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Clean one-pot synthesis of 1,2,4-oxadiazoles under solvent-free conditions using microwave irradiation and potassium fluoride as catalyst and solid support

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ABSTRACT

Potassium fluoride was found to be an efficient catalyst and solid support for the synthesis of 3,5-disubstituted-1,2,4-oxadiazoles. In this work, a one-pot method for the synthesis of these compounds from the reaction of nitriles with hydroxylamine hydrochloride and acyl chloride in the presence of potassium fluoride under solvent-free conditions using microwave irradiation has been developed. The advantages of using potassium fluoride as a solid support in comparison to conventional solid supports are simple operation and convenient separation of the products.

1. Introduction

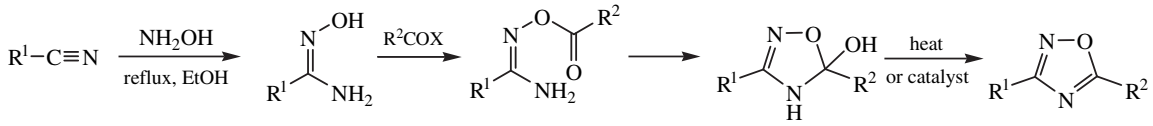
1,2,4-oxadiazole derivatives are important heterocyclic compounds with a wide range of biological activity. This ring system has been used as a urea *bioisostere* in β_3 adrenergic receptor agonists.[1] Furthermore, derivatives containing the 1,2,4-oxadiazole ring systems have been employed as antitumor, anesthetic, and anti-schistosomal agents, coronary artery dilators, muscle relaxants, monoamine oxidase as well as aldose reductase inhibitors.[2–6] In addition, they have also been used as dipeptide mimics.[7]

The drive to environmentally sustainable or so-called 'green chemistry' has provided one of the greatest challenges for the chemists of today. The so-called green technologies are looking for alternative ways to reduce drastic prerequisites for reactions. Among the proposed solutions, solvent-free conditions hold a leading position. So, it is now often claimed that 'the best solvent is no solvent'.[8]

Recently, the use of inorganic solid supports as catalysts has been developed for solvent free reactions, which has led to higher selectivity, milder conditions, and an easier experimental procedure. Such reagents not only simplify purification processes but also help to prevent release of reaction residues into the environment.[9]

In general 1,2,4-oxadiazoles are prepared in two steps by the *O*-acylation of an amidoxime with an activated carboxylic acid derivative, typically an active acyl chloride, followed by cyclization and cyclodehydration (Scheme 1).[10–17]

Recently, new methods have also been reported in the literature for the synthesis of these useful heterocycles. Among them, reactions that require heating for long periods of time, the use of microwave irradiation in the presence of solvent or under solvent-free conditions have been reported as well.[18–22] However, some of these methods suffer from harsh reaction conditions which exclude additional functionality on the oxadiazole. Many other methods are not one-pot procedures and require amidoximes as starting materials.



Scheme 1. Three-step sequence for the transformation of nitriles to 1,2,4-oxadiazoles.

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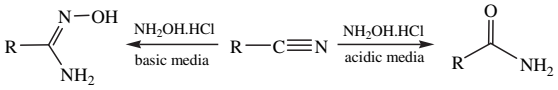
Adib and co-workers have reported a one-pot, three-component reaction between nitriles, hydroxylamine, and aldehydes under microwave irradiation and solvent-free conditions, which shows a huge improvement over previous methods, but aerial oxidation and higher temperature (160 °C) are required for the completion of the reaction.[23] Also, we knew that for the conversion of nitriles to amidoximes with hydroxylamine hydrochloride, basic media is required because in acidic media the nitrile would undergo hydrolysis to the corresponding amide (Scheme 2).[24] So, for a one-pot synthesis of 1,2,4-oxadiazoles using nitrile as starting material we need basic media.



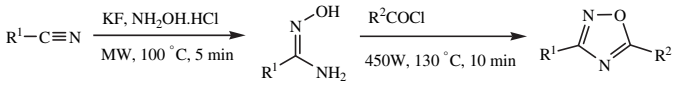
Scheme 2. Conversion of nitriles to amide and amidoxime in acidic and basic media.

Bases such as NaH or NaOEt at room temperature or pyridine with heating[25–29] and tetrabutylammonium fluoride[30,31] in dichloromethane have been reported for the cyclization and cyclodehydration of formed intermediates. Therefore, it seems that strong bases can promote this reaction. Consequently, we chose potassium fluoride as a strong base as well as a reagent for the sequesterisation of by-products. An aqueous potassium fluoride solution can dissolve by-products such as amidoxime intermediates at the end of the reaction and 1,2,4-oxadiazole can be separated by simple filtration.

Potassium fluoride has proven to be a versatile reagent in organic synthesis. Examples relevant to the discussion presented here include decarboxylation,[32] Michael addition,[33] and various Knoevenagel reactions.[34–37] As part of our ongoing interest on developing efficient methods for the synthesis of useful heterocycles,[38–44] we wish to report a general and convenient method for the synthesis of 1,2,4-oxadiazoles from readily available starting materials.

2. Results and discussions

Due to the beneficial pharmacological properties of certain molecules containing the 1,2,4-oxadiazole moiety, a new synthetic route, which could provide a greener procedure in which some aspects of green chemistry could be met is desirable. Our main strategy in this work was to develop a microwave-induced organic reaction enhancement methodology, which is extremely fast, cleaner than conventional reactions and lead to higher atom economy (less chemical waste). We have also found that the use of KF as a strong base and solid support for the synthesis of these compounds, starting from nitrile and hydroxylamine hydrochloride under solvent-free conditions is a cleaner methodology. Thus by combining these two facts, the synthesis of 3,5-disubstituted 1,2,4-oxadiazoles was performed under optimized condition (Scheme 3).



Scheme 3. Optimized condition for the synthesis of 3,5-disubstituted 1,2,4-oxadiazoles.

The reactions were carried out by first mixing the nitrile and hydroxylamine hydrochloride in the presence of potassium fluoride under microwave irradiation. After a few minutes and nearly complete conversion as indicated by TLC monitoring, to the corresponding amidoxime intermediate, acyl halide was added and the mixture again irradiated for the appropriate time. After completion of the reaction, water was added which dissolved the by-products and the desired 1,2,4-oxadiazole was easily separated by simple filtration.

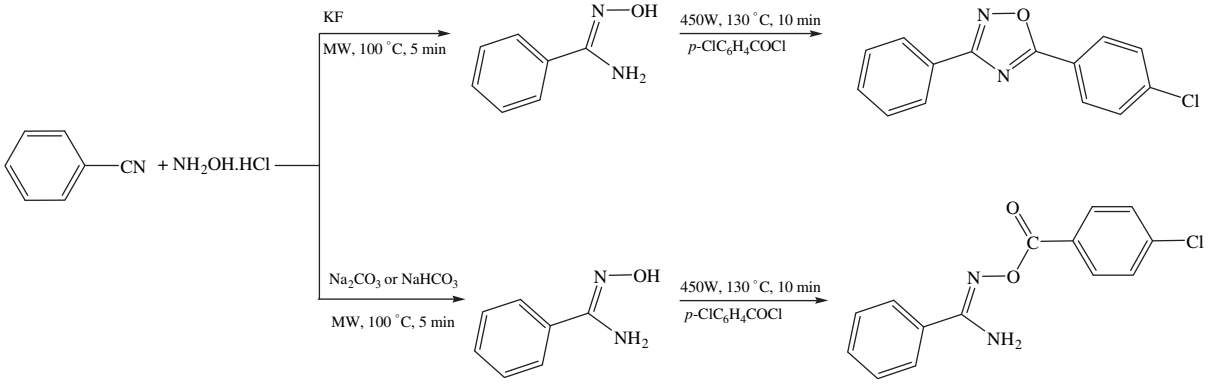
In order to find out what would be obtained using other bases, the reaction of benzonitrile with *p*-chlorobenzoyl chloride and hydroxylamine hydrochloride in the presence of sodium carbonate or sodium bicarbonate was performed under similar conditions, which gave only the corresponding *O*-acylamidoxime as the major product and yield for the required product was very low (Scheme 4). The same reaction was also performed at higher temperature and power, which again gave the *O*-acylamidoxime.

To understand the ability of this new methodology in the synthesis of 3,5- disubsituted 1,2,4-oxadiazoles, we chose a variety of structurally divergent nitriles and acyl chlorides possessing a wide range of functional groups. The results of which are summarized in Table 1. The electronic effects and the nature of the substituents on the nitrile and acyl chloride did not show strongly obvious effects in terms of yields.

Finally, we compared this method with methods that have been presented in the literature (Table 2). These results prove superior catalytic activity of KF as solid support and strong base in this transformation.

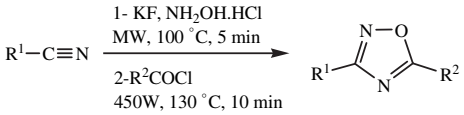
3. Conclusion

In summary, we have developed a microwave-enhanced, rapid, and efficient method for the synthesis of 3,5-disubstituted 1,2,4-oxadiazoles under solvent-free condition. The main advantages of this method are: (i) a one pot reaction with use of nitrile as starting material, (ii) solvent-free conditions, (iii) microwave irradiation, (iv) elimination of insoluble solid support such as MgO, Al_2O_3, which is an complicating factor in the work-up step, (v) avoiding



Scheme 4. Effect of condition on the formation of products.

Table 1
One-pot synthesis of 1,2,4-oxadiazoles under solvent-free condition using microwave irradiation



Entry	R^1	R^2	Yield[a] (%)
1	C_6H_5	C_6H_5	94
2	C_6H_5	p-$CH_3OC_6H_4$	92
3	C_6H_5	p-$NO_2C_6H_4$	92
4	C_6H_5	m-$NO_2C_6H_4$	91
5	C_6H_5	p-Cl C_6H_4	95
6	p-ClC_6H_4	p-Cl C_6H_4	95
7	p-BrC_6H_4	p-Br C_6H_4	93
8	p-ClC_6H_4	m-$NO_2C_6H_4$	93
9	p-$CH_3C_6H_4$	p-ClC_6H_4	92
10	p-BrC_6H_4	m-$NO_2C_6H_4$	97
11	o-ClC_6H_4	p-ClC_6H_4	95
12	o-ClC_6H_4	m-$NO_2C_6H_4$	89
13	2,4-$Cl_2C_6H_4$	p-$CH_3C_6H_4$	90
14	2,4-$Cl_2C_6H_4$	C_6H_4	89
15	p-BrC_6H_4	p-FC_6H_4	93
16	$C_6H_5CH_2$	p-$NO_2C_6H_4$	95
17	$C_6H_5CH_2$	p-FC_6H_4	92

[a] Isolated yield (over two steps, based on nitrile).

4.2. General experimental procedure for the preparation of 1,2,4-oxadizaole derivatives

A mixture of nitrile (2 mmol), hydroxylamine hydrochloride (2.2 mmol, finely ground), potassium fluoride (1 g) were mixed and ground in a mortar and pestle until a fine homogeneous powder was obtained (5 min). The mixture was then irradiated under microwave irradiation for 5 min at 100 °C. In the next step, the required acyl chloride (3 mmol) was added to the mixture, shaken for 5 min and irradiated again for 10 min at 450 W at 130 °C. Water (10 mL) was then added to the reaction mixture and the precipitated solids were filtered after vigorous stirring. The crude 1,2,4-oxadiazole was further recrystallized from 95% ethanol. Spectral data for selected known compounds are:

3-Phenyl-5-(*p*-methoxyphenyl)-1,2,4-oxadiazole[10](Table 1, Entry 2, 0.496 g, 92%) as a white solid, mp 107–108 °C; ν_{max} (KBr) 3028, 2919, 1608, 1558 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 3.87 (3H, s, *OMe*), 7.17–7.20 (2H, d, *J* 9 Hz, *CH*), 7.55–7.62 (3H, m, *CH*), 8.06–8.09 (2H, m, *CH*), 8.12–8.15 (2H, d, *J* 9 Hz, *CH*); δ_C (75 MHz, DMSO-d_6) δ 175.2, 168.1, 163.1, 131.5, 129.9, 129.2, 127.0, 126.2, 115.6, 55.6.

3-Phenyl-5-(*m*-nitrophenyl)-1,2,4-oxadiazole[10](Table 1, Entry 4, 0.491 g, 91%) as a white solid, mp 145–147 °C; ν_{max} (KBr) 2916, 1618, 1529, 1450 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 7.54–7.64 (3H, m, *CH*), 7.93 (1H, t, *J* 8.01 Hz, *CH*), 8.06–8.08 (2H, m, *CH*), 8.50–8.56 (2H, m, *CH*), 8.78–8.79 (1H, m, *CH*); δ_C (75 MHz, DMSO-d_6) 173.6, 168.4, 148.1, 133.8, 131.8, 131.4, 129.3, 127.5, 127.1, 125.7, 124.7, 122.4.

3,5-Bis(*p*-chlorophenyl)-1,2,4-oxadiazole[17](Table 1, Entry 6, 0.553 g, 95%) as a white solid, mp 183 °C; ν_{max} (KBr) 2921, 1606, 1555, 1478 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 7.67 (2H, d, *J* 8.4 Hz, *CH*), 7.74 (2H, d, *J* 8.4 Hz, *CH*), 8.09 (2H, d, *J* 9.0 Hz, *CH*), 8.19 (2H, d, *J* 9.0 Hz, *CH*); δ_C (75 MHz, DMSO-d_6) 174.8, 167.5, 138.3, 136.5, 129.8, 129.5, 128.9, 125.2, 124.8, 122.1.

3-(*p*-Chlorophenyl)-5-(*m*-nitrophenyl)-1,2,4-oxadiazole[26](Table 1, Entry 8, 0.560 g, 93%) as a milky solid, mp 167–168 °C; ν_{max} (KBr) 2925, 1621, 1597, 1540 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 7.63–7.67 (2H, d, *J* 9 Hz, *CH*), 7.94 (1H, t, *J* 8.1 Hz, *CH*), 8.09 (2H, d, *J* 9 Hz, *CH*), 8.51–8.57 (2H, m, *CH*), 8.79–8.80 (1H, m, *CH*); δ_C (75 MHz, DMSO-d_6) 173.8, 167.6, 148.1, 136.6, 133.9, 131.5, 129.5, 128.9, 127.6, 124.6, 122.2.

3-(*p*-Methylphenyl)-5-(*p*-chlorophenyl)-1,2,4-oxadiazole[27](Table 1, Entry 9, 0.479 g, 92%) as a white solid, mp 138–140 °C; ν_{max} (KBr) 3087, 2953, 1608, 1493 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 7.40 (2H, d, *J* 8.1 Hz, *CH*), 7.73 (2H, d, *J* 8.5 Hz, *CH*), 7.97 (2H, d, *J* 8.1 Hz, *CH*), 8.18 (2H, d, *J* 8.5 Hz, *CH*); δ_C (75 MHz, DMSO-d_6) 174.3, 168.2, 141.6, 138.0, 129.7, 129.6, 126.9, 123.1, 122.2.

Table 2
Comparison of different methods for the synthesis of 1,2,4-oxadiazole derivatives

Entry	Condition	Time	Temperature °C	Power level W	Yield %	Ref.
1	Solvent (DMF)[a]	6 h	115	—	45–69	16
2	Solid support[a,b]/ solvent (DMF, pyridine)	12 h	25–35	—	21–52	13
3	Solvent[a] (THF)	1–24 h	25–35	—	20–98	30
4	Solvent[a] (Toluene)	6–12 h	120	—	62–91	22
5	Solid support[a,b]	4 min	60	—	37–58	19
6	PASP[a,b,c]/solvent (THF)	15 min	150	—	90–98	20
7	Solvent free[d]/ air oxidation	3 min	160	—	92–97	23
8	Solid support[d]/ solvent free	2–4 min	—	600	41–70	24
9	Solid support[d,e]/ solvent free	10 min	130	450	89–97	This method

[a] These methods used amidoxime as starting material.
[b] These solid supports can act as an complicating in the aqueous work-up.
[c] Polymer-assisted solution-phase.
[d] These methods used nitrile as starting material.
[e] This solid support is dissolved in water at the end of reaction.

the use of silica gel for purification of the products, (vi) performing the work-up in aqueous media and (vii) higher yields and milder reaction conditions.

4. Experimental

4.1. General

Melting points were recorded on a Buchi *B*-540 apparatus and are uncorrected. IR spectra were recorded on an ABB Bomem Model FTLA 200–100 instrument. ^1H and ^{13}C NMR spectra were measured with a Bruker DRX-300 Avance spectrometer at 300 and 75 MHz using TMS as an internal standard. Chemical shifts are reported (δ) relative to TMS, and coupling constants (*J*) are reported in Hertz (Hz). Mass spectra were recorded on Shimadzu QP 1100 EX mass spectrometer with 70 eV ionization potential. Elemental analysis of new compounds was done with a Vario EL III 0 Serial No. 11024054 instrument and their results favorably agreed with calculated values. The reactions were performed in microwave oven (Delongi, model number CE290DN). Chemicals were obtained from Merck and Sigma–Aldrich and used without further purification.

3-(*p*-Bromophenyl)-5-(*m*-nitrophenyl)-1,2,4-oxadiazole[21](Table 1, Entry 10, 0.669 g, 97%) as a milky solid, mp 168–169 °C; ν_{max} (KBr) 2918, 1595, 1524, 1397 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 7.79–7.83 (2H, m, C*H*), 7.96 (1H, t, *J* 8.1 Hz, C*H*), 8.02–8.07 (2H, m, C*H*), 8.53–8.60 (2H, m, C*H*), 8.29 (1H, t, *J* 1.8 Hz, C*H*); δ_C (75 MHz, DMSO-d_6) 173.9, 167.7, 148.2, 133.9, 132.4, 131.5, 129.1, 127.6, 125.5, 124.9, 124.6, 122.5.

3-(*o*-Chlorophenyl)-5-(*p*-chlorophenyl)-1,2,4-oxadiazole[12](Table 1, Entry 11, 0.553 g, 95%) as a white solid, mp 154–156 °C; ν_{max} (KBr) 2950, 1612, 1486, 1467 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 7.57 (1H, dt, *J* 7.0, 1.0 Hz, C*H*), 7.63 (1H, dt, *J* 7.5, 1.7 Hz, C*H*), 7.70–7.71 (1H, m, C*H*), 7.75 (2H, d, *J* 8.5 Hz, C*H*), 7.99(1H, dd, J 7.6, 0.9 Hz, C*H*), 8.20 (2H, d, *J* 8.5 Hz, C*H*); δ_C (75 MHz, DMSO-d_6) 174.0, 167.1, 138.2, 132.6, 132.1, 131.7, 130.7, 129.7, 127.6, 125.2, 121.9.

3-(*o*-Chlorophenyl)-5-(*m*-nitrophenyl)-1,2,4-oxadiazole[26](Table 1, Entry 12, 0.537, 89%) as a pale yellow solid, mp 154–156 °C; ν_{max} (KBr) 3082, 2873, 1616, 1594 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 7.59 (1H, dt, *J* 4.4, 8 Hz, C*H*), 7.64 (1H, dt, *J* 1.4, 7.4 Hz C*H*), 7.71 (1H, dd, *J* 1.1, 7.2 Hz, C*H*), 7.96 (1H, t, *J* 7.3 Hz, C*H*), 8.03 (1H, dd, *J* 1.5, 6.4 Hz, C*H*), 8.54–8.60 (2H, m, C*H*), 8.83 (1H, s, C*H*); δ_C (75 MHz, DMSO-d_6) 173.2, 167.3, 148.2, 133.9, 132.8, 132.2, 131.8, 131.5, 130.8, 127.7, 127.6, 125.0, 124.5, 122.5.

3-(2,4-Dichlorophenyl)-5-(*p*-methylphenyl)-1,2,4-oxadiazole[18] (Table 1, Entry 13, 0.542 g, 90%) as a yellow solid, mp 145–146 °C; ν_{max} (KBr) 3025, 1616, 1591, 1555 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 3.22 (3H, s, CH_3), 7.44 (2H, d, *J* 8.03 Hz, C*H*), 7.62 (1H, dd, *J* 8.44, 1.83 Hz, C*H*), 7.57 (1H, d, *J* 1.92, C*H*), 8.01 (1H, d, *J* 9.00 Hz, C*H*), 8.03 (2H, d, *J* 8.4 Hz, C*H*); δ_C (75 MHz, DMSO-d_6) 174.9, 166.1, 143.7, 136.3, 133.1, 132.7, 130.2, 129.9, 127.7, 124.3, 120.2, 21.0.

3-(2,4-Dichlorophenyl)-5-(phenyl)-1,2,4-oxadiazole[24](Table 1, Entry 14, 0.519 g, 89%) as a yellow solid, mp 141–143 °C; ν_{max} (KBr) 3070, 1609, 1592, 1568 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 7.64–7.69 (3H, m, C*H*), 7.72–7.77 (1H, m, C*H*), 7.90 (1H, d, *J* 2.0 Hz, C*H*), 8.03 (1H, d, *J* 8.4 Hz, C*H*), 8.16–8.21 (2H, m, C*H*); δ_C (75 MHz, DMSO-d_6) 175.0, 166.4, 136.6, 133.5, 133.2, 133.0, 130.4, 129.6, 128.1, 128.0, 124.4, 123.0.

Spectral data for new compounds are: 3-(*p*-bromophenyl)-5-(*p*-flourophenyl)-1,2,4-oxadiazole (Table 1, Entry 15, 0.634 g, 93%) as a white solid, mp 177–179 °C; Found: C, 52.47; H, 2.49; N, 8.75. $C_{14}H_8BrFN_2O$ requires C, 52.68; H, 2.51; N, 8.78; ν_{max} (KBr) 2924, 1612, 1500, 1407 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 7.01 (1H, s, C*H*), 7.34 (1H, s, C*H*), 7.49–8.00 (4H, m, C*H*), 8.24 (2H, s, C*H*); δ_C (75 MHz, DMSO-d_6) 174.7, 167.5, 165.9, 132.3, 132.3, 128.9, 125.2, 119.9, 116.8, 115.4; MS(70 eV) *m*/*z* 320 (77 M^++2), 318 (75 M^+), 199(85), 197(85), 123(74), 90 (76%).

3-Benzyl-5-(*p*-nitrophenyl)-1,2,4-oxadiazole (Table 1, Entry 16, 0.530 g, 95%) as a white solid, mp 139–141 °C; Found: C, 63.75; H, 4.21; N, 14.41. $C_{15}H_{11}N_3O_3$ requires C, 64.06; H, 3.91; N, 14.94; ν_{max} (KBr) 3020, 2922, 1607, 1518 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 4.20 (2H, s, CH_2), 7.23–7.37 (5H, m, C*H*), 8.31 (2H, d, *J* 9 Hz, C*H*), 8.38 (2H, d, *J* 9 Hz, C*H*); δ_C (75 MHz, DMSO-d_6) 173.4, 170.3, 149.8, 135.4, 129.3, 128.6, 128.5, 126.9, 124.5, 31.33; MS(70 eV) *m*/*z* 281 (63M+), 150(100), 131(91), 91(50%).

3-Benzyl-5-(*p*-flourophenyl)-1,2,4-oxadiazole (Table 1, Entry 17, 0.463 g, 92%) as a white solid, mp 107–108 °C; Found: C, 70.21; H, 4.20; N, 10.58. $C_{15}H_{11}FN_2O$ require C, 70.86; H, 4.33; N, 11.02; ν_{max} (KBr) 3031, 2926, 1612, 1567 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 4.15 (2H, s, CH_2), 7.24–7.32 (5H, m, C*H*), 7.38–7.46 (2H, m, C*H*), 8.08–8.15 (2H, m, C*H*); δ_C (75 MHz, DMSO-d_6) 174.2, 169.9, 166.4, 163.1, 135.6, 130.7, 130.5, 128.9, 128.5, 126.8, 120.0, 120.0, 116.9, 116.6, 31.3; MS(70 eV) *m*/*z* 254 (59M+), 123(100), 103(58), 95(67%).

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