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Friedländer synthesis of poly-substituted quinolines in the presence of dodecylphosphonic acid (DPA) as a highly efficient, recyclable and novel catalyst in aqueous media and solvent-free conditions

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ABSTRACT

Poly-substituted quinolines were synthesized in the presence of a catalytic amount of dodecylphosphonic acid (DPA) in aqueous media and solvent- free conditions. The reactions proceed very well under relatively mild conditions, and DPA can be recycled.

1. Introduction

Quinolines and their derivatives are very important biological compounds that occur widely in natural products. Some members of this family have displayed interesting physiological activities and found attractive applications in medicinal chemistry, being used as antimalarial,[1] antibacterial,[2] anti-inflammatory,[3] antihypertensive,[4] and antiplatelet agents, and as tyrosine kinase inhibiting agents.[5,3a,6,7] In addition, quinolines are valuable synthons used in a variety of nano-structures and meso-structures with enhanced electronic and photonic functions.[8] Also, quinolines have been employed in the study of bioorganic and bioorganometallic processes.[9] There has been tremendous interest in developing efficient methods for quinoline synthesis.[10,11] Among these methods, the Friedländer annulation is still one of the most simple and straightforward procedures for the synthesis of poly-substituted quinolines.

The Friedländer quinoline synthesis involves a condensation reaction between an aromatic *ortho*-aminoaryl ketone or aldehyde with an aldehyde or ketone containing an α-methylene group, and then a cyclodehydration.[12] This reaction is generally carried out by refluxing either an aqueous or an alcoholic solution of reactants in the presence of a base at high temperature, 150–220 °C, in the absence of a catalyst.[13] However, under basic- or thermal-catalysis conditions, *ortho*-aminobenzophenone does not react with simple ketones, such as cyclohexanone and β-keto esters.[14] Brønsted acid catalysts such as hydrochloric acid, sulfuric acid, *p*-toluenesulfonic acid, and polyphosphoric acid have been widely used.[15] Also, modified methods, employing Lewis acid[16] and inorganic salt catalysts,[15] ionic liquids,[17] microwave conditions,[18] and molecular iodine,[19] have been reported for this reaction. Many of these procedures have significant drawbacks such as low yields of the products, long reaction times, and harsh reaction conditions. Moreover, this reaction is usually carried out in polar and in aprotic solvents such as acetonitrile, THF, DMSO, and DMF leading to tedious work-up procedures. The main disadvantage of almost all existing methods is that the catalysts cannot be recovered during the work-up procedure. Thus, the development of simple, convenient, and environmentally benign methods for the synthesis of quinolines is still required. For these reasons, the use of solid and heterogeneous catalysts in organic reactions in aqueous media and solvent-free conditions, have drawn the attention of chemists for the Friedländer quinoline synthesis. A review of the literature showed that there is only one report on the use of a Brønsted acid as a catalyst in the Friedländer reaction in pure water.[20] The Brønsted acid, in this report, was hydrochloric acid (1N, pH 1), which is a strong, volatile, and corrosive acid. Also, it was found that sulfamic acid[21] and *p*-toluenesulfonic acid[18b] are the only Brønsted acids that have been used for the synthesis of quinolines via the Friedländer protocol under solvent-free conditions.

To overcome the problems associated with hydrochloric acid, herein, we describe the utility of dodecylphosphonic acid (Fig. 1), which is a mild, non-volatile and non-corrosive organic acid, as an efficient solid surfactant-type Brønsted acid catalyst in pure water and solvent-free conditions for the Friedländer reaction.

Despite the applications of dodecylphosphonic acid (DPA) as a fire proofing agent,[22] an activator of 5-lipoxygenase,[23] an adjuvant for positive electrostatic developers,[24] germicides,[25] and glycolysis inhibitors,[26] there is no report on its application in organic

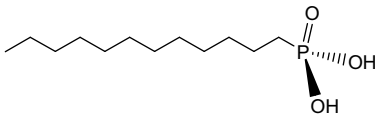

Figure 1.

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reactions. So, due to its amphipathic structure and low acidity, we decided to apply DPA as a mild solid surfactant-type Brønsted acid catalyst in the Friedländer synthesis of quinolines in pure water (method A) and solvent-free conditions (method B). In order to optimize the reaction conditions in aqueous media, the effect of temperature and amount of the Brønsted acid (5 mol %, 10 mol %, and 20 mol %, respectively) were investigated on the reaction of 2-aminobenzophenone and ethyl acetoacetate in the presence of DPA (Scheme 1).

These studies showed (a) the reaction did not occur at all at a temperature lower than 90 °C, and (b) the reaction did not proceed in the absence of catalyst and gave the best results in 10 mol % of DPA. A lower amount of DPA, 5 mol %, led to smaller yield and a higher amount, 20 mol %, did not show any improvement in the yield or reaction time.

With optimized conditions, we next studied the generality and efficiency of DPA in pure water and solvent-free conditions in several example reactions (Scheme 2).

Various 1,3-diketones such as 1,3-cyclohexadione, 1,3-cyclopentadione, 2,4-pentadione, acetoacetophenone, and cyclic ketones including cyclohexanone and cyclopentanone reacted with 2-aminobenzophenone to produce, efficiently, the corresponding substituted quinolines (Table 1).

In addition, substituted 2-aminoaryl ketones such as 2-aminoacetophenone and 2-amino-5-chlorobenzophenone reacted smoothly with α-methylene ketones, Table 1, to produce a range of quinoline derivatives. In all cases, the products were isolated by simple extraction with DCM. The crude products were purified and recrystallized from a mixture of diethyl ether/*n*-hexane or by silica gel column chromatography. In the case of reactions in aqueous media, the catalyst was separated by evaporation of water, and reused directly without any activation. For example, the reaction of 2-aminobenzophenone and ethyl acetoacetate afforded the corresponding quinoline in 85%, 83%, and 80% yields over three runs.

Furthermore, both methods A and B were clean, free of side reactions, and thus provided easy access to substituted quinolines with good to excellent yields in relatively short times. Also, these methods had simple, experimental, and work-up procedures.

For comparison of these methods with the aqueous hydrochloric acid method,[20] we ran several reactions with the same substrates, the corresponding data are shown in Table 2. This study showed, in general, that DPA gives comparable and in some of the cases, including the reactions of 2-aminobenzophenone and 5-chloro-2-aminobenzophenone with cyclopentanone, cyclohexanone, and 1-phenyl-butan-1,3-dione, better results. However, in most of the examples, the use of DPA under solvent-free conditions produced better yields.

In summary, we have reported the first application of DPA in organic synthesis, and introduced two new mild and efficient methods, A and B, for the synthesis of quinolines and polycyclic quinolines via Friedländer condensation of 2-aminoarylketones with α-methylene ketones using DPA as a recyclable catalyst in pure water and in solvent-free procedures. The easy preparation of DPA, (it is also commercially available) along with the simple experimental procedure, and the ease of recovery and reuse of this novel catalyst makes these methods simple and convenient for the synthesis of quinolines and their derivatives.

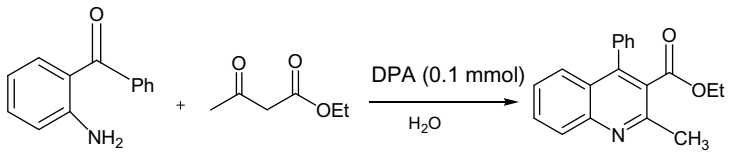
2. General procedure

2.1. Preparation of dodecylphosphonic acid (DPA)

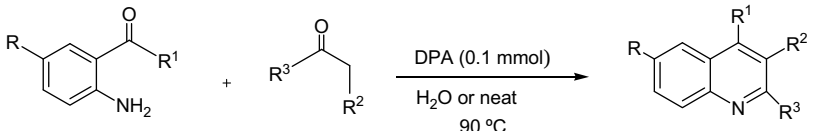
A mixture of 5 ml (0.02 mol) of 1-bromododecane and 3.9 ml (0.02 mol) of triethylphosphite was heated for 4 h at 160–190 °C with continuous removal of the ethyl bromide formed. Then 21 ml of HBr (40%) was added at room temperature, and the mixture was refluxed with stirring for 3 h. Next, HBr and water were removed by simple distillation to afford DPA as a yellow solid, which was washed with pentane and recrystallised from hexane to give the pure product as colorless crystals. Mp 98 °C (Lit. 98–99 °C).[27]

2.2. Preparation of quinolines and polyheterocycles under aqueous media (method A)

A mixture of 2-amino-substituted ketone (**1a, 1b, 1c**, 1 mol) and ketone (**2**, 1.5 mol) was added to 0.1 mol of dodecylphosphonic acid (DPA) in 10 ml of water. The reaction mixture was heated at 90 °C with stirring for the appropriate time mentioned in Table 1. The extent of reaction was monitored by TLC. The crude mixture was extracted with dichloromethane (2 × 10 ml) and the combined organic layer was dried over anhydrous calcium chloride and filtered. Evaporation of the solvent gave a crude product, which was purified by silica gel column chromatography with petroleum ether (bp 60 °C) and ethyl acetate (4:1) to give the pure product. Distillation of the aqueous layer allowed the DPA to be recovered and used again.



Scheme 1.



1a; R=H, R^1=Ph

1b; R=Cl, R^1=Ph

1c; R=H, R^1=CH_3

2

3a-o

Scheme 2.

Table 1
DPA-catalyzed Friedländer reaction between 2-aminoaryl ketones and various α-methylene ketones

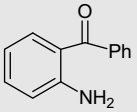
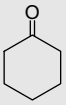
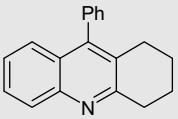
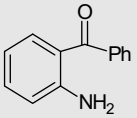
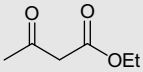
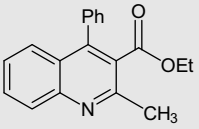
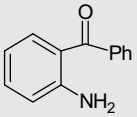
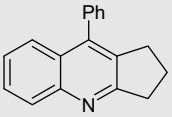
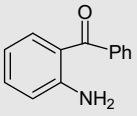
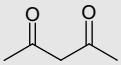
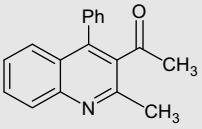
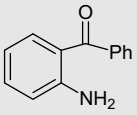
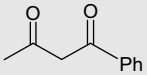
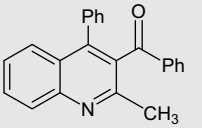
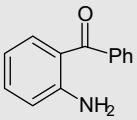
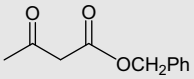
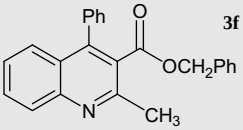
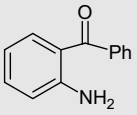
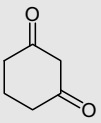
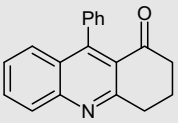
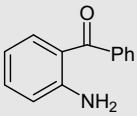
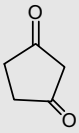
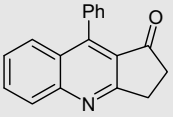
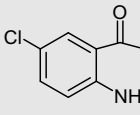
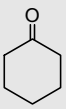
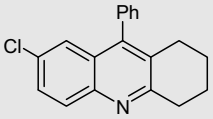
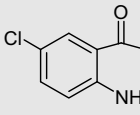
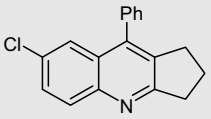
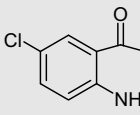
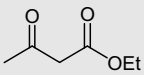
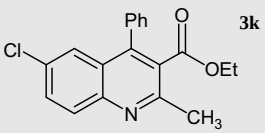
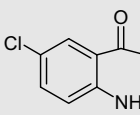
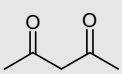
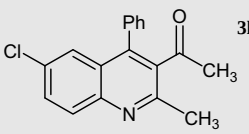
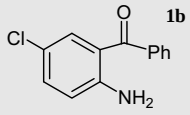
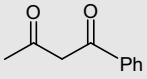
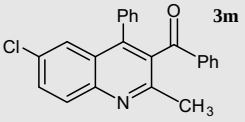
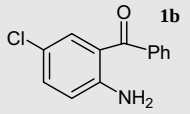
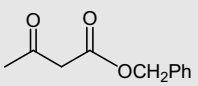
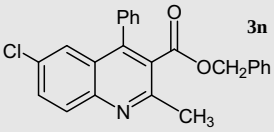
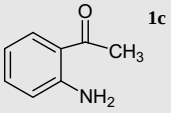
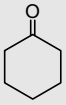
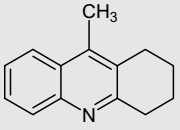
Entry	2-Aminoketone **1a–c**	Ketone **2**	Quinoline **3a–o**	Mp (°C) Found (Lit.)	Yield[a] (%) (A/B)	Time (min) (A/B)
1	 **1a**		 **3a**	138–141	78/95	60/43
2	 **1a**		 **3b**	93 (97)[17]	85/90	140/30
3	 **1a**		 **3c**	133–135 (135)[28]	65/70	90/33
4	 **1a**		 **3d**	112–115 (114)[29]	73/90	54/45
5	 **1a**		 **3e**	133–134	69/89	41/46
6	 **1a**		 **3f**	90–93	70/75	70/20
7	 **1a**		 **3g**	151–153	52/95	75/16
8	 **1a**		 **3h**	171–175	53/85	120/14
9	 **1b**		 **3i**	159 (163)[14]	72/97	35/10
10	 **1b**		 **3j**	100 (105)[14]	70/91	162/25
11	 **1b**		 **3k**	102–104 (108)[14]	82/98	96/20
12	 **1b**		 **3l**	154 (151)[14]	58/93	45/14

Table 1 (*continued*)

Entry	2-Aminoketone **1a–c**	Ketone **2**	Quinoline **3a–o**	Mp (°C) Found (Lit.)	Yield[a] (%) (A/B)	Time (min) (A/B)
13	 **1b**		 **3m**	209–211	71/90	60/49
14	 **1b**		 **3n**	121–123	70/89	39/
15	 **1c**		 **3o**	78 (78)[14]	50/88	127/34

[a] Isolated yields.

2.3. Preparation of quinolines and polyheterocycles under solvent-free conditions (method B)

A mixture of 2- amino-substituted ketone (**1a, 1b, 1c**, 1 mol), ketone (**2**, 1.5 mol), and dodecylphosphonic acid (DPA) (0.1 mol) was heated at 90 °C with stirring for the appropriate time mentioned in Table 1. The extent of reaction was monitored by TLC. The crude mixture was extracted with dichloromethane (10 ml), and the combined organic layer was dried over anhydrous calcium chloride and then filtered. Evaporation of the solvent gave the crude product, which was purified by silica gel column chromatography with *n*-hexane and ethyl acetate (4:1) to give the pure product.

Known products were characterized by comparison of their melting point and spectra with authentic samples. New compounds were characterized by melting point, IR, ^{1}H NMR, ^{13}C NMR, CHN, and mass spectral analysis as follows.

2.3.1. 9-Phenyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinoline (3a)

Pale yellow solid, mp 138–141 °C. IR (KBr): 3068, 2931, 2862, 1575, 1485, 761, 705 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.72 (m, 2H), 1.84 (m, 2H), 2.52 (t, J = 6.3 Hz, 2H), 3.12 (t, J = 6.59 Hz, 2H), 7.16 (m, 1H), 7.23 (m, 1H), 7.40 (m, 6H), 7.93 (d, J = 8.3 Hz, 1H). ^{13}C NMR (63 MHz, $CDCl_3$): δ 22.8, 22.9, 27.9, 34.1, 125.1, 125.5, 126.4, 127.5, 128.1, 128.4, 128.8, 136.9, 146.2, 146.5, 158.8. EIMS: *m/z* (%): 259 (M^+, 100), 230 (13.1), 203 (1.3), 182 (13.0), 149 (4.6), 121 (10.6), 77 (8.2), 57 (17.2).

2.3.2. (2-Methyl-4-phenylquinoline-3-yl)(phenyl)methanone (3e)

Pale yellow solid, mp 133–134 °C. IR (KBr): 3058, 2912, 1674, 1577, 767, 702 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.56 (s, 3H), 7.18 (m, 7H), 7.35 (m, 2H), 7.54 (m, 3H), 7.68 (m, 1H), 8.09 (d, J = 8.4 Hz, 1H). ^{13}C NMR (63 MHz, $CDCl_3$): δ 24.03, 125.08, 126.04, 126.30, 127.81, 128.06, 128.24, 128.71, 129.04, 129.80, 129.89, 132.24, 133.31, 134.61, 136.95, 145.34, 147.59, 154.40, 197.48. EIMS: *m/z* (%): 323 (M^+, 19), 322 (100), 306 (9), 246 (48), 218 (26), 217 (40), 189 (6), 176 (27), 105 (38), 77 (66), 51 (13).

2.3.3. Benzyl 2-methyl-4-phenylquinoline-3-carboxylate (3f)

White solid, mp 90–93 °C. IR (KBr): 3070, 2916, 1720, 1566, 1488, 887, 763 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.76 (s, 3 H), 5.03 (s, 2H), 7.08 (m, 2H), 7.36 (m, 3H), 7.41 (m, 2H), 7.42 (m, 4H), 7.44 (d, J = 10.3 Hz, 1H), 7.71 (m, 1H), 8.09 (d, J = 8.4 Hz, 1H). ^{13}C NMR (63 MHz, $CDCl_3$): δ 23.8, 67.28, 124.87, 126.22, 126.27, 126.87, 128.10, 128.12, 128.24, 128.31, 128.37, 128.66, 129.14, 130.07, 134.59, 135.28, 145.98, 147.51, 154.29, 168.11. EIMS: *m/z* (%): 353 (M^+, 25), 308 (13), 246 (18), 218 (10), 149 (20), 107 (2), 91 (66), 77 (5), 57 (100). Anal. Calcd for $C_{24}H_{19}NO_2$: C, 81.58; H, 5.38; N, 3.96. Found: C, 81.34; H, 5.51; N, 3.89.

2.3.4. 9-Phenyl-3,4-dihydroacridin-1(2*H*)-one (3g)

Pale yellow solid, mp 151–153 °C. IR (KBr): 3039, 2974, 1689, 1550, 1481, 771, 702 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.19 (m, 2H), 2.62 (t, J = 6.32 Hz, 2H), 3.29 (t, J = 6.17 Hz, 2H), 7.10 (m, 2H), 7.36 (m, 5H), 7.67 (m, 1H), 7.99 (d, J = 8.45 Hz, 1H). ^{13}C NMR (63 MHz, $CDCl_3$): δ 21.35, 34.59, 40.57, 123.63, 126.20, 127.32, 127.80, 127.88, 128.00, 128.30, 131.50, 137.42, 148.43, 151.15, 161.97, 197.64. EIMS: *m/z* (%): 273 (M^+, 87), 272 (98), 245 (39), 244 (100), 217 (36), 189 (19), 176 (9), 137 (21), 127 (11), 120 (22), 108 (26), 94 (22), 77 (4), 51 (4), 43 (4).

2.3.5. 9-Phenyl-2,3-dihydrocyclopenta[*b*]quinolin-1-one (3h)

Pale yellow solid, mp 171–175 °C. IR (KBr): 2931, 1712, 1566, 833, 771 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.74 (m, 2H), 3.36 (m, 2H), 7.27 (m, 2H), 7.44 (m, 4H), 7.73 (m, 2H), 8.04 (d, J = 8.42 Hz, 1H). ^{13}C NMR (63 MHz, $CDCl_3$): δ 28.43, 36.53, 123.59, 126.34, 126.42, 127.87, 128.17, 128.61, 128.79, 129.15, 130.65, 131.91, 132.96, 148.74, 151.0, 170.72, 203.28. EIMS: *m/z* (%): 259 (M^+, 85), 258 (100), 230 (38), 189 (3), 176 (19), 129 (19), 114 (32), 100 (19), 84 (16), 77 (4), 51 (3). Anal. Calcd for $C_{18}H_{13}NO$: C, 83.39; H, 5.02; N, 5.40. Found: C, 82.88; H, 5.08; N, 5.11.

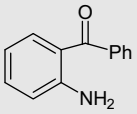
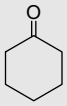
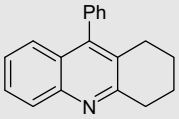
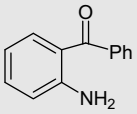
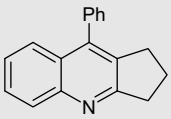
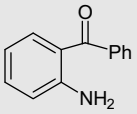
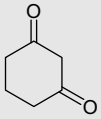
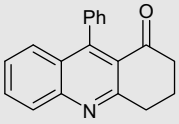
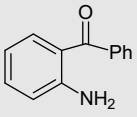
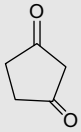
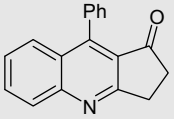
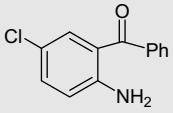
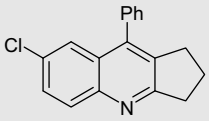
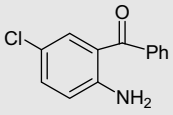
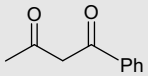
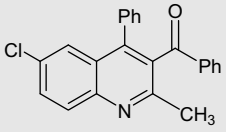
2.3.6. (6-Chloro-2-methyl-4-phenylquinolin-3-yl)(phenyl) methanone (3m)

White solid, mp 209–211 °C. IR (KBr): 2923, 2846, 1674, 1234, 786, 702 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.54 (s, 3H), 7.18 (m, 7H), 7.38 (m, 1H), 7.48 (m, 3H), 7.62 (d, J = 2.28 Hz, 1H), 7.99 (d, J = 8.9 Hz, 1H). ^{13}C NMR (63 MHz, $CDCl_3$): δ 23.96, 124.80, 125.91, 128.03, 128.30, 128.38, 129.01, 129.69, 130.36, 130.78, 132.24, 133.00, 133.48, 133.91, 136.67, 144.56, 145.96, 154.84, 199.95. EIMS: *m/z* (%): 357 (M^+, 58), 280 (24), 217 (25), 176 (18), 149 (49), 105 (43), 77 (45), 71 (52), 57 (75), 43 (100). Anal. Calcd for $C_{23}H_{16}ClNO$: C, 77.20; H, 4.47; N, 3.91. Found: C, 77.68; H, 4.76; N, 3.48.

2.3.7. Benzyl 6-chloro-2-methyl-4-phenylquinoline-3-carboxylat*e* (3n)

White solid, mp 121–123 °C. IR (KBr): 3078, 3039, 1720, 1581, 1481, 1226, 833, 740, 709 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ

Table 2
Comparison of the isolated yields obtained in the presence of DPA in water and solvent-free conditions, and HCl (1 N)

Entry	2-Aminoketone	Ketone	Quinoline	HCl (aq)[a] yield (%)	DPA(aq)[b] yield (%)	DPA[c] yield (%)
1				—	70	91
2				10	65	70
3				95	52	95
4				90	53	85
5				30	70	91
6				40	71	90

[a] HCl (1 N), H_2O, 60 °C.
[b] DPA (0.1 mmol), H_2O, 90 °C.
[c] DPA (0.1 mmol), solvent-free, 90 °C.

2.66 (s, 3H), 4.95 (s, 2H), 7.00 (m, 2H), 7.20-7.26 (m, 5H), 7.37 (m, 3H), 7.46 (m, 1H), 7.58 (m, 1H), 7.94 (d, J = 8.95 Hz, 1H). ^{13}C NMR (63 MHz, $CDCl_3$): δ 23.72, 67.42, 125.00, 125.68, 126.92, 127.04, 127.65, 128.21, 128.28, 128.32, 128.41, 128.63, 129.03, 130.32, 130.96, 132.16, 134.43, 134.55, 145.88, 154.68, 167.74. EIMS: *m/z* (%): 387 (M^+, 32), 342 (14), 310 (4), 296 (4), 280 (12), 252 (5), 217 (12), 189 (5), 176 (10), 107 (2), 91 (100), 77 (6), 65 (12), 51 (3).

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