4*). To the best of our knowledge, it is the first time that this kind of tandem reaction was applied to a pyridine derivative giving the corresponding 4-azaphthalides and 5-azaisocoumarins which are easily separated and may both show biological activity.

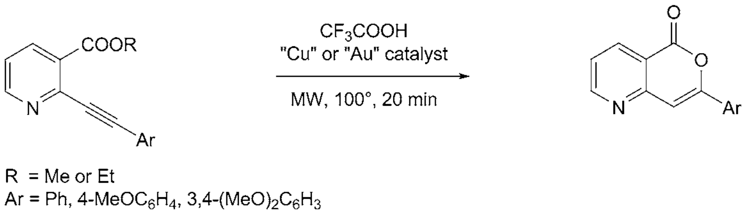
Introduction. – Phthalides (=isobenzofuran-1(3*H*)-ones) [1] and isocoumarins (=1*H*-2-benzopyran-1-ones) [2] are important classes of O-containing heterocycles often seen in naturally occurring and biologically active compounds. One of the most attractive routes for the synthesis of these compounds is the use of 2-halogenobenzoic acids and terminal alkynes as starting materials. Usually, this process was performed in a one-pot two-step reaction: a *Sonogashira* coupling [3] of 2-iodobenzoic acid with terminal alkynes followed by an intramolecular cyclization of the 2-alkynylbenzoic acid, which often results in a mixture of a (3*Z*)-3-alkylidenephthalide, and a 3-alkyl- or 3-arylisocoumarin *via* 5-*exo-dig* and 6-*endo-dig* cyclizations, respectively (*Scheme 1*) [4]. *Kundu* and co-workers described this heteroannulation process as stereospecific for the phthalide, since only the (3*Z*)-isomers of the 3-alkylidenephthalides were obtained [4a].

Scheme 1



Up to now, some *o*-halogenoheteroarenecarboxylic acids have already been used as starting materials in this reaction, including 3-iodothiophene-2-carboxylic acid, 2-bromothiophene-3-carboxylic acid [5], and 3-bromobenzo[*b*]thiophene-2-carboxylic acid or the corresponding methyl esters [6]. To the best of our knowledge, the use of halogenopyridine derivatives has not been fully explored in this process: only three examples of the synthesis of 7-aryl-5*H*-pyrano[4,3-*b*]pyridin-5-one, resulting from a copper- or gold-catalyzed/*Lewis* acid mediated 6-*endo-dig* intramolecular cyclization under microwave (MW) irradiation of the corresponding methyl or ethyl 2-(2-arylethynyl)nicotinates (= methyl or ethyl 2-(2-arylethynyl)pyridine-3-carboxylic acids), have already been described by *Bihel* and co-workers [7] (*Scheme 2*). However, in this reaction, they have synthesized and isolated the *Sonogashira* product separately.

Scheme 2

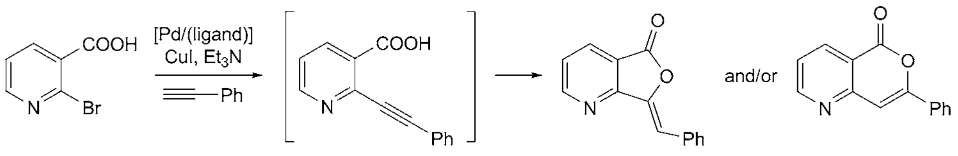


Recently, the use of 10% Pd/C–Ph_3P–CuI has been reported as an efficient catalytic system for the one-pot coupling/cyclization process from 2-iodobenzoic acids and terminal alkynes [4d]. Because of the easy recovery of Pd along with the reduced burden of metal contamination to the products, the use of Pd/C as heterogeneous catalyst is known to be advantageous compared to other Pd-catalysts or -salts.

Herein, we report for the first time the synthesis of 4-azaphthalides (= furo[3,4-*b*]pyridin-5(7*H*)-ones) and 5-azaisocoumarins (= 5*H*-pyrano[4,3-*b*]pyridin-5-ones) in a tandem *Sonogashira* coupling/intramolecular cyclization from 2-bromonicotinic acid (= 2-bromopyridine-3-carboxylic acid) and ethynylarenes or 3-ethynylthiophene in the presence of Pd/C–Ph_3P–CuI and of Et_3N as the base. The reactions were performed under either normal heating or under MW irradiation.

Results and Discussion. – Optimization experiments were carried out on the reaction of 2-bromonicotinic acid with ethynylbenzene in the presence of a Pd species as the catalyst with the ligand Ph_3P, CuI as a co-catalyst, and Et_3N as the base, and by changing some parameters (*Scheme 3*, *Table 1*). In all the reactions, an excess of

Scheme 3



1a **1b**

Table 1. *Effect of Conditions on the One-pot Pd-catalyzed Reaction of 2-Bromonicotinic Acid with Ethynylbenzene*

Entry	Catalytic system	Solvent	Temperature (time)[a])	Products (yield [%])
1	10% Pd/C–Ph$_3$P–CuI	dioxane	35° (1.5 h) and 90° (2 h)	**1a** (41) + **1b** (27)
2	10% Pd/C–Ph$_3$P–CuI	EtOH	35° (1.5 h) and 70° (2 h)	**1a** (n.o.[b])) + **1b** (20)
3	[PdCl$_2$(Ph$_3$P)$_2$]–CuI	dioxane	35° (1.5 h) and 90° (2 h)	**1a** (32) + **1b** (35)

[a]) See *General Procedure* in the *Exper. Part.* [b]) Not observed.

ethynylbenzene (1.5 equiv.) was used, as it is well known that an important side reaction, namely the *Glaser*-type oxidative dimerization of the alkyne moiety, usually occurs in the presence of Cu^{I} [8].

Recently, *Pal* has shown that during the optimization of the reaction conditions for the Pd/C-mediated synthesis of an isocoumarin, the corresponding phthalide was isolated as the major product when 1,4-dioxane was used as solvent [9]. Thus, with the Pd/C–Ph$_3$P–CuI system and Et$_3$N in 1,4-dioxane (*Table 1*, *Entry 1*), the 4-azaphthalide (7*Z*)-7-benzylidenefuro[3,4-*b*]pyridin-5(7*H*)-one (**1a**) was obtained as the major product and the 5-azaisocoumarin 7-phenyl-5*H*-pyrano[4,3-*b*]pyridin-5-one (**1b**) [7] as the minor product, *via* a *5-exo-dig* and a *6-endo-dig* cyclization of the *Sonogashira* intermediate, respectively. No reaction was observed in DMF or toluene.

We tried to increase the regioselectivity of the reaction with the intention to get only one product. It has been observed by *Pal* and co-workers that the 2-iodobenzoic acid reacts smoothly with terminal alkynes in the presence of Pd/C–Ph$_3$P–CuI as the catalytic system and Et$_3$N in EtOH to give in good yields only the corresponding isocoumarins [4d]. In our case, with EtOH as solvent, 5-azaisocoumarin **1b** was indeed the only expected product but in a low yield (*Table 1*, *Entry 2*), besides a considerable amount of the alkyne dimer. We then changed the catalytic system to [PdCl$_2$(Ph$_3$P)$_2$], which had been shown to exhibit greater selectivity for phthalides [4a,b]. In our system, in the presence of this catalyst, both 4-azaphthalide **1a** and 5-azaisocoumarin **1b** were isolated in almost equal amounts (*Table 1*, *Entry 3*). Stirring for a longer time (overnight) at 90° (or 70° with EtOH) had no effect on the product yields.

Finally, the conditions described in *Table 1*, *Entry 1* seemed to be the best even in view of the formation of both products. Having these results in hands, several reactions were performed with different ethynylarenes or 3-ethynylthiophene in the presence of Pd/C–Ph$_3$P–CuI and Et$_3$N as the base in dry dioxane (*Scheme 4*). The results of these experiments are listed in *Table 2*.

Scheme 4

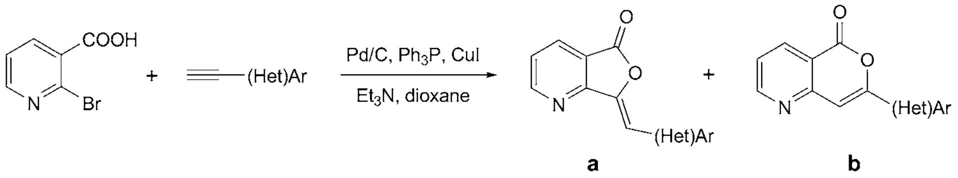


Table 2. *Synthesis of 4-Azaphthalides* (**a**) *and 5-Azaisocoumarins* (**b**) *from 2-Bromonicotinic Acid and Ethynylarenes*[a])

Entry	(Het)Ar of (Het)Ar–C≡CH	Products (yield [%])	
		4-Azaphthalides	5-Azaisocoumarins
1	3-MeO–C_6H_4	**2a** (55)	**2b** (n.o.)[b])
2	4-MeO–C_6H_4	**3a** (44)	**3b** (26)
3	2-MeO–C_6H_4	**4a** (25)	**4b** (40)
4	3-F–C_6H_4	**5a** (40)	**5b** (21)
5	4-F–C_6H_4	**6a** (40)	**6b** (16)
6	2-F–C_6H_4	**7a** (45)	**7b** (18)
7	4-Me_2N–C_6H_4	**8a** (n.o.)[b])	**8b** (n.o.)[b])
8	thiophen-3-yl	**9a** (50)	**9b** (n.o.)

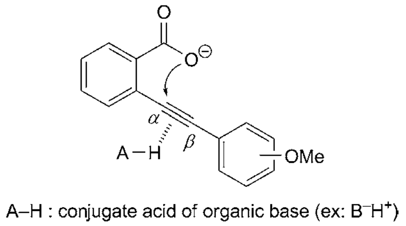
[a]) Conditions: 2-bromonicotinic acid (1 equiv.), ArC≡CH (1.5 equiv.), 10% Pd/C (3 mol-%), Ph_3P (12 mol-%), CuI (6 mol-%), Et_3N (5 equiv.), and dry dioxane; 1.5 h at 35° and 2 h at 90°, under Ar (see *General Procedure* in the *Exper. Part.*). [b]) Only formed and isolated when the reaction was performed under MW irradiation (*Table 4*).

From 1-ethynyl-3-methoxybenzene (*Table 2*, *Entry 1*), 4-azaphthalide **2a** was formed in good yield (55%), and only traces of the corresponding 5-azaisocoumarin **2b** were obtained. With 1-ethynyl-4-methoxybenzene, 4-azaphthalide **3a** was the major product (44%), but 5-azaisocoumarin **3b** [7] was also isolated in 26% yield (*Table 2*, *Entry 2*). These two results corroborate the observation made by *Kanazawa* and *Terada* [10] for the organic base-catalyzed intramolecular cyclization, according to which the presence of electron-donating groups at the phenyl ring of the *Sonogashira* products diminish the electrophilic nature at the β-position of the triple bond, thus favoring the formation of the *5-exo-dig* cyclized products. In our case, the 5-*exo-dig* cyclization of the carboxylate to the triple bond (→ product of type **a**) may also be assisted by the conjugate acid of Et_3N (*Scheme 5*).

In contrast to these previous results, with 1-ethynyl-2-methoxybenzene, the 4-azaphthalide **4a** was isolated in 25% yield only, and the corresponding 5-azaisocoumarin **4b** was the major product (40%) (*Table 2*, *Entry 3*). In fact, *Kanazawa* and *Terada* have also observed that the presence of a 2-MeO group at the arenyl moiety substituting the alkyne could diminish the yield of the phthalide [10] (though in their case, it still remains the major product).

The influence of the position of the substituent was not observed when different ethynylfluorobenzenes were used as starting materials (*Table 2*, *Entries 4–6*). In these cases, the expected 4-azaphthalides **5a**–**7a** were always formed as the major products

Scheme 5



(40–45%), and the 5-azaisocoumarins **5b**–**7b** were the minor products (16–21%). Finally, a reaction involving the electron-rich 4-ethynyl-*N*,*N*-dimethylaniline (=4-ethynyl-*N*,*N*-dimethylbenzenamine) was also tried, but only traces of the expected products **8a** and **8b** were observed by ^{1}H-NMR measurements (*Table 2*, *Entry 7*). With the electron-rich 3-ethynylthiophene, the 4-azaphthalide **9a** was obtained regioselectively in 50% yield (*Table 2*, *Entry 8*), whereas with the electron-deficient 3-ethynylpyridine, neither the corresponding 4-azaphthalide nor the 5-azaisocoumarin was formed, but only the dimer of the alkyne was produced.

The same reactions described in *Schemes 3* and *4* were performed under microwave irradiation. The reaction of ethynylbenzene as starting material was first studied to determine the most effective conditions (*Table 3*). The 4-azaphthalide **1a** and the 5-azaisocoumarin **1b** (*cf.* *Scheme 3* and *Table 1*) were obtained after MW irradiation of the solution at 35° for 7.5 min and then at 90° for 10 min (*Table 3*, *Entry 1*). Doubling the time of irradiation at 35° (*Table 3*, *Entry 2*) allowed the formation of these compounds in higher yields (40% of **1a** and 18% of **1b**), similar to those obtained under normal heating (41 and 27%, resp.; *Table 1*, *Entry 1*). On the other hand, when the reaction mixture was irradiated at 90° immediately after the addition of the ethynylbenzene, only the alkyne dimer was obtained (*Table 3*, *Entry 3*).

Table 3. *Determination of the Most Efficient Reaction Temperature and Time under MW and the Conditions Described in* Table 2

Entry	Solvent	Temperature (time)	Results [%]
1	dioxane	35° (7.5 min) and 90° (10 min)	**1a**(28) + **1b** (6)
2	dioxane	35° (15 min) and 90° (10 min)	**1a** (40) + **1b** (18)
3	dioxane	90° (20 min)	n.o.[a])

[a]) Only the ethynylbenzene dimer was formed.

It was then decided to use the conditions defined in *Table 3*, *Entry 2*, to perform the reactions under MW with the other terminal alkynes. Under these conditions, most of the corresponding 4-azaphthalides and 5-azaisocoumarins (*Table 4*, *Entries 2–5*) were obtained in comparable yields to those obtained by conventional heating (*cf.* *Table 2*). With 1-ethynyl-3-methoxybenzene (*Table 4*, *Entry 1*), the 4-azaphthalide **2a** was obtained in 45% yield, which is lower than the yield obtained under classical heating (55%; *Table 2*, *Entry 1*), together with the 5-azaisocoumarin **2b** in 16% yield, which was not isolated previously (*Table 2*, *Entry 1*). Under MW irradiation, we were also able to isolate products **8a** and **8b** resulting from the reaction of 2-bromonicotinic acid with 4-ethynyl-*N*,*N*-dimethylaniline (*Table 4*, *Entry 6*), which were not formed by classical heating (*Table 2*, *Entry 7*). The reaction with 3-ethynylthiophene (*Table 4*, *Entry 7*) afforded the 4-azaphthalide **9a** in a good yield (52%) and, as previously observed, the corresponding 5-azaisocoumarin was not formed. We also tried to perform a reaction with 3-ethynylpyridine, but as it has already been observed by heating, only the dimer of the alkyne was obtained.

Table 4. *Results and Yields of the Synthesis of 4-Azaphthalides and 5-Azaisocoumarins Performed under Microwave Irradiation* (Conditions of *Table 3*, *Entry 2*)

Entry	(Het)Ar of (Het)Ar–C≡CH	Products (yield [%])	
		4-Azaphthalides	5-Azaisocoumarins
1	3-MeO–C_6H_4	**2a** (45)	**2b** (16)
2	4-MeO–C_6H_4	**3a** (43)	**3b** (23)
3	2-MeO–C_6H_4	**4a** (21)	**4b** (41)
4	3-F–C_6H_4	**5a** (38)	**5b** (18)
5	2-F–C_6H_4	**7a** (45)	**7b** (11)
6	4-Me_2N–C_6H_4	**8a** (24)	**8b** (16)
7	thiophen-3-yl	**9a** (52)	n.o.[a])

[a]) Not observed.

Conclusions. – We described for the first time the synthesis of 4-azaphthalides and 5-azaisocoumarins from 2-bromonicotinic acid and terminal alkynes by a tandem Pd/C–CuI–Ph_3P–NEt_3 mediated reaction of *Sonogashira*/5-*exo-dig* or 6-*endo-dig* intramolecular cyclization, performed under either classical heating or MW irradiation. The corresponding 4-azaphthalides and 5-azaisocoumarins were obtained and readily separated. The 4-azaphthalides were usually the major products, and from 1-ethynyl-3-methoxybenzene, it was the only product isolated after heating, but both compounds were found after MW irradiation. The regioselectivity for the corresponding 4-azaphthalide was only achieved when 3-ethynylthiophene was used as starting material, and this with both procedures. From 4-ethynyl-*N*,*N*-dimethylaniline, the corresponding 4-azaphthalide and 5-azaisocoumarin were only obtained under MW irradiation. Both the 4-azaphthalides and 5-azaisocoumarins obtained in this work may present interesting biological activities.

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Experimental Part

General. The reactions were monitored by TLC and carried out either under conventional heating in *Schlenk* tubes dried under vacuum with a heat gun, or under microwave irradiation in an appropriate tube at constant temp., in a microwave-accelerated reaction system, model *MARS*® (version 194A04, Copyright 1997, 2006 by *CEM Corporation*). The temp. was measured and controlled by a built-in IR detector. Column chromatography (CC): *Macherey-Nagel* silica gel (SiO_2; 230–400 mesh); solvent gradient from neat petroleum ether (40–60°) to Et_2O/petroleum ether (40–60°), in steps of 10% of Et_2O each time until the isolation of the products; monitoring by TLC. M.p.: *Stuart SMP3*; uncorrected. IR Spectra: *Bomem FTLA-2000-104*, nujol mulls unless stated otherwise, in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: *Varian Unity Plus* at 300 and 75.4 MHz, resp., or *Bruker Avance III* at 400 and 100.6 MHz, resp; 2D $^1H/^{13}C$ correlations for the assignment of some signals (HMSC, HMBC). EI- and HR-MS: recorded by the mass spectrometry service of the University of Vigo, Spain; in m/z (rel. %).

General Procedure. Conditions A: In a dry *Schlenk* tube, 2-bromonicotinic acid, 10% Pd/C (3 mol-%), Ph_3P (12 mol-%), CuI (6 mol-%), and Et_3N (5 equiv.) were successively added under Ar to dry dioxane (2.5 ml per 0.5 mmol of 2-bromonicotinic acid), and the resulting soln. was stirred for 30 min at 35°. Then, ethynylarene was added, and the mixture was stirred for 1 h at 35° and then for 2 h at 90°. *Conditions B:* The 2-bromonicotinic acid, 10% Pd/C (3 mol-%), Ph_3P (12 mol-%), CuI (6 mol-%), and Et_3N (5 equiv.) were added under Ar in an appropriate tube containing dry dioxane (2.5 ml per 0.5 mmol of 2-bromonicotinic acid), and the resulting soln. was irradiated under microwave (power max. 400 W) at 35° for 5 min. Then, the ethynylarene was added, and the mixture was irradiated at 35° for 10 min (power max. 800 W) and at 90° for 10 min (power max. 1600 W). *General Workup for Both Procedures:* After cooling, $CHCl_3$ was added, the mixture was transferred to a round-bottom flask, and the solvents were evaporated. The resulting oil was submitted to CC (SiO_2) to give the corresponding products as solids.

*(7Z)-7-(Phenylmethylidene)furo[3,4-*b*]pyridin-5(7*H*)-one* (**1a**) *and 7-Phenyl-5*H*-pyrano[4,3-*b*]pyridin-5-one* (**1b**). From 2-bromonicotinic acid (101 mg, 0.500 mmol) and ethynylbenzene (78.0 mg, 0.750 mmol). CC (40% Et_2O/petroleum ether): **1a** (*A:* 46.0 mg, 41%; *B:* 45.0 mg, 40%) as a yellow solid. Recrystallization from Et_2O/petroleum ether gave yellow crystals. M.p. 145–147°. IR: 1776 (C=O). ^1H-NMR (400 MHz, $CDCl_3$): 6.96 (*s*, PhC*H*=C); 7.35–7.38 (*m*, 1 arom. H); 7.42–7.48 (*m*, 3 arom. H); 7.89–7.91 (*m*, 2 arom. H); 8.24 (*dd*, *J* = 7.6, 1.6, H–C(4)); 8.92 (*d*, *J* = 4.8, 1.6, H–C(2)). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 108.73 (Ph*C*H=C); 117.33 (C); 124.08 (C(3)); 128.83 (2 CH); 129.14 (CH); 130.74 (2 CH); 132.48 (C); 133.71 (C(4)); 143.69 (C(7)); 156.18 (C(2)); 158.53 (C); 164.78 (C=O). EI-MS: 224.07 (6, $[M+1]^+$), 223.06 (46, M^+), 222.06 (100, $[M-1]^+$), 167.07 (18), 166.06 (27). HR-MS: 223.0631 (M^+, $C_{14}H_9NO_2^+$; calc. 223.0633).

Compound **1b** was isolated from CC (60% Et_2O/petroleum ether): yellow solid (*A:* 30.0 mg, 27%; *B:* 20.0 mg, 18%). Recrystallization from Et_2O/petroleum ether gave yellow crystals. M.p. 135–136° ([7]: 136–137°). Spectroscopic data: already reported in the lit. similar to the ones obtained in this work.

*(7Z)-7-[(3-Methoxyphenyl)methylidene]furo[3,4-*b*]pyridin-5(7*H*)-one* (**2a**) *and 7-(3-Methoxyphenyl)-5*H*-pyrano[4,3-*b*]pyridin-5-one* (**2b**). From 2-bromonicotinic acid (101 mg, 0.500 mmol) and 1-ethynyl-3-methoxybenzene (99.0 mg, 0.750 mmol). CC (40% Et_2O/petroleum ether): **2a** (*A:* 70.0 mg, 55%; *B:* 57.0 mg, 45%) as a beige solid. Recrystallization from Et_2O/petroleum ether gave yellow crystals. M.p. 152–153°. IR: 1781 (C=O). ^1H-NMR (400 MHz, $CDCl_3$): 3.90 (*s*, MeO); 6.92–6.95 (*m*, 2 arom. H, ArC*H*=C); 7.33–7.38 (*m*, 1 arom. H); 7.46–7.50 (*m*, 3 arom. H); 8.24 (*dd*, *J* = 8.0, 1.6, H–C(4)); 8.92 (*dd*, *J* = 4.8, 1.6, H–C(2)). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 55.33 (MeO); 108.72 (Ar*C*H=C); 115.32 (CH); 115.52 (CH); 117.40 (C); 123.50 (CH); 124.14 (C(3)); 129.77 (CH); 133.70 (C); 133.78 (C(4)); 143.80 (C(7)); 156.15 (C(2)); 158.50 (C); 159.80 (MeO–*C*); 164.68 (C=O). EI-MS: 254.08 (9, $[M+1]^+$), 253.07 (60, M^+), 252.07 (100, $[M-1]^+$), 238.05 (6, $[M-15]^+$). HR-MS: 253.0739 (M^+, $C_{15}H_{11}NO_3^+$; calc. 253.0739).

Compound **2b** was only isolated under MW irradiation (*Conditions B:* 20.0 mg, 16%) after CC (60% Et_2O/petroleum ether) as a yellow pale solid. Recristallization from Et_2O/petroleum ether gave off-white crystals. M.p. 178–180°. IR: 1731 (C=O). ^1H-NMR (400 MHz, $CDCl_3$): 3.90 (*s*, MeO); 7.02–7.50 (*m*, 1 arom. H); 7.23 (*s*, H–C(8)); 7.39–7.46 (*m*, 3 arom. H); 7.50–7.53 (*m*, 1 arom. H); 8.56 (*dd*, *J* = 8.0, 1.6, H–C(4)); 8.95 (*dd*, *J* = 4.8, 1.6, H–C(2)). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 55.48 (MeO); 103.96 (C(8)); 110.70 (CH); 116.91 (CH); 116.99 (C); 118.11 (CH); 122.89 (C(3)); 130.04 (CH); 132.69 (C); 137.59 (C(4)); 155.01 (C); 156.38 (2 CH); 157.14 (C(7)); 160.06 (MeO–*C*); 161.98 (C=O). EI-MS: 254.08 (15, $[M+1]^+$), 253.07 (100, M^+). HR-MS: 253.0738 (M^+, $C_{15}H_{11}NO_3^+$; calc. 253.0739).

*(7Z)-7-[(4-Methoxyphenyl)methylidene]furo[3,4-*b*]pyridin-5(7*H*)-one* (**3a**) *and 7-(4-Methoxyphenyl)-5*H*-pyrano[4,3-*b*]pyridin-5-one* (**3b**). From 2-bromonicotinic acid (101 mg, 0.500 mmol) and 1-ethynyl-4-methoxybenzene (99.0 mg, 0.750 mmol). CC (40% Et$_2$O/petroleum ether): **3a** (*A:* 56.0 mg, 44%; *B:* 55.0 mg, 43%) as an offwhite solid. Recrystallization from Et$_2$O/petroleum ether gave off-white crystals. M.p. 164–165°. IR: 1768 (C=O). ^{1}H-NMR (400 MHz, CDCl$_3$): 3.87 (*s*, MeO); 6.94 (*s*, ArC*H*=C); 6.97 (*d*, $J = 7.0$, H–C(3′), H–C(5′)); 7.44 (*dd*, $J = 8.0, 4.8$, H–C(3)); 7.87 (*d*, $J = 7.0$, H–C(2′), H–C(6′)); 8.23 (*dd*, $J = 8.0, 1.6$, H–C(4)); 8.90 (*dd*, $J = 4.8, 1.6$, H–C(2)). ^{13}C-NMR (100.6 MHz, CDCl$_3$): 55.35 (MeO); 108.85 (Ar*C*H=C); 114.40 (C(3′,5′)); 117.00 (C); 123.64 (C(3)); 125.28 (C(1′)); 132.49 (C(2′,6′)); 133.77 (C(4)); 142.15 (C(7)); 156.04 (C(2)); 158.56 (C); 160.43 (MeO–*C*); 164.98 (C=O). EI-MS: 254.08 (17, $[M+1]^+$), 253.08 (100, M^+), 252.08 (59, $[M-1]^+$). HR-MS: 253.0741 (M^+, $C_{15}H_{11}NO_3^+$; calc. 253.0739).

Compound **3b** was isolated from CC (60% Et$_2$O/petroleum ether): off-white solid (*A:* 33.0 mg, 26%; *B:* 29.0 mg, 23%). Recrystallization from Et$_2$O/petroleum ether gave off-white crystals. M.p. 178–180° ([7]: 177–178°). Spectroscopic data: already described in the lit. similar to the ones obtained in this work.

*(7Z)-7-[(2-Methoxyphenyl)methylidene]furo[3,4-*b*]pyridin-5(7*H*)-one* (**4a**) *and 7-(2-Methoxyphenyl)-5*H*-pyrano[4,3-*b*]pyridin-5-one* (**4b**). From 2-bromonicotinic acid (101 mg, 0.500 mmol) and 1-ethynyl-2-methoxybenzene (99.0 mg, 0.750 mmol). CC (40% Et$_2$O/petroleum ether): **4a** (*A:* 34.0 mg, 25%; *B:* 29.0 mg, 21%) as an off-white solid. Recrystallization from Et$_2$O/petroleum ether gave off-white crystals. M.p. > 300° (dec.). IR: 1772 (C=O). ^{1}H-NMR (400 MHz, CDCl$_3$): 3.93 (*s*, MeO); 6.93–6.95 (*m*, 1 arom. H); 7.04–7.08 (*m*, 1 arom. H); 7.33–7.37 (*m*, 1 arom. H); 7.46 (*dd*, $J = 8.0, 4.6$, H–C(3)); 7.54 (*s*, ArC*H*=C); 8.24 (*dd*, $J = 8.0, 1.6$, H–C(4)); 8.30 (*dd*, $J = 8.0, 1.6$, H–C(6′)); 8.94 (*dd*, $J = 4.6, 1.6$, H–C(2)). ^{13}C-NMR (100.6 MHz, CDCl$_3$): 55.59 (MeO); 103.03 (Ar*C*H=C); 110.62 (CH); 117.29 (C); 120.99 (CH); 121.44 (C); 123.82 (C(3)); 130.66 (CH); 131.66 (CH); 133.74 (C(4)); 143.51 (C(7)); 156.12 (C(2)); 157.90 (MeO–*C*); 158.72 (C); 165.04 (C=O). EI-MS: 254.08 (2, $[M+1]^+$), 253.08 (10, M^+), 252.06 (1, $[M-1]^+$), 223.06 (14, $[M-30]^+$), 222.05 (100, $[M-\mathrm{MeO}]^+$). HR-MS: 253.0742 (M^+, $C_{15}H_{11}NO_3^+$; calc. 253.0739).

Compound **4b** was isolated from CC (60% Et$_2$O/petroleum ether): yellow pale solid (*A:* 51.0 mg, 40%; *B:* 52.0 mg, 41%). Recrystallization from Et$_2$O/petroleum ether gave yellow pale crystals. M.p. 187–189°. IR: 1720 (C=O). ^{1}H-NMR (400 MHz, CDCl$_3$): 3.99 (*s*, MeO); 7.03–7.12 (*m*, 2 arom. H); 7.41–7.46 (*m*, H–C(3), 1 arom. H); 7.72 (*s*, H–C(8)); 7.99–8.02 (*m*, 1 arom. H); 8.56 (*dd*, $J = 7.8, 1.6$, H–C(4)); 8.95 (br. *s*, H–C(2)). ^{13}C-NMR (100.6 MHz, CDCl$_3$): 55.60 (MeO); 108.65 (C(8)); 111.47 (CH); 117.02 (C); 120.01 (C); 120.83 (CH); 122.73 (C(3)); 128.93 (CH); 131.64 (CH); 137.49 (C(4)); 154.21 (C(7)); 155.46 (C); 156.03 (C(2)); 157.70 (MeO–*C*); 162.21 (C=O). EI-MS: 254.08 (16, $[M+1]^+$), 253.08 (100, M^+), 226.08 (5, $[M-27]^+$), 225.08 (32, $[M-28]^+$). HR-MS: 253.0741 (M^+, $C_{15}H_{11}NO_3^+$; calc. 253.0739).

*(7Z)-7-[(3-Fluorophenyl)methylidene]furo[3,4-*b*]pyridin-5(7*H*)-one* (**5a**) *and 7-(3-Fluorophenyl)-5*H*-pyrano[4,3-*b*]pyridin-5-one* (**5b**). From 2-bromonicotinic acid (101 mg, 0.500 mmol) and 1-ethynyl-3-fluorobenzene (90.0 mg, 0.750 mmol). CC (50% Et$_2$O/petroleum ether): **5a** (*A:* 51.0 mg, 40%; *B:* 48.0 mg, 38%) as a yellow pale solid. Recrystallization from Et$_2$O/petroleum ether gave off-white crystals. M.p. 174–176°. IR: 1736 (C=O). ^{1}H-NMR (300 MHz, CDCl$_3$): 6.92 (*s*, ArC*H*=C); 7.04–7.10 (*m*, 1 arom. H); 7.37–7.44 (*m*, H–C(5′)); 7.51 (*dd*, $J = 7.7, 4.7$, H–C(3)); 7.61–7.69 (*m*, 2 arom. H); 8.26 (*dd*, $J = 7.7, 1.7$, H–C(4)); 8.94 (*dd*, $J = 4.7, 1.7$, H–C(2)). ^{13}C-NMR (75.4 MHz, CDCl$_3$): 107.33 (*d*, $J = 2.9$, ArCH=C); 116.07 (*d*, $J = 21.3$, CH); 117.04 (*d*, $J = 22.8$, CH); 117.52 (C); 124.44 (C(3)); 126.52 (*d*, $J = 2.9$, C(6′)); 130.24 (*d*, $J = 8.3$, C(5′)); 133.83 (C(4)); 134.50 (*d*, $J = 8.3$, C(1′)); 144.46 (C(7)); 156.31 (C(2)); 158.34 (C); 161.26 (C); 164.48 (C); 164.52 (C–F, C=O). EI-MS: 242.06 (8, $[M+1]^+$), 241.05 (54, M^+), 240.05 (100, $[M-1]^+$). HR-MS: 241.0539 (M^+, $C_{14}H_8FNO_2^+$; calc. 241.0539).

Compound **5b** was isolated from CC (70% Et$_2$O/petroleum ether): yellow pale solid (*A:* 27.0 mg, 21%; *B:* 23.0 mg, 18%). Recrystallization from Et$_2$O/petroleum ether gave yellow pale crystals. M.p. 161–163°. IR: 1744 (C=O). ^{1}H-NMR (400 MHz, CDCl$_3$): 7.17–7.22 (*m*, 1 arom. H); 7.25 (*s*, H–C(8)); 7.46–7.50 (*m*, H–C(3), H–C(5′)); 7.62–7.66 (*m*, 1 arom. H); 7.71–7.73 (*m*, 1 arom. H); 8.57 (*dd*, $J = 7.8, 1.4$, H–C(4)); 8.98 (br. *s*, H–C(2)). ^{13}C-NMR (100.6 MHz, CDCl$_3$): 104.55 (C(8)); 112.75 (*d*, $J = 24.1$, CH); 117.30 (C); 117.72 (*d*, $J = 21.1$, CH); 121.28 (*d*, $J = 3.0$, C(6′)); 123.24 (C(3)); 130.66 (*d*, $J = 8.0$, C(5′)); 133.53 (*d*, $J = 8.0$, C(1′)); 137.61 (C(4)); 154.77 (C); 155.87 (C(7)); 156.41 (C(2)); 161.67 (C=O); 162.03 (*d*, $J = 246.5$, C(3′)). EI-MS: 242.06 (15, $[M+1]^+$), 241.06 (100, M^+), 240.06 (5, $[M-1]^+$), 213.06 (56, $[M-28]^+$). HR-MS: 241.0543 (M^+, $C_{14}H_8FNO_2^+$; calc. 241.0539).

*(7Z)-7-[(4-Fluorophenyl)methylidene]furo[3,4-*b*]pyridin-5(7*H*)-one* (**6a**) *and 7-(4-Fluorophenyl)-5*H*-pyrano[4,3-*b*]pyridin-5-one* (**6b**). From 2-bromonicotinic acid (101 mg, 0.500 mmol) and 1-ethynyl-4-fluorobenzene (90.0 mg, 0.750 mmol). CC (50% Et$_2$O/petroleum ether): **6a** (*A:* 48.0 mg, 40%) as a yellow pale solid. Recrystallization from Et$_2$O/petroleum ether gave off-white crystals. M.p. 177–179°. IR: 1739 (C=O). ^{1}H-NMR (400 MHz, CDCl$_3$): 6.94 (*s*, ArC*H*=C); 7.12–7.16 (*m*, H–C(3′), H–C(5′)); 7.49 (*dd*, $J = 7.6$, 4.8, H–C(3)); 7.89–7.92 (*m*, H–C(2′), H–C(6′)); 8.25 (*dd*, $J = 7.6$, 1.6, H–C(4)); 8.93 (*dd*, $J = 4.8$, 1.6, H–C(2)). ^{13}C-NMR (100.6 MHz, CDCl$_3$): 107.55 (Ar*C*H=C); 116.04 (*d*, $J = 21.1$, C(3′,5′)); 117.30 (C); 124.17 (C(3)); 128.81 (*d*, $J = 3.0$, C(1′)); 132.67 (*d*, $J = 8.0$, C(2′,6′)); 133.81 (C(4)); 143.37 (C(7)); 156.26 (C(2)); 158.51 (C); 163.02 (*d*, $J = 251.5$, C–F); 164.73 (C=O). EI-MS: 242.06 (7, $[M+1]^+$), 241.05 (69, M^+), 240.04 (100, $[M-1]^+$). HR-MS: 241.0535 (M^+, $C_{14}H_8FNO_2^+$; calc. 241.0539).

Compound **6b** was isolated from CC (70% Et$_2$O/petroleum ether): off-white solid (*A:* 19.0 mg, 16%). Recrystallization from Et$_2$O/petroleum ether gave off-white crystals. M.p. 171–173°. IR: 1739 (C=O). ^{1}H-NMR (400 MHz, CDCl$_3$): 7.18–7.22 (*m*, H–C(3′), H–C(5′), H–C(8)); 7.44 (*dd*, $J = 7.6$, 4.8, H–C(3)); 7.91–7.95 (*m*, H–C(2′), H–C(6′)); 8.56 (*dd*, $J = 7.6$, 2.0, H–C(4)); 8.95 (*dd*, $J = 4.8$, 2.0, H–C(2)). ^{13}C-NMR (100.6 MHz, CDCl$_3$): 103.44 (C(8)); 116.22 (*d*, $J = 22.0$, C(3′,5′)); 116.82 (C); 122.92 (C(3)); 127.62 (*d*, $J = 3.0$, C(1′)); 127.80 (*d*, $J = 9.0$, C(2′,6′)); 137.61 (C(4)); 154.98 (C); 156.40 (C); 156.43 (C(2)); 161.85 (C=O); 164.26 (*d*, $J = 251.5$, C–F). EI-MS: 242.06 (14, $[M+1]^+$), 241.05 (100, M^+), 214.05 (18, $[M-27]^+$), 213.06 (84, $[M-28]^+$). HR-MS: 241.0536 (M^+, $C_{14}H_8FNO_2^+$; calc. 241.0539).

*(7Z)-7-[(2-Fluorophenyl)methylidene])furo[3,4-*b*]pyridin-5(7*H*)-one* (**7a**) *and 7-(2-Fluorophenyl)-5*H*-pyrano[4,3-*b*]pyridin-5-one* (**7b**). From 2-bromonicotinic acid (101 mg, 0.500 mmol) and 1-ethynyl-2-fluorobenzene (90.0 mg, 0.750 mmol). CC (30% Et$_2$O/petroleum ether): **7a** (*A:* 55.0 mg, 45%; *B:* 55.0 mg, 45%) as a yellow pale solid. Recrystallization from Et$_2$O/petroleum ether gave off-white crystals. M.p. 199–201°. IR: 1744 (C=O). ^{1}H-NMR (400 MHz, CDCl$_3$): 7.10–7.15 (*m*, H–C(3′)); 7.23–7.27 (*m*, 2 arom. H); 7.28 (*s*, ArC*H*=C); 7.32–7.38 (*m*, 1 arom. H); 7.50 (*dd*, $J = 8.0$, 4.8, H–C(3)); 8.25 (*dd*, $J = 8.0$, 1.6, H–C(4)); 8.29–8.34 (*m*, H–C(5′)); 8.95 (*dd*, $J = 4.8$, 1.6, H–C(2)). ^{13}C-NMR (100.6 MHz, CDCl$_3$): 99.98 (*d*, $J = 8.0$, Ar*C*H=C); 115.45 (*d*, $J = 22.0$, C(3′)); 117.51 (C); 120.68 (*d*, $J = 11.1$, C); 124.37 (C(3)); 124.57 (*d*, $J = 8.0$, CH); 130.73 (*d*, $J = 8.0$, CH); 131.58 (*d*, $J = 2.0$, C(5′)); 133.75 (C(4)); 144.73 (*d*, $J = 2.0$, C(7)); 156.34 (C(2)); 158.40 (C); 160.93 (*d*, $J = 253.5$, C–F); 164.62 (C=O). EI-MS: 242.06 (6, $[M+1]^+$), 241.05 (38, M^+), 240.05 (33, $[M-1]^+$), 223.06 (15, $[M-18]^+$), 222.05 (100, $[M-19]^+$). HR-MS: 241.0540 (M^+, $C_{14}H_8FNO_2^+$; calc. 241.0539).

Compound **7b** was isolated from CC (40% Et$_2$O/petroleum ether): off-white solid (*A:* 22.0 mg, 18%; *B:* 13.0 mg, 11%). Recrystallization from Et$_2$O/petroleum ether gave off-white crystals. M.p. 165–167°. IR: 1746 (C=O). ^{1}H-NMR (400 MHz, CDCl$_3$): 7.23–7.33 (*m*, H–C(3′), H–C(5′)); 7.43–7.49 (*m*, H–C(3); H–C(8), 1 arom. H); 8.00–8.04 (*m*, 1 arom. H); 8.57 (*dd*, $J = 8.0$, 1.6, H–C(4)); 8.98 (*dd*, $J = 4.6$, 1.6, H–C(2)). ^{13}C-NMR (100.6 MHz, CDCl$_3$): 108.94 (*d*, $J = 15.1$, C(8)); 116.68 (*d*, $J = 23.1$, C(3′)); 117.26 (C); 119.68 (*d*, $J = 10.1$, C); 123.23 (C(3)); 124.64 (*d*, $J = 4.0$, C(5′)); 128.65 (CH); 132.02 (*d*, $J = 9.1$, CH); 137.52 (C(4)); 151.97 (*d*, $J = 5.0$, C); 154.93 (C); 156.36 (C(2)); 160.33 (*d*, $J = 254.5$, C–F); 161.70 (C=O). EI-MS: 242.05 (16, $[M+1]^+$), 241.06 (100, M^+), 240.04 (4, $[M-1]^+$), 222.05 (9, $[M-19]^+$), 214.06 (14, $[M-27]^+$), 213.06 (88, $[M-28]^+$). HR-MS: 241.0542 (M^+, $C_{14}H_8FNO_2^+$; calc. 241.0539).

*(7Z)-7-{[4-(Dimethylamino)phenyl]methylidene}furo[3,4-*b*]pyridin-5(7*H*)-one* (**8a**) *and 7-[4-(Dimethylamino)phenyl]-5*H*-pyrano[4,3-*b*]pyridin-5-one* (**8b**). From 2-bromonicotinic acid (101 mg, 0.500 mmol) and 4-ethynyl-*N*,*N*-dimethylbenzenamine (109.0 mg, 0.750 mmol). CC (50% Et$_2$O/petroleum ether): **8a** (*B:* 32.0 mg, 24%) as a yellow solid. Recrystallization from Et$_2$O/petroleum ether gave yellow pale crystals. M.p. 166–168°. IR: 1734 (C=O). ^{1}H-NMR (400 MHz, CDCl$_3$): 3.06 (*s*, Me$_2$N); 6.76 (*d*, $J = 9.0$, H–C(3′), H–C(5′)); 6.92 (*s*, ArC*H*=C); 7.38 (*dd*, $J = 7.8$, 4.8, H–C(3)); 7.82 (*d*, $J = 9.0$, H–C(2′), H–C(6′)); 8.21 (*dd*, $J = 7.8$, 1.6, H–C(4)); 8.87 (*dd*, $J = 4.8$, 1.6, H–C(2)). ^{13}C-NMR (100.6 MHz, CDCl$_3$): 40.18 (Me$_2$N); 110.05 (Ar*C*H=C); 112.10 (C(3′,5′)); 116.46 (C); 122.91 (C(3)); 132.51 (C(2′,6′)); 133.63 (C); 133.68 (C(4)); 140.78 (C(7)); 150.71 (C); 155.96 (C(2)); 158.65 (C); 165.34 (C=O). EI-MS:

267.11 ($[M+1]^+$, 16), 266.11 (100, M^+), 265.10 (10, $[M-1]^+$). HR-MS: 266.1056 (M^+, $C_{16}H_{14}N_2O_2^+$; calc. 266.1055).

Compound **8b** was isolated from CC (60% Et_2O/petroleum ether): yellow solid (*B:* 21.0 mg, 16%). Recrystallization from Et_2O/petroleum ether gave yellow pale crystals. M.p. 196–198°. IR: 1741 (C=O). ^{1}H-NMR (400 MHz, $CDCl_3$): 3.07 (*s*, Me_2N); 6.76 (*d*, *J* = 7.0, H–C(3′), H–C(5′)); 7.04 (*s*, H–C(8)); 7.32 (*dd*, *J* = 8.0, 4.6, H–C(3)); 7.81 (*d*, *J* = 7.0, H–C(2′), H–C(6′)); 8.50 (*dd*, *J* = 8.0, 1.8, H–C(4)); 8.87 (*dd*, *J* = 4.6, 1.8, H–C(2)). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 40.12 (Me_2N); 99.95 (C(8)); 111.76 (C(3′,5′)); 115.94 (C); 118.38 (C); 121.66 (C(3)); 127.03 (C(2′,6′)); 137.60 (C(4)); 151.92 (C); 155.78 (C); 156.18 (C(2)); 158.42 (C(7)); 162.52 (C=O). EI-MS: 267.11 (17, $[M+1]^+$), 266.11 (100, M^+), 265.10 (18, $[M-1]^+$). HR-MS: 266.1051 (M^+, $C_{16}H_{14}N_2O_2^+$; calc. 266.1055).

*(7Z)-7-(Thiophen-3-ylmethylidene)furo[3,4-*b*]pyridin-5(7*H*)-one* (**9a**). From 2-bromonicotinic acid (101 mg, 0.500 mmol) and 3-ethynylthiophene (84.0 mg, 0.750 mmol). CC (50% Et_2O/petroleum ether): **9a** (*A:* 58.0 mg, 50%; *B:* 60.0 mg, 52%) as a brown solid. Recrystallization from Et_2O/petroleum ether gave beige crystals. M.p. 122–123°. IR ($CHCl_3$): 1785 (C=O). ^{1}H-NMR (400 MHz, $CDCl_3$): 7.03 (*s*, ArC*H*=C)); 7.38–7.40 (*dd*, *J* = 2.8, 4.8, H–C(5′)); 7.46 (*dd*, *J* = 7.6, 4.6, H–C(3)); 7.64 (*dd*, *J* = 4.8, 1.2, H–C(4′)); 7.83–7.84 (*m*, H–C(2′)); 8.23 (*dd*, *J* = 7.6, 1.6, H–C(4)); 8.91 (*dd*, *J* = 4.8, 1.6, H–C(2)). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 103.08 (Ar*C*H=C); 117.56 (C); 123.91 (C(3)); 126.20 (C(5′)); 128.45 (C(2′)); 128.95 (C(4′)); 133.76 (C(4)); 133.79 (C); 142.80 (C(7)); 156.18 (C(2)); 158.37 (C); 164.63 (C=O). EI-MS: 230.02 (17, $[M+1]^+$), 229.02 (95, M^+), 228.01 (100, $[M-1]^+$). HR-MS: 229.0197 (M^+, $C_{12}H_7NO_2S^+$; calc. 229.0198).

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