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On the reactivity of activated alkynes in copper and solvent-free Huisgen's reaction

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Dedicated to Henri B. Kagan; a great scientist and human being, a mentor and a friend

ABSTRACT

Terminal alkynes substituted by a carbonyl-type electron-withdrawing group have been found to undergo Huisgen's cycloaddition with azides at room temperature in a solvent-free manner; without a need of either heating or catalysis. Metallic salts, other than the copper ones also efficiently catalyzed the reactions. The yields were good and the products isolated mainly as their 1,4-disubstituted isomer.

1. Introduction

Since the introduction of the click-chemistry concept, several reactions were used to quickly and efficiently construct molecular architectures.[1] One of the most studied reactions in this field is the copper(I)-catalyzed version of Huisgen's 1,3-dipolar cycloaddition between organic alkynes and azides (copper-catalyzed alkyne–azide cycloaddition or CuAAC) leading to the 1,2,3-triazole ring (Scheme 1).[2]

This catalyzed variation of the initial Huisgen's reaction presents various advantages: the reaction usually do not need heating to proceed, the cycloaddition is relatively fast and, furthermore, it gives selectively the corresponding 1,4-disubstituted triazole isomer over the 1,5-one. Several conditions to conduct the CuAAC have been proposed since it's discovery ranging from in situ generation of copper(I) species from redox systems starting with cupric salts or copper itself[3] to the use of soluble cuprous salt or complexes,[4] as well as metallic copper (wire, nanoparticles, and clusters)[5] and copper(I)-supported catalysts (polymers, minerals, and ionic liquids).[6] In the field of supported catalysts, we explored the use of polymer and clay supports, in solution and solvent-free conditions.[7] During our work on Wyoming montmorillonite (Wy), and its use as a Huisgen catalyst in solution after adsorption of copper(I) iodide (Wy·CuI), we observed interesting reactivity behaviors that were worthy to be explored in more detail.

2. Results and discussion

In order to ascertain the catalytic activity of Wy·CuI, the modified clay was first tested in the [3+2] reaction between phenylacetylene **1a**, methyl propiolate **1b**, and benzyl azide **2a** as models (Table 1). Blanks were also run using the reference sodium-rich Wyoming montmorillonite (S-Wy-2) and the same after complete sodium-exchange procedure (Wy-Na).

When the reaction was run in solution in methylene chloride, phenylacetylene **1a** did not react with benzyl azide **2a** in the presence of S-Wy-2 and Wy-Na or in the absence of clay. When Wy·CuI was used, the corresponding triazole **1a2a** as its sole 1,4-isomer was quantitatively formed. The same was true when the solvent-free procedure was applied; only Wy·CuI gave rise to the complete transformation into the 1,4-isomer of triazole **1a2a**.

In the case of methyl propiolate **1b**, the results were quite different and interesting. In solution, the formation of the triazole **1b2a** was observed even when S-Wy-2 and Wy-Na were used in 50% and 39% conversion, respectively, and in a 9 to 1 ratio in favor of the 1,4-isomer.

Even when no additives were present, the conversion reached 10% in the same ratio. Furthermore, Wy·CuI gave a complete conversion and selectivity for the corresponding **1b2a**. The results were even better when the reaction was run under solvent-free conditions. Yields in the presence of S-Wy-2 and Wy-Na increased up to 80%, and without additive to 50%, all in a 9:1 ratio. Once again, Wy·CuI selectively and quantitatively gave the 1,4-isomer of **1b2a**.

From these results, Wy·CuI was working equally well with phenyl **1a** or methoxycarbonyl **1b**-substituted acetylene, both under solution and solvent-free conditions.

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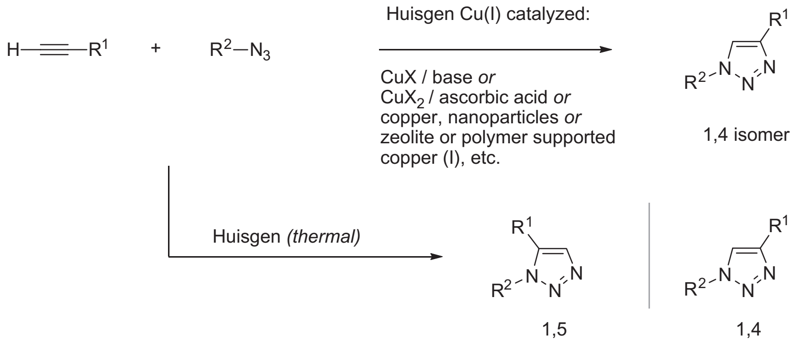


Scheme 1. Huisgen's reaction between azides and alkynes: original thermal (1,4/1,5-isomers) and copper(I)-catalyzed (1,4-isomer) conditions.

For phenylacetylene **1a**, this substance did not react in solution or neat, in the presence or absence of clays (S-Wy-2 and Wy-Na). Methyl propiolate **1b** reacted without additive in solution or neat in conversion reaching 10% and 50%, respectively. The addition of both clays (S-Wy-2 and Wy-Na) increased the yields to 50% in solution and 80% in the solvent-free conditions.

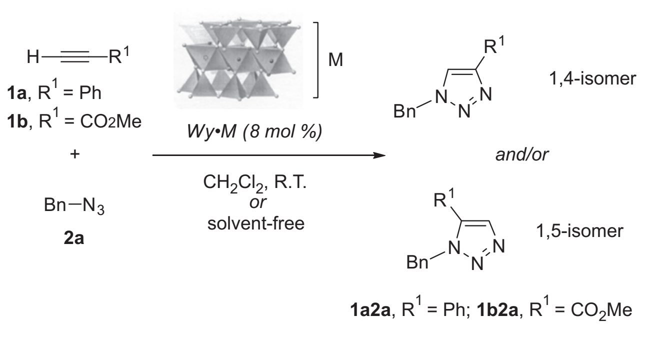
These results led to three observations: (1) The best results were obtained using the solvent-free approach, (2) acetylene bearing an electron-withdrawing group such as an ester **1b** was reacting while the one substituted with a stabilizing group such as phenyl **1a** did not; and (3) the presence of clays (S-Wy-2 and Wy-Na) seemed to have a catalytic effect on the reaction under both conditions.

In order to gain a better understanding of the phenomena taking place here, we decided to conduct a more complete study based on these initial results. Dilution in these cases seems to have deleterious effect on the conversion, thus solvent-free conditions were selected.

Since the presence of an electron-withdrawing group, such as an ester, seemed to be in part responsible for the reactivity, alkynes bearing a carbonyl-type substituent were chosen.

The presence of copper traces in the clays S-Wy-2 and Wy-Na cannot be accounted for the reactions happening when they were added since no copper was detected below 50 ppm by elemental analysis. Furthermore, phenylacetylene **1a** failed to react in the presence of these clays, but reacted perfectly in the presence of Wy·CuI (4.57% copper by elemental analysis). When looking at natural sodium-rich Wyoming montmorillonite composition: $(Ca_{0.12}K_{0.05}Na_{0.32})[Al_{3.01}Fe_{0.41}Mg_{0.54}Mn_{0.01}Ti_{0.02}][Al_{0.02}Si_{7.98}]O_{20}(OH)_4$, the major metallic oxides constituents, excluding Na and Ca, are Si (62.9%), Al (19.6%) Fe (3.7%), and Mg (3.0%). The hypothesis that metals included in the clays can have a catalytic influence was made.

Table 1
Results of the reaction of alkynes **1a** and **1b** with the azide **2a** to form triazoles **1a2a** and **1a2b** in the presence of Wy[a]



Solvent	Triazole	S-Wy-2[b] %, ratio[c]	Wy-Na[b] %, ratio[c]	Wy·CuI[b] %, ratio[c]	—[b] %, ratio[c]
CH_2Cl_2	**1a2a**	0	0	99, 10:0	0
	1b2a	50, 9:1	39, 9:1	99, 10:0	10, 9:1
None	**1a2a**	0	0	99, 10:0	0
	1b2a	80, 10:1	80, 9:1	99, 10:0	50, 9:1

[a] On a 0.5 mmol scale: 1 equiv alkyne, 1.1 equiv azide, 2 mL solvent (0.25 M), 18 h reaction time, room temperature.

[b] 55 mg of clay (Wy·CuI = 8 mol % Cu). —: without additives.

[c] Estimated by ^1H NMR: conversion %, ratio 1,4: 1,5 isomers. All compounds gave correct IR, ^1H, ^{13}C NMR, and LC–MS analyses.

Thus for the study, the behavior in Huisgen's reaction of alkynes bearing a carbonyl (ester, carboxylic acid, ketone, and amide) was studied under solvent-free conditions on three azides, in the presence or absence of additives representative of the main metals found in the clays (SiO_2, Al_2O_3, $FeCl_3$, and $MgCl_2$), as well as copper salts ($CuCl_2$ and CuI) and Wy·CuI; the results are presented in Table 2.

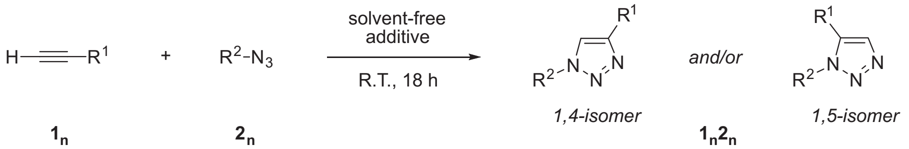
When phenylacetylene **1a** was mixed with benzyl azide **2a**, ethyl azidoacetate **2b**, or 2-acetoxyethyl azide **2c**, no reaction was observed in the absence or presence of SiO_2, Al_2O_3, $FeCl_3$, $MgCl_2$, and $CuCl_2$. The use of CuI gave the 1,4-isomer of triazoles **1a2a** and **1a2b** in very good yields, but surprisingly not the formation of **1a2c**. With Wy·CuI, all three triazoles were formed in high yields and complete selectivity.

The reaction of methyl propiolate **1b** with the three azides **2a**, **2b**, and **2c**, without additives, gave fair yields (50–75%) of the corresponding triazoles **1b2a**, **1b2b**, and **1b2c** with 1,4- to 1,5-isomeric ratios of 90 to 10. By adding SiO_2, Al_2O_3, $FeCl_3$, $MgCl_2$, and $CuCl_2$ to the reagents, the yields were better (80–99%) with mainly ratios of 90 to 10, with only a few being in the range of 85:15 to 80:20. The addition of either CuI or Wy·CuI gave a complete transformation into the awaited triazoles as their 1,4-isomer.

Propiolic acid **1c** was found to be quite reactive under solvent-free conditions, with or without additives. It was also the sole compound in this study to exhibit a noticeable exothermal reaction with the azides. Reactions with **2a**–**c**, without additives, gave a complete conversion into the triazoles **1c2a**, **1c2b**, and **1c2c** with good selectivities for their 1,4-isomer (91:9 and 87:13). The addition of SiO_2, Al_2O_3, $FeCl_3$, $MgCl_2$, and $CuCl_2$ did not really improve the results. Nevertheless, the triazoles were still formed in very good yields (83–99%), once again mainly at the 90:10 level for the selectivities, with some in the range of 95:5 and 85:15. The use of CuI and Wy·CuI also gave high yields for the three triazoles. However, the selectivity for the 1,4-isomer was not complete in these cases and ranged between 92:8 and 95:5. The same selectivities were obtained even by changing the order of addition of the reagents in this specific case (CuI and Wy·CuI).

The next molecule tested was acetylacetylene (butyn-3-one, **1d**). The reactions of the ketone **1d** with the azides without additives gave good yields between 77% and 83% in triazoles **1d2a**,

Table 2
Reactivity of alkynes **1n** toward azides **2n** under solvent-free conditions in the presence of additives[a]



1_n **2_n** **1_n2_n**

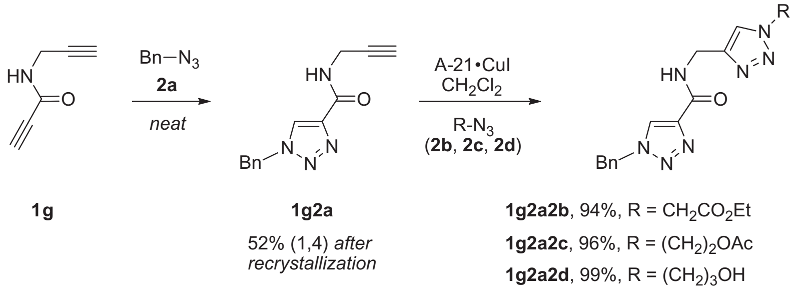
Alkyne	Azide Additive	$PhCH_2N_3$ **2a** %, ratio [b]	$EtO_2CCH_2N_3$ **2b** %, ratio[b]	$AcOCH_2CH_2N_3$ **2c** %, ratio[b]
≡—Ph		**1a2a**	**1a2b**	**1a2c**
1a	None	0	0	0
	SiO_2	0	0	0
	Al_2O_3	0	0	0
	$FeCl_3$	0	0	0
	$MgCl_2$	0	0	0
	$CuCl_2$	0	0	0
	CuI	94, 100:0	99, 100:0	0, 100:0
	Wy·CuI	99, 100:0	90, 100:0	99, 100:0
≡—CO_2CH_3		**1b2a**	**1b2b**	**1b2c**
1b	None	50, 89:11	72, 90:10	76, 90:10
	SiO_2	84, 86:14	99, 80:20	98, 86:14
	Al_2O_3	82, 90:10	99, 90:10	99, 90:10
	$FeCl_3$	83, 88:12	—	99, 90:10
	$MgCl_2$	81, 90:10	96, 90:10	99, 90:10
	$CuCl_2$	84, 94:6	99, 87:13	99, 90:10
	CuI	94, 100:0	99, 100:0	99, 100:0
	Wy·CuI	99, 100:0	99, 100:0	99, 100:0
≡—CO_2H		**1c2a**	**1c2b**	**1c2c**
1c	None	99, 91:9	99, 87:13	99, 91:9
	SiO_2	99, 93:7	99, 91:9	92, 89:11
	Al_2O_3	94, 91:9	99, 94:6	92, 87:13
	$FeCl_3$	99, 96:4	83, 88:12	91, 92:8
	$MgCl_2$	94, 94:6	99, 92:8	97, 93:7
	$CuCl_2$	93, 92:8	99, 82:18	84, 83:17
	CuI	99, 94:6	99, 95:5	99, 92:8
	Wy·CuI	90, 93:7	99, 92:8	99, 93:7
≡—$COCH_3$		**1d2a**	**1d2b**	**1d2c**
1d	None	77, 94:6	77, 94:6	83, 94:6
	SiO_2	65, 93:7	81, 94:6	79, 91:9
	Al_2O_3	77, 92:8	80, 93:7	78, 93:7
	$FeCl_3$	81, 96:4	—	—
	$MgCl_2$	79, 92:8	80, 92:8	78, 93:7
	$CuCl_2$	84, 95:5	83, 88:12	84, 94:6
	CuI	83, 94:6	82, 95:5	87, 96:4
	Wy·CuI	99, 100:0	99, 100:0	99, 100:0
≡—CONHPh		**1e2a**	**1e2b**	**1e2c**
1e	None	53, 85:15	57, 81:19	65, 86:14
	SiO_2	96, 90:10	99, 87:13	91, 78:22
	Al_2O_3	92, 91:9	54, 78:22	94, 76:24
	$FeCl_3$	81, 92:8	83, 88:12	87, 88:12
	$MgCl_2$	79, 88:12	58, 78:22	82, 90:10
	$CuCl_2$	82, 95:5	83, 88:12	90, 92:8
	CuI	96, 100:0	94, 100:0	86, 100:0
	Wy·CuI	98, 100:0	91, 100:0	90, 100:0
≡—$CH(OEt)_2$		**1f2a**	**1f2b**	**1f2c**
1f	None	3, 72:28	2, 83:17	2, 83:17
	SiO_2	3, 76:24	3, 71:29	4, 85:15
	Wy·CuI	80, 100:0	93, 100:0	96, 100:0

[a] On a 0.5 mmol scale: 1 equiv alkyne, 1.1 equiv azide, 8 mol % additive, 18 h reaction time, room temperature.

[b] Estimated by ^1H NMR: conversion %, ratio 1,4: 1,5 isomers. —: product chelating Fe, no interpretable results available. All compounds gave correct mp, IR, ^1H, ^{13}C NMR, and LC–MS analyses.

1d2b, and **1d2c** with a 94:6 selectivity. The addition of the above-mentioned additives gave global conversions in the same range (65–84%) with similar selectivites than without additives (88:12 to 96:4). The addition of CuI gave similar yields (84%), but some of the 1,5-isomer was observed in this case (95:5 ratio). However, Wy·CuI gave complete conversion and selectivity for the 1,4-isomers of triazoles **1d2a–c**.

Finally the reactivity of an amide derivative, namely *N*-phenylpropiolamide **1e**, was evaluated.[8] The reaction with azides **2a–c** without additives gave moderate yields (53–65%) with lower selectivities between 81:19 and 86:14 in favor of the 1,4-isomer of **1e2a–c**. The addition of SiO_2, Al_2O_3, $FeCl_3$, $MgCl_2$, and $CuCl_2$ improved the conversion in most cases (79–99%) with some exceptions (54–58%), but selectivities were variable being for each one



Scheme 2. Examples of sequential Huisgen reactions using a bisalkyne containing activated/unactivated alkynes to access dissymmetric bistriazoles.

third lower, equal, and higher than without additives. The use of copper(I) catalyst also gave in these cases a complete selectivity for the 1,4-isomers in good yields both for CuI (86–96%) and for Wy·CuI (90–98%).

When looking at the results as a function of the additive used, the average yields observed for Huisgen's cycloaddition without them (76%) was increased in each case. The order was found to be SiO_2 (90%), $CuCl_2$ (89%), $Al_2O_3/FeCl_3$ (87%), and $MgCl_2$ (85%). Copper(I) catalysis gave higher average yields of 93% (CuI) and 97% (Wy·CuI). It thus seemed that the use of such additives has a positive effect on the global yields in this series.

The effect seemed to be related to the presence of the additives since reactions conducted in their absence are giving lower conversions. The effect cannot be attributed to the nature of the vial in which the reaction was performed, since the use of borosilicate or plastic test tubes did not change the outcome of the reactions. If a catalytic effect is taking place here, it is possible that it can be due to either the adsorption or the dispersion of the reagents onto the additives, or by chelation. Complexation of the metals by the carbonyl groups, or hydrogen bonding with silanols in the case of silica, may increase the reactivity of the alkynes by a Lewis acid-type catalysis. As an added proof, the reactions of propiolaldehyde diethyl acetal **1f** (Table 2), where the carbonyl is masked, only gave 2–4% conversion in the absence of additives or in the presence of silica, which gave the best results in this study. Once again the use of Wy·CuI gave the triazoles **1f2a–c** in good yields 80–96% and complete 1,4-selectivity.

In the case of $CuCl_2$, using these conditions, it did not seem that copper(I) was formed during its use since phenylacetylene **1a** did not react. The formation of the copper(I) species has been reported while using copper(II) salts ($CuCl_2$, $Cu(OAc)_2$, and $CuSO_4$) in water or alcoholic solvents.[9] The cuprous species generation was a result of either oxidation of the alcohol or some Glaser coupling initially taking place. Phenylacetylene **1a** was found to react with azides in these cases. However, the formation of some copper(I) cannot be completely ruled out while using the activated alkynes **1b–e**, even if a total 1,4-selectivity was not observed here.

In order to demonstrate the utility of this study, we present herein a first example of application using a bisalkyne incorporating both an activated and an unactivated acetylene (Scheme 2). *N*-Propargylpropiolamide (**1g**)[10] was first mixed with benzyl azide (**2a**) in solvent- and additive-free conditions to form **1g2a** in 84% yield and in a 76:24 ratio in favor of the 1,4-isomer.[11] The reaction occurred only on the activated alkyne, no reaction was observed on the propargyl side-chain. Recrystallization in ethanol gave 52% of the pure 1,4-isomer of **1g2a** which was used in the following steps.

The triazole–alkyne **1g2a** was then reacted with ethyl azidoacetate **2b**, 2-acetoxyethyl azide **2c**, and 3-azidopropanol **2d**. Since **1g2a** is a solid, we decided to use a solution approach for this second step using our previously described polymer-supported copper(I) catalyst (Amberlyst A-21·CuI) in methylene chloride. The corresponding bistriazoles were obtained solely as their 1,4-isomers in 94% **1g2a2b**, 96% **1g2a2c**, and 99% **1g2a2d** isolated yields.

3. Conclusion

Herein we have presented our findings on the behavior of carbonyl-bearing acetylenes in Huisgen's cycloaddition under solvent-free conditions. It was determined that these 'activated' alkynes reacted spontaneously with azides in moderate to good yields. The addition of natural clays, or the use of metallic salts and oxides, was found to have an effect on the efficiency of the reaction of activated acetylenes. A catalytic influence was proposed based on the presence of a carbonyl group on these alkynes and its complexation with metals. Unactivated alkynes do not react under these conditions, in the presence or absence of the additives. This gave us the opportunity to present a first example of a sequential and regioselective formation of dissymmetric bistriazoles based on reactivity differences for a molecule bearing both activated and unactivated acetylenes. This approach has many applications to selectively introduce triazole rings to functionalize or form derivatives and analogues of chiral natural products, such as amino acids or peptides. Results on this subject will be presented in due course.

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11. *Typical procedure:* CAUTION—Organic azides are potentially explosive and should be handled with care.

   1-Benzyl-N-(prop-2-yn-1-yl)-1H-1,2,3-triazole-4-carboxamide **1g2a**: Benzyl azide (**2a**, 73 mg, 0.55 mmol) was added to *N*-propargylpropiolamide **1g** (54 mg, 0.5 mmol) in a small test tube. The mixture was stirred for 18 h at room temperature. The product **1g2a** was obtained as a 76:24 mixture of 1,4- and 1,5-isomers (101 mg, 84%). After crystallization from EtOH, the pure 1,4-isomer was isolated as a pale yellow solid (64 mg, 52%). $C_{13}H_{12}N_4O$, $M = 240.26$ g mol^{-1}, mp: 204 °C; FTIR: ν 3015, 2944, 1741, 1654, 1568, 1362, 1213, 1057 and 715 cm^{-1}. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.10 (t, $J = 2.4$ Hz, 1H), 4.01 (dd, $J = 5.9$, 2.4 Hz, 2H), 5.67 (s, 2H), 7.34–7.43 (m, 5H), 8.71 (s, 1H), and 8.98 (t, $J = 5.9$ Hz, 1H) ppm; ^{13}C NMR (DMSO-d_6, 75.5 MHz): δ 27.9, 53.1, 72.6, 81.2, 126.8, 128.0, 128.3, 128.8, 135.6, 142.5 and 159.4 ppm; LC–MS: ELSD pur. 98%; $R_t = 4.19$ min; m/z: 241 ([M+H]$^+$) and 263 ([M+Na]$^+$).

   Ethyl 2-(4-{[(1-benzyl-1H-1,2,3-triazol-4-yl)formamido]methyl}-1H-1,2,3-triazol-1-yl)acetate **1g2a2b**: The triazole–alkyne **1g2a** (48 mg, 0,2 mmol) was dissolved in CH_2Cl_2 (2 mL), and ethyl azidoacetate **2b** (28 mg, 0.55 mmol) and Amberlyst A-21·CuI (13 mg, 8 mol %) were sequentially added. The suspension was stirred at room temperature for 18 h, before being filtered and the polymer was washed with CH_2Cl_2 (2×1 mL). After evaporation, product **1g2a2b** was obtained as a yellow solid (174 mg, 94%). $C_{17}H_{19}N_7O_3$, $M = 369.15$ g mol^{-1}, mp: 217 °C; FTIR: ν 3341, 3278, 3011, 1745, 1650, 1568, 1362, 1222, 831 and 731 cm^{-1}. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.22 (t, $J = 7.1$ Hz, 3H), 4.17 (q, $J = 7.1$ Hz, 2H), 4.51 (dd, $J = 5.8$, 0.3 Hz, 2H), 5.35 (s, 2H), 5.67 (s, 2H), 7.35–7.40 (m, 5H), 7.95 (s, 1H), 8.69 (s, 1H), and 9.10 (t, $J = 4.9$ Hz, 1H) ppm; ^{13}C NMR (DMSO-d_6, 75.5 MHz): δ 14.2, 34.4, 50.5, 53.3, 61.7, 126.9, 128.2, 128.5, 129.1, 135.9, 159.8 and 167.5 ppm; LC–MS: ELSD pur. 99%; $R_t = 4.33$ min; m/z: 370 ([M+H]$^+$) and 392 ([M+Na]$^+$).