Synthesis of Pyrazoles by a One-Pot Tandem Cyclization–Dehydrogenation Approach on Pd/C/K-10 Catalyst

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Abstract: A novel one-pot synthesis of substituted pyrazoles from chalcones and hydrazines via a tandem cyclization–dehydrogenation approach is described. This process is based on the use of a bifunctional noble-metal/solid-acid catalyst, Pd/C/K-10 montmorillonite and microwave irradiation under solvent-free conditions. The cyclization of chalcones with hydrazines readily takes place on the strong solid acid while the presence of the metal ensures the formation of the aromatic product through dehydrogenation. The reactions are complete in 30 minutes providing good yields and high selectivities.

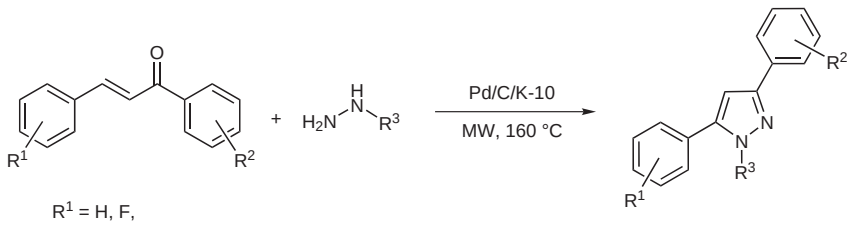
Key words: chalcones, hydrazines, bifunctional catalysis, microwave heating, pyrazoles

Heteroaromatic compounds possess a wide range of biological effects and thus attract significant attention.[1] Pyrazoles, an important group among heteroaromatics are particularly known for their wide range of biological activity.[2] They are used as anticancer agents,[2a,b] show anti-inflammatory and molluscicidal activity,[2c] are estrogen receptor agonists,[2d] and are active cyclooxygenase-2 inhibitors.[2e] Due to the importance of these compounds, extended efforts were made toward their synthesis. The several methods available for the synthesis of these heteroaromatics include cycloadditions and cyclocondensations.[3] As these methods may result in isomers the interest turned to regioselective cyclizations.[3a,4] Many of these methods provide excellent results; however, they usually involve multiple steps. In most regioselective methods the process involves a cyclization and an oxidation step to ensure the formation of the heteroaromatic system.[3a,4] These oxidation methods require stoichiometric amount of oxidant, which is not preferable under the tightening of environmental regulations. Considering the importance of pyrazoles, the development of sustainable green synthetic methods is highly desirable.

Our basic idea is to combine the cyclization and oxidation reactions into a two steps/one-pot approach by using a special bifunctional noble-metal/solid-acid catalyst. In earlier papers we have already described the fundamental advantages of such catalytic systems. Applications include the chemoselective C=O hydrogenation of α,β-unsaturated carbonyl compounds[5] and reduction of C=O bonds to CH_2,[6] a green alternative to the traditional Clemmensen reduction.

The major thrust of this work is to provide an environmentally benign one-pot approach for the synthesis of pyrazoles using the combination of bifunctional (metal/acid) heterogeneous catalysis and microwave irradiation. The presence of solid acid will ensure rapid cyclization, while the metal effectively dehydrogenates the dihydropyrazoles to the final product. The schematic depiction of the process is shown in Scheme 1.

To test our hypothesis we have chosen the cyclization of chalcone with phenylhydrazine as a probe reaction. Based on our experience, we have selected K-10 montmorillonite as a solid-acid catalyst,[7] while Pt and Pd were selected as metals for the dehydrogenation.[8] As a first step, several supported metal catalysts have been studied. The reaction was carried out using a general procedure that followed the common practice for solvent-free reactions. All reactions were carried out in a CEM Discover microwave reactor at constant temperatures. The reactants and catalyst were mixed together with the minimum amount of dichloromethane. Evaporation of the solvent gave a dry



R^1 = H, F,
R^2 = H, OMe, F, Me,
R^3 = Me, Ph, 3-$CF_3C_6H_4$, 4-$NO_2C_6H_4$

Scheme 1 Microwave-assisted one-pot synthesis of pyrazoles from chalcones and hydrazines by bifunctional Pd/C/K-10 catalyst

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Table 1 Effect of Catalyst on the Microwave-Assisted Synthesis of Pyrazoles from Chalcone and Phenylhydrazine[a]

Entry	Catalyst	Yield (%)[b]	Pyrazole (%)[c]	Dihydropyrazole (%)[c]
1	5% Pt/Al_2O_3	85	89	11
2	5% Pd/Al_2O_3	35	98	–
3	5% Pd/K-10	90	41	59
4	10% Pt/K-10	91	90	10
5	5% Pt/C	25	95	5
6	K-10	92	77	23
7	10% Pd/C	50	99	–
8	10% Pd/C/K-10	92	92	8

[a] Conditions: 160 °C, 200 W, 20 min, ratio of chalcone:phenylhydrazine = 1:1.
[b] Determined by GC-MS, based on chalcone.
[c] Selectivity was determined by GC.

mixture that was transferred to a reaction vial and irradiated for a specified time at the given temperature. The results are summarized in Table 1.

The data show that the reaction is strongly catalyst-dependent. Catalysts with neutral or moderately acidic supports give high selectivity toward the aromatic product. The overall yields, however, are low, due to their inability to efficiently catalyze the cyclization process. It appears that the K-10 montmorillonite itself is able to provide an aromatic product, although with moderate selectivity. The combination of the metal and K-10 gave the best results. In terms of the metal, both Pt and Pd are effective in the dehydrogenation step, although Pd gives higher selectivities toward pyrazoles. Based on these results, we have selected Pd/C/K-10, a mechanical mixture of 5% Pd/C and K-10 montmorillonite, for further studies. Another reason for selecting this catalyst is the commercial availability of its components. This feature makes the process easily reproducible compared to tailored Pt or Pd/K-10 catalyst.

As a next step, two other parameters, such as the ratio of reactants and reaction time were examined to optimize our probe reaction. The results are collected in Table 2.

As the data indicate, the 1:1.5 chalcone-to-phenylhydrazine ratio is the most beneficial for the reaction. Excess phenylhydrazine appears to be necessary for high yields. Although almost quantitative cyclization occurs at over 50% phenylhydrazine excess, it suppresses the dehydrogenation process. This is probably due to the hydrogen donor properties of hydrazines. We have also observed that longer reaction times favor the formation of aromatic products. Reaction times over 30 minutes, however, resulted in product decomposition.

After selecting the catalyst, reaction time, and reactant ratio for the reaction (Scheme 1) we optimized the reaction temperature. The results are tabulated in Table 3.

Table 2 Effects of Reactant Ratio and Reaction Time on the Microwave-Assisted Synthesis of Pyrazoles from Chalcone and Phenylhydrazine on Pd/C/K-10 Catalyst[a]

Entry	Ratio of **1**:**2**	Time (min)	Yield (%)[b]	Pyrazole (%)[c]	Dihydropyrazole (%)[c]
1	1:0.8	20	60	85	15
2	1:1	20	75	89	11
3	1:1.5	10	81	69	31
4	1:1.5	20	96	92	8
5	1:1.5	30	96	99	1
6	1:2	20	96	58	42

[a] Conditions: 160 °C, 200 W.
[b] Determined by GC-MS, based on chalcone.
[c] Selectivity was determined by GC.

Table 3 Effect of Temperature on the Microwave-Assisted Synthesis of Pyrazoles from Chalcone and Phenylhydrazine on Pd/C/K-10 Catalyst[a]

Entry	Temp (°C)	Yield (%)[b]	Pyrazole (%)[c]	Dihydropyrazole (%)[c]
1	100	94	25	75
2	120	93	76	33
3	140	89	92	8
4	160	96	92	8
5	180	90	98	2

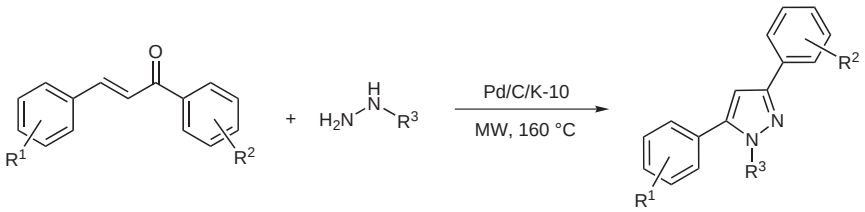
[a] Conditions: 160 °C, 200 W, 20 min, ratio of chalcone:phenylhydrazine = 1:1.5.
[b] Determined by GC-MS, based on chalcone.
[c] Selectivity was determined by GC.

The data indicate that the temperature does not significantly affect the cyclization or the conversion of the starting materials. In contrast, the dehydrogenation step shows strong temperature dependence; below 140 °C, the aromatization is not satisfactory. The analysis of these data suggested the use of 160 °C for further reactions.

Based on the above data (Tables 1– 3), we concluded that the reaction takes place in very high yields and excellent selectivities under optimized conditions, although adjustment in the reaction time may be necessary when using other reactants. To widen the scope of the approach, we have selected several chalcones and phenylhydrazines and carried out the reaction in order to synthesize a variety of substituted pyrazoles. The results are summarized in Table 4.

The results show that the reactions took place efficiently; the yields and selectivities are excellent with a few exceptions. The substituents show significant effect on neither the yields nor the selectivities. The minor amount of byproducts usually includes the intermediate dihydropyrazoles. The other byproduct, a pyrazole isomer, was

Table 4 Microwave-Assisted, One-Pot Synthesis of Pyrazoles from Chalcones and Hydrazines by Pd/C/K-10 Catalyst at 160 °C

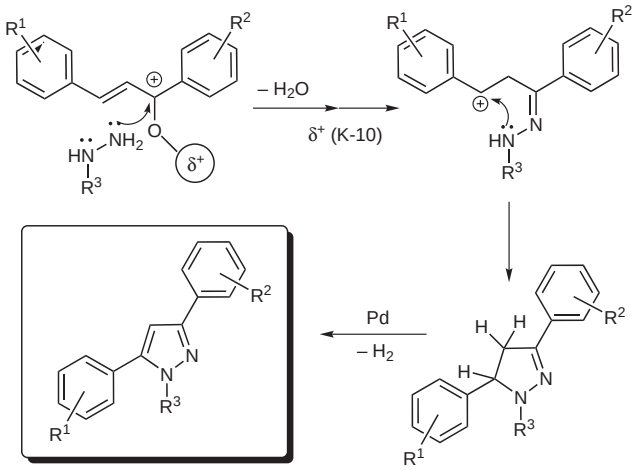


Entry	R^1	R^2	R^3	Time (min)	Yield (%)[a]	Selectivity (%)[b]
1	H	H	Ph	30	95	99
2	H	H	Me	30	98	96
3	H	H	3-$CF_3C_6H_4$	20	98	94
4	H	H	4-$NO_2C_6H_4$	30	80	85
5	H	4-OMe	Ph	30	86	91
6	H	4-OMe	3-$CF_3C_6H_4$	30	98	98
7	4-F	4-F	Ph	30	92	95
8	4-F	4-F	3-$CF_3C_6H_4$	30	85	100
9	H	4-Me	Ph	30	96	98

[a] Isolated yields after flash chromatography, based on chalcone.
[b] For pyrazole, determined by GC-MS.

formed in traces. The first can be explained by the imperfect dehydrogenation step, while the second is the result of unexpected coupling between the chalcones and phenylhydrazine. The combined amount of byproducts usually does not exceed 1–2%.

The results indicate that our original idea for designing a one-pot approach is feasible. The proposed model for the reaction mechanism involves contribution from both the solid acid and the metal. The first step is the activation of chalcone by K-10 montmorillonite (depicted as δ^+ – a Lewis acid center). This material is a widely used catalyst in environmentally friendly synthetic processes.[7] Its use is highly beneficial over liquid acids; it is solid, noncorrosive, inexpensive, and recyclable. In addition, it is commercially available and can be used without any pretreatment. Its strong acidity (H_o = –8) makes a wide range of reactions possible, while the high surface area (220–270 $m^2\ g^{-1}$) ensures excellent reaction rates. It is an excellent catalyst for microwave-assisted organic synthesis (MAOS), an area that has attracted significant interest in recent years.[9] The chalcone activation occurs at the carbonyl group, which results in the formation of a carbocationic intermediate and continues as a traditional condensation reaction with the NH_2 group of the phenylhydrazine. The catalyst then produces a benzylic cation and the hydrazone undergoes a cyclization reaction to form dihydropyrazole. In the last step the metal component takes a leading role and dehydrogenates the intermediate to the final aromatic product (Scheme 2).



Scheme 2 Proposed mechanism for the Pd/C/K-10-catalyzed synthesis of substituted pyrazoles via one-pot electrophilic cyclization–dehydrogenation tandem reaction

The structure of the final products suggests a step-by-step cyclization; the concerted mechanism is highly improbable under the extremely polar conditions.

Our efforts on the scale-up of the procedure indicated that a tenfold increase in reactant amounts did not decrease the yield (95%), although 10% longer reaction time and 50% more catalyst was needed. This suggests the realistic possibility of future larger scale-ups.

In conclusion, the proposed bifunctional solid-acid/noble-metal (Pd/C/K-10) catalyst is efficient in the described one-pot cyclization–dehydrogenation reaction. It makes the synthesis of a wide variety of pyrazoles possible from commercially available chalcones and hydrazines. The protocol is assisted by microwave irradiation and the products are obtained in good to excellent yields and high selectivities in short reaction times. Solvent-free conditions, solid catalyst, short reaction times and easy product isolation make this approach an attractive alternative for the environmentally benign synthesis of the target compounds.

Chalcones, hydrazines, K-10 montmorillonite and the metal catalyst were purchased from Aldrich and Engelhard and used without further purification. The reactions were carried out at constant temperatures in a Discover Benchmate microwave reactor, with continuous stirring. The temperature was measured and controlled by a built-in infrared detector. The ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were obtained on a 300 MHz Varian NMR spectrometer in $CDCl_3$. Tetramethylsilane, $CFCl_3$ (for ^{19}F NMR), or the residual solvent signal were used as reference. The MS identification of the products has been carried out by an Agilent 6850 GC and 5973 MS system (70 eV electron-impact ionization) using a 30 m long DB-5 type column (J&W Scientific). The melting points are uncorrected and were recorded on a MEL-TEMP apparatus.

General Procedure for the Synthesis of Substituted Pyrazoles

The mixture of chalcone (1.0 mmol) and phenylhydrazine (1.5 mmol) were dissolved in CH_2Cl_2 (3 mL) in a round-bottomed flask. Then the mechanically premixed combination of Pd/C (21 mg) and K-10 (500 mg) was added. After 10 min stirring, the solvent was evaporated in vacuo. The dry mixture was placed into a reaction vial and irradiated in the microwave reactor (CEM Discover Benchmate, 160 °C). During optimization the reaction was monitored by TLC and GC-MS. When the reaction was completed, CH_2Cl_2 was added to the cold mixture, stirred for 10 min, and the catalyst was removed by filtration. The products have been purified by flash chromatography.

1,3,5-Triphenylpyrazole (Table 4, Entry 1)[4b]

Colorless crystals, mp 137–139 °C (hexane–CH_2Cl_2, 80:20).

^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 7.93 (dd, 2 H, *J* = 7.2, 1.5 Hz, Ar), 7.27–7.45 (m, 13 H, Ar), 6.82 (s, 1 H, CH).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 151.9, 144.3, 140.1, 133.0, 130.5, 128.9, 128.7, 128.6, 128.4, 128.2, 127.9, 127.4, 125.8, 125.2, 105.2.

MS [$C_{21}H_{16}N_2$ (296)]: *m/z* (%) = 296 (100) [M^+], 297 (23), 295 (66), 192 (15), 190 (15), 165 (30), 77 (87), 51 (34).

1-Methyl-3,5-diphenyl-1*H*-pyrazole (Table 4, Entry 2)[4b]

Colorless needles, mp 58–60 °C (hexane–CH_2Cl_2, 80:20).

^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 7.83 (dd, 2 H, *J* = 8.1, 1.2 Hz, Ar), 7.38–7.48 (m, 7 H, Ar), 7.24–7.35 (m, 1 H, Ar), 6.61 (d, 1 H, *J* = 1.2 Hz, CH), 3.93 (s, 3 H, CH_3).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 150.4, 145.0, 133.3, 130.6, 128.7, 128.6, 128.59, 128.51, 127.5, 125.4, 103.2, 37.5.

MS [$C_{16}H_{14}N_2$ (234)]: *m/z* (%) = 234 (100) [M^+], 235 (17), 233 (26), 189 (18), 103 (13), 102 (13), 77 (32), 51 (15).

3,5-Diphenyl-1-[3-(trifluoromethyl)phenyl]-1*H*-pyrazole (Table 4, Entry 3)

Yellow oil.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 7.93 (d, 2 H, *J* = 8.1 Hz, Ar), 7.73 (s, 1 H, Ar), 7.45 (t, 2 H, *J* = 7.2 Hz, Ar), 7.34–7.39 (m, 7 H, Ar), 7.26–7.30 (m, 2 H, Ar), 6.84 (s, 1 H, CH).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 153.3, 144.3, 140.0, 133.1, 130.7, 129.3, 128.77, 128.72, 128.70, 128.2, 127.9, 125.8, 123.7, 121.8, 116.3, 105.9.

^{19}F NMR (282.4 MHz, $CFCl_3$): δ = –63.13 (s, 3 F, CF_3).

MS [$C_{22}H_{15}F_3N_2$ (364)]: *m/z* (%) = 364 (100) [M^+], 365 (23), 363 (51), 248 (8), 189 (11), 89 (9), 77 (17).

1-(4-Nitrophenyl)-3,5-diphenyl-1*H*-pyrazole (Table 4, Entry 4)[4c]

Yellow-orange solid, mp 119–121 °C (hexane–CH_2Cl_2, 80:20).

^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 8.19 (d, 2 H, *J* = 8.7 Hz, Ar), 7.92 (dd, 2 H, *J* = 7.8, 1.5 Hz, Ar), 7.55 (d, 2 H, *J* = 9.0 Hz, Ar), 7.30–7.46 (m, 8 H, Ar), 6.86 (s, 1 H, CH).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 153.3, 145.7, 144.9, 144.8, 132.2, 130.0, 129.0, 128.9, 128.8, 128.7, 128.5, 125.8, 124.46, 124.41, 116.3, 111.6, 107.1.

MS [$C_{21}H_{15}N_3O_2$ (341)]: *m/z* (%) = 341 (100) [M^+], 342 (31), 340 (24), 294 (49), 293 (21), 207 (75), 191 (26), 77 (15).

3-(4-Methoxyphenyl)-1,5-diphenyl-1*H*-pyrazole (Table 4, Entry 5)[4d]

Colorless solid, mp 138–140 °C (hexane–CH_2Cl_2, 80:20).

^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 7.92 (d, 2 H, *J* = 8.4 Hz, Ar), 7.19–7.44 (m, 10 H, Ar), 6.85 (d, 2 H, *J* = 8.4 Hz, Ar), 6.77 (s, 1 H, CH), 3.81 (s, 3 H, OCH_3).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 159.5, 153.3, 144.1, 140.1, 133.0, 129.9, 128.8, 128.5, 127.8, 127.3, 125.7, 125.2, 122.9, 113.8, 104.6, 55.2.

MS [$C_{22}H_{18}N_2O$ (326)]: *m/z* (%) = 326 (100) [M^+], 327 (27), 325 (32), 311 (18), 180 (9), 152 (8), 77 (37), 51 (14).

3-(4-Methoxyphenyl)-5-phenyl-1-[3-(trifluoromethyl)phenyl]-1*H*-pyrazole (Table 4, Entry 6)

Yellow oil.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 7.85 (d, 2 H, *J* = 7.8 Hz, Ar), 7.72 (s, 1 H, Ar) 7.26–7.54 (m, 8 H, Ar), 6.98 (d, 2 H, *J* = 7.8 Hz, Ar), 6.77 (s, 1 H, CH), 3.86 (s, 3 H, OCH_3).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 159.7, 152.3, 144.4, 140.4, 130.1, 129.2, 128.7, 128.6, 127.8, 127.1, 125.3, 123.6, 123.5, 121.8, 121.7, 116.3, 114.0, 105.5, 55.3.

^{19}F NMR (282.4 MHz, $CFCl_3$): δ = –63.12 (s, 3 F, CF_3).

MS [$C_{23}H_{17}F_3N_2O$ (394)]: *m/z* (%) = 394 (100) [M^+], 395 (23), 379 (21), 178 (18), 145 (46), 77 (28), 63 (23).

3,5-Bis(4-fluorophenyl)-1-phenyl-1*H*-pyrazole (Table 4, Entry 7)[4e]

Colorless solid, mp 92–94 °C (hexane–CH_2Cl_2, 80:20).

^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 7.87 (m, 2 H, Ar), 7.34 (s, 5 H, Ar), 7.22–7.24 (m, 2 H, Ar), 7.11 (t, 2 H, *J* = 8.4 Hz, Ar), 7.01 (t, 2 H, *J* = 8.4 Hz, Ar), 6.73 (s, 1 H, CH).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 164.3, 161.2, 151.0, 143.4, 139.7, 130.5, 130.4, 128.9, 127.5, 127.4, 127.3, 125.2, 115.7, 115.6, 115.47, 115.40, 104.8.

^{19}F NMR (282.4 MHz, $CFCl_3$): δ = –112.68 (m, 1 F, ArF), –114.13 (m, 1 F, ArF).

MS [$C_{21}H_{14}F_2N_2$ (332)]: *m/z* (%) = 332 (100) [M^+], 333 (22), 331 (57), 225 (8), 210 (13), 208 (8), 183 (17).

3,5-Bis(4-fluorophenyl)-1-[3-(trifluoromethyl)phenyl]-1*H*-pyrazole (Table 4, Entry 8)
Yellow oil.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 7.85–7.90 (m, 2 H, Ar), 7.15 (s, 1 H, Ar), 7.52–7.59 (m, 1 H, Ar), 7.42–7.46 (m, 2 H, Ar), 7.23–7.28 (m, 2 H, Ar), 7.13 (t, 2 H, *J* = 8.4 Hz, Ar), 7.06 (t, 2 H, *J* = 8.4 Hz, Ar), 6.76 (s, 1 H, CH).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 164.5, 161.1, 151.7, 143.6, 140.1, 130.6, 130.5, 129.4, 128.7, 127.8, 127.5, 127.4, 126.1, 123.96 (q, *J* = 4.2 Hz), 121.85 (q, *J* = 4.2 Hz), 116.02, 115.6, 105.7.

^{19}F NMR (282.4 MHz, $CFCl_3$): δ = –63.12 (s, 3 F, CF_3), –111.85 (m, 1 F, ArF), –113.59 (m, 1 F, ArF).

MS [$C_{22}H_{13}F_5N_2$ (400)]: *m/z* (%) = 400 (100) [M^+], 401 (22), 399 (54), 266 (12), 225 (13), 145 (44), 95 (33).

1,5-Diphenyl-3-*p*-tolyl-1*H*-pyrazole (Table 4, Entry 9)[4d]
Colorless solid, mp 126–128 °C (hexane–CH_2Cl_2, 80:20).

^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 7.81 (d, 2 H, *J* = 8.1 Hz, Ar), 7.21–7.37 (m, 12 H, Ar), 6.79 (s, 1 H, CH), 2.38 (s, 3 H, CH_3).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 151.9, 144.1, 140.1, 137.6, 130.5, 130.1, 129.2, 128.8, 128.6, 128.3, 128.1, 127.2, 125.6, 125.2, 105.0, 21.3.

MS [$C_{22}H_{18}N_2$ (310)]: *m/z* (%) = 310 (100) [M^+], 311 (19), 309 (55), 191 (12), 165 (19), 77 (65), 51 (28).

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