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Reaction of Diimines and Benzyne

Ashraf A. Aly, Nasr K. Mohamed, Alaa A. Hassan, Aboul-Fetouh E. Mourad

Chemistry Department, Faculty of Science, El-Minia University, El-Minia, Egypt.

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Abstract: The reaction between benzyne and the Schiff bases **1a,b** and **15a,b** leads to the 1,4-bis(2'-substituted acridin-10-yl)benzene **4a,b**, the N-phenylarylamines **10a,b** and the 10-(4'-formylphenyl)-substituted acridines **11a,b** (from **1a,b**) and the 2-substituted acridine-10-carboxyaldehyde **18a,b** (from **15a,b**). Cyclohexyl (4-cyclohexyliminomethylbenzylidine)amine **1c** reacts with benzyne by an ene-reaction to give cyclohexenyl[(4-cyclohexyliminomethylphenyl)benzylidine]amine **14**.

Introduction

The Diels-Alder reaction has been of prime importance in organic synthesis for a long time[1-3], and among the numerous dienophiles employed arynes (dehydrobenzenes) have also been added to a variety of dienes[4,5].

We are interested in preparing fused polycyclic compounds related to [2.2]paracyclophane using the Diels-Alder reaction[6,7], especially the reactions which involve benzyne as a dienophile[8]. Because of the potential importance of the Diels-Alder reaction for the preparation of six-membered nitrogen heterocycles, we try to utilize this reaction with benzyne to synthesize such nitrogen heterocycles which have medicinal and industrial importance. Preparation of these compounds usually requires several steps and proceeds with relatively poor yields.

The highly reactive parent system, benzyne, reacts with imines to give N-(o-anilinobenzhydryl)-aniline[9] and phenanthridine derivatives[10] as well as acridines[11] via [2+2] and/or [4+2] cycloaddition reactions. Acridine derivatives have a wide range of applications in dye chemistry and are of medicinal importance as antitumor reagents[12,13].

We have recently reported that cyclohexyl-(4-cyclohexyliminomethylbenzylidine)amine as well as N,N'-bis-(aryl)-benzene-1,4-diylidmethylidenediamines react with tetracyanoethylene (TCNE), 1,4-benzo- and naphtho-quinone derivatives to give novel pyrrole, imidazolidine, quinoline, quinoxaline, indole and carbazole derivatives[14,15]. On the other hand, 3,4,5,6-tetrachloro-1,2-benzoquinone (o-CHL) provided a transient condensation product with the above diimines which underwent [4+2] cycloaddition

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reaction with a second molecule of diimine[16]. The behavior of these diimines towards some selected electron deficient compounds have also been investigated[17].

Results and discussion

Reaction of N,N'-bis-(aryl)-benzene-1,4-diylidmethylidenediamine **1a,b** with benzyne gave the 1,4-bis(2'-substituted acridine-10-yl)benzene **4**, the N-phenylarylamines **10**, and the 10-(4'-formylphenyl)-2-substituted acridines **11** (Scheme 1). Since, the reaction of benzyne with imines was described as a [2+2] cycloaddition reaction[11], proceeding via a benzazetidine, we postulate that the reaction products **4** (20-30%) are also obtained by [2+2] cycloaddition processes between two moles of benzyne with the two azomethine groups in **1** forming the cycloadducts **2** initially. Ring opening of these bis-benzazetidines followed by electrocyclization and aromatization, then provides compound **4**. Bis-acridine derivatives **4** were actually expected in this cycloaddition, because acridine derivatives have been also obtained by the reaction of monoimines with benzyne[10,11].

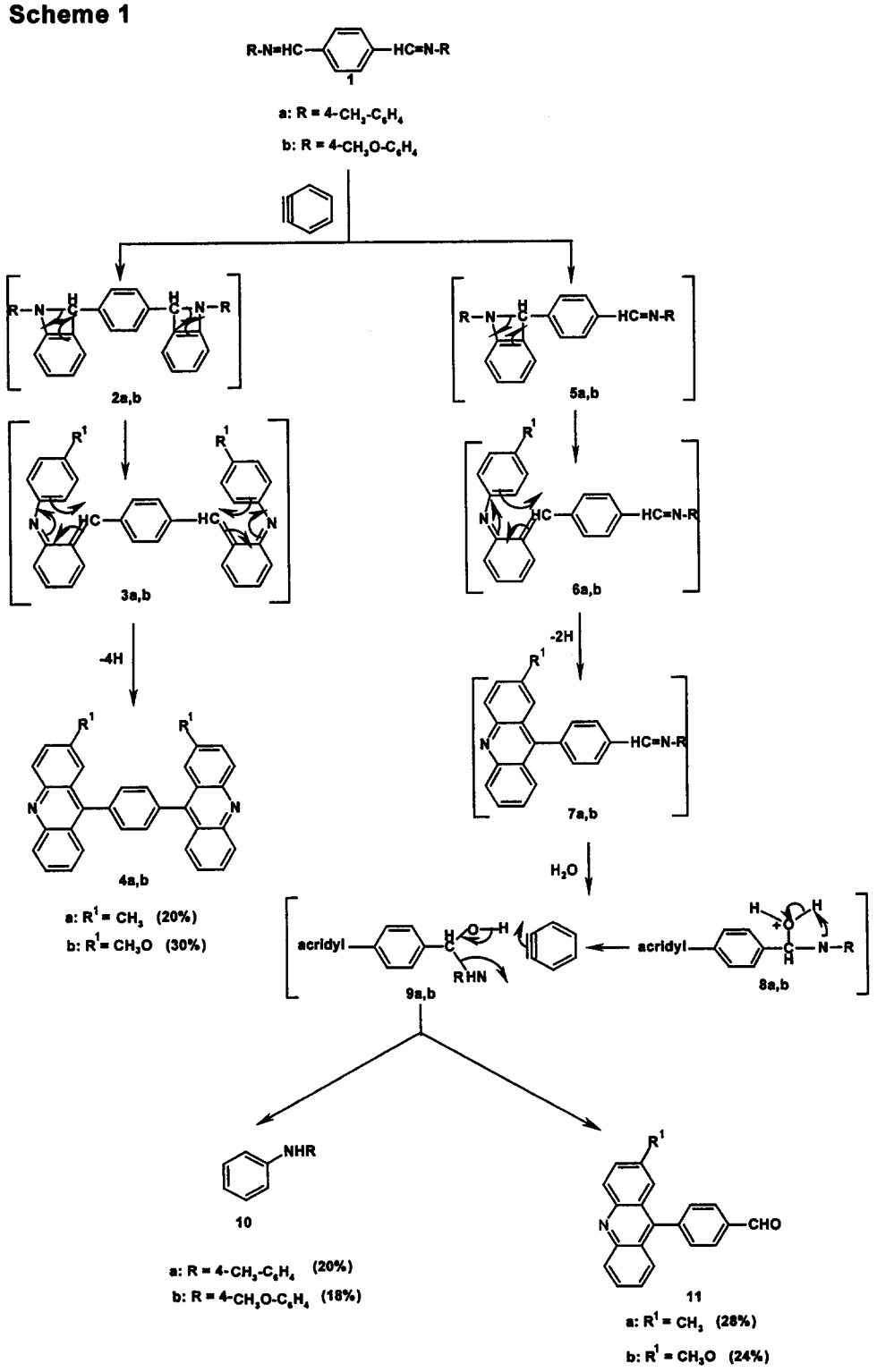
The mass spectrum of **4a** showed a molecular ion peak at *m/z* 460, and the elemental analysis confirmed the molecular formula of this compound as $C_{34}H_{24}N_2$. The ^{1}H-NMR spectrum showed the aromatic protons as a double-doublet at δ 8.09 (J = 3.00, 9.00 Hz) for two protons, and one doublet at δ 7.85 (J = 8.98 Hz) for two protons. It also revealed two multiplets, one at δ 7.02-7.40 for ten protons and other at δ 6.56-6.78 for four protons. Finally, the ^{1}H-NMR spectrum also displayed a singlet at δ 2.38 for six protons of the two methyl groups.

Formation of the N-phenylarylamines **10a,b** and the 10-(4'-formylphenyl)-2-substituted acridines **11a,b** is suggested to proceed according to the mechanism outlined in Scheme 1. In this case the reaction sequence would start by formation of the monoadducts **7a,b** via **5a,b** and **6a,b** as described above. Hydrolysis of **7a,b** could then furnish **9a,b** which could be allowed by another molecule of benzyne and ultimately provide with **10a,b** and **11a,b**.

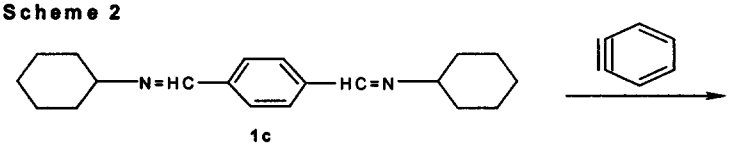
Interestingly, the reaction of cyclohexyl-(4-cyclohexyliminomethylbenzylidine)amine **1c** with benzyne afforded compound **14** (26%) (Scheme 2). The mass spectrum and elemental analysis of **14** suggest the molecular formula as $C_{26}H_{30}N_2$. Its ^{1}H-NMR spectrum revealed a singlet at δ 8.39 for one azomethine-CH group, whereas the cyclohexyl protons appeared as two muliplets, one at δ 1.30-2.04 for fifteen protons and another for four protons at δ 3.30-3.52, in addition to the olefinic proton which was recorded as a muliplet at δ 6.50-6.55. The ^{13}C-NMR spectrum exhibited the imine carbons at δ 140.25 and δ 138.60, as well as the two cyclohexene-C signals at δ 127.16 and 126.38; in addition, eight aromatic carbon signals are detected.

In a similar experiment in which benzyne was treated with the N,N'-bis(aryl)-ethane-1,2-diylidenediamines **15a,b**, the acridine carboxyaldehyde **18** and the N-phenylarylamine **10** were isolated,

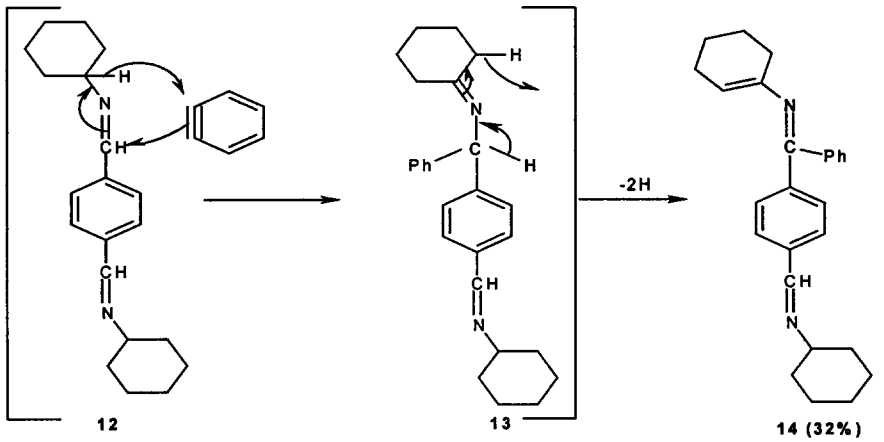
Scheme 1


R-N=HC
HC=N-R
1
a: R = 4-CH3-C6H4
b: R = 4-CH3O-C6H4
2a,b
5a,b
3a,b
6a,b
-4H
-2H
4a,b
7a,b
a: R1 = CH3 (20%)
b: R1 = CH3O (30%)
H2O
acridyl
RHN
9a,b
8a,b
NHR
10
a: R = 4-CH3-C6H4 (20%)
b: R = 4-CH3O-C6H4 (18%)
CHO
11
a: R1 = CH3 (28%)
b: R1 = CH3O (24%)

Scheme 2

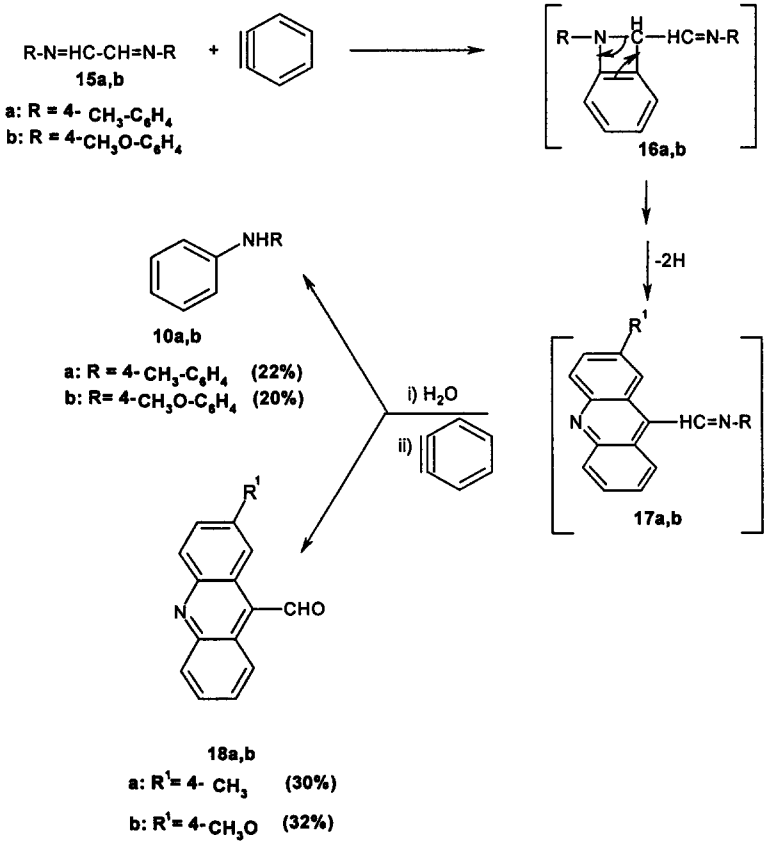


1c



12 13 14 (32%)

Scheme 3



respectively (Scheme 3).

Experimental

Melting points are uncorrected. IR spectra were obtained on Shimadzu 470 spectrophotometer using potassium bromide pellets. ^{1}H-NMR (400.134 MHz) and ^{13}C-NMR (100.6 MHz) spectra were measured on Bruker AM 400 with TMS as an internal standard. Coupling constants are expressed in Hz. Mass spectra were recorded on a Finnigan MAT 8430 instrument at 70 eV. Elemental analyses were performed by the microanalytical unit at Cairo University. For preparative layer chromatography (PLC), glass plates (20 x 48 cm) were covered with a slurry of silica gel Merck PF_{254} and air-dried using the solvents listed for development. Zones were detected by quenching of indicator fluorescence upon exposure to 254 nm light; elution of the different bands with either toluene or toluene/ethyl acetate provided the pure products.

Starting Materials:

N,N'-Bis(aryl)benzene-1,4-diyldimethylidenediamines **1a,b**, cyclohexyl-(4-cyclohexyliminomethyl-benzylidine)amine **1c** and N,N'-bis(aryl)-ethane-1,2-diylidene-diamine **15a,b** were prepared according to the literature (16, 18 and 19).

Reaction of benzyne with 1a-c and 15a,b (General procedure):

Benzenediazonium carboxylate (prepared from anthranilic acid)[20] (10-15 mmol) was added slowly to the heated solutions of **1** and **15** (2 mmol) in 30 ml of acetonitrile during 6-8 h. The reaction mixture was refluxed for 12-24 h. (reaction progress was followed by TLC analysis). The solvent was then concentrated and the residue was filtered off. In case of compounds **1a,b** and **15a,b**, the filtrate was purified by PLC using toluene as an eluent giving zones from which **4**, **10**, **11** and **18** were separated. Reaction of **1a,b** with benzyne provided compound **10** as the fastest migrating zone, followed by compound **11** as the second zone, whereas the third zone contained **4**. Reaction of **15a,b** with benzyne gave **10** as the first migrating zone and **18** as the second one.

In case of **1c**, the residue was washed several times with acetonitrile and the resulting brown precipitate was then dissolved in acetone and subjected to PLC using toluene/ethyl acetate (5:1) as eluent to give only one zone which contained compound **14**. All zones were extracted with acetone and products recovered which were recrystallized from the stated solvents.

*1,4-Bis (2'-methylacridin-10-yl)benzene (**4a**)*

This compound was obtained 180 mg (20%), m.p. 150-152 °C, as brown crystals, (benzene); ^{1}H-

NMR ($CDCl_3$): δ 2.38 (s, 6H, 2 CH_3), 6.56-6.78 (m, 4H, Ar-H), 7.02-7.40 (m, 10H, Ar-H), 7.85 (d, 2H, Ar-H, J= 8.98 Hz), 8.09 (dd, 2H, Ar-H, J= 3.00, 9.00 Hz); IR (KBr): ν_{max} 3115-3030 cm^{-1} (Ar-CH), 2995-2880 (ali.-CH), 1610 (C=N); MS (70 eV): *m/z* (%) 460 (M^+, 18), 447 (60), 340 (18), 306 (100), 305 (82), 289 (10), 192 (38), 168 (44), 153 (98), 136 (22), 122 (20); Analysis: $C_{34}H_{24}N_2$(460.578): calc. C, 88.67; H, 5.25; N, 6.08; found: C, 88.48; H, 5.12; N, 6.23.

*1,4-Bis (2'-methoxyacridin-10-yl)benzene (**4b**)*

This compound was obtained 150 mg (30%), m.p. 178-180 ^{0}C, as brown crystals, (benzene); ^{1}H-NMR ($CDCl_3$): δ 3.68 (s, 6H, 2 OCH_3), 6.62-6.82 (m, 4H, Ar-H), 7.10-7.55 (m, 10H, Ar-H), 7.91 (d, 2H, Ar-H, J= 8.98 Hz), 8.14 (dd, 2H, Ar-H, J= 3.00, 9.02 Hz); IR (KBr): ν_{max} 3080-3015 cm^{-1} (Ar-CH), 2990-2875 (ali.-CH), 1612 (C=N); MS (70 eV): *m/z* (%) 492 (M^+, 18), 478 (58), 426 (38), 323 (100), 305 (82), 285 (60), 251 (32), 223 (16), 208 (48), 190 (24), 170 (90),138 (22), 126 (18), 92 (46); Analysis: $C_{34}H_{24}N_2O_2$ (492.576): calc. C, 82.91; H, 4.91; N, 5.69; found: C, 82.72; H, 4.80; N, 5.56.

*10-(4'-Formylphenyl)-2-methylacridine (**11a**)*

This compound was obtained 166 mg (28%), m.p. 300-302 ^{0}C, as yellow crystals,, (benzene); ^{1}H-NMR ($CDCl_3$): δ 2.39 (s, 3H, CH_3), 6.85 (dd, 2H, Ar-H, J= 3.00, 8.90 Hz), 6.96 (dd, 2H, Ar-H, J= 2.98, 8.92 Hz), 7.12-7.45 (m, 5H, Ar-H), 7.81 (d, 1H, J= 8.90 Hz), 8.19 (dd, 1H, J= 3.00, 9.00 Hz), 10.00 (s, 1H, CHO); IR (KBr): ν_{max} 3050-3010 cm^{-1} (Ar-CH), 2995-2883 (ali.-CH), 1705 (CO), 1600 (C=N); MS (70 eV): *m/z* (%) 297 (M^+, 8), 282 (6), 281 (20), 267 (6), 246 (6), 192 (100), 167 (4), 105 (20); Analysis: $C_{21}H_{15}NO$ (297.356): calc. C, 84.82; H, 5.08; N, 4.71; found C, 84.65; H, 4.89; N, 4.55.

*10-(4'-Formylphenyl)-2-methoxyacridine (**11b**)*

This compound was obtained 150 mg (24%), m.p. 310-312 ^{0}C as yellow crystals, (benzene); ^{1}H-NMR ($CDCl_3$) δ 3.70 (s, 3H, OCH_3), 6.89 (dd, 2H, Ar-H, J= 3.00, 8.90 Hz), 7.02 (dd, 2H, Ar-H, J= 2.98, 9.00 Hz), 7.20-7.61 (m, 5H, Ar-H), 7.85 (d, 1H, J= 8.96 Hz), 8.24 (dd, 1H, J= 3.00, 9.00 Hz), 10.20 (s, 1H, CHO); IR (KBr): ν_{max} 3062-3008 cm^{-1}(Ar-CH), 2990-2880 (ali.-CH), 1710 (CO), 1605 (C=N); MS (70 eV): *m/z* (%) 313 (M^+, 12), 282 (22), 260 (34), 208 (100), 183 (16), 167 (60), 136 (40); Analysis: $C_{21}H_{15}NO_2$ (313.355): calc. C, 80.49; H, 4.82; N, 4.47; found C, 80.67; H, 4.71; N, 4.39.

*Cyclohex-1-enyl[(4-cyclohexyliminomethylphenyl)benzylidine]amine (**14**)*

This compound was obtained 236 mg (32%), m.p.> 300 ^{0}C as orange crystals, (ethanol); ^{1}H-NMR (DMSO): δ 1.30-2.04 (m, 15H, cyclohexyl-CH), 3.30-3.52 (m, 4H, cyclohexyl-CH), 6.50-6.55 (m, 1H, cyclohexene-CH), 6.95-7.29 (m, 9H, Ar-H), 8.39 (s, 1H, azomethine-CH); ^{13}C-NMR (DMSO): δ 20.19, 20.35, 21.35, 22.30, 23.98, 24.17, 24.34, 24.60, 28.88, 29.90 (cyclohexyl-C), 126.38, 127.16 (cyclohexene-C), 128.40, 131.08, 131.90, 132.40, 132.49, 132.64, 133.00, 133.93 (Ar-C), 138.60 (Ph-C=N), 140.25 (CH=N); IR (KBr): ν_{max} 3010-3000 cm^{-1} (Ar-CH), 2990-2870 (ali.-CH),1608 (C=N); MS (70 eV): *m/z* (%) 370 (M^+, 90), 327 (100), 285 (8), 241 (12), 219 (12), 199 (14), 160 (16), 137 (38), 119 (52), 92 (18), 56 (34), 43 (22), 42 (50); Analysis: $C_{26}H_{30}N_2$ (370.357): calc. C, 84.28; H,8.16; N, 7.56; found: C, 84.10; H, 8.33; N, 7.69.

*2-Methylacridine-10-carboxyaldehyde (**18a**)*

This compound was obtained 150 mg (30%), m.p. 125-127 ^{0}C, as red crystals (acetonitrile); ^{1}H-NMR ($CDCl_3$) δ 2.35 (s, 3H, CH_3), 7.60-8.30 (m, 5H, Ar-H), 8.11 (d, 1H, J= 8.90 Hz), 8.44 (d, 1H, Ar-H, J= 8.90 Hz), 9.88 (s, 1H, CHO); IR (KBr):ν_{max} 3065-3010 cm^{-1} (Ar-CH), 2995-2885 (ali.-CH), 1710 (CO), 1610 (C=N); MS (70 eV): *m/z* (%) 221 (M^+, 8), 206 (60), 192 (68), 178 (100), 167 (68), 149 (32), 139 (12), 115 (4), 105 (6), 92 (12), 83 (14), 77 (18); Analysis: $C_{15}H_{11}NO$ (221.258): calc. C, 81.43; H, 5.01; N, 6.33; found C, 81.28; H, 4.89; N, 6.14.

*2-Methoxyacridine-10-carboxyaldehyde (**18b**)*

This compound was obtained 184 mg (32%), m.p. 138-140 ^{0}C, as red crystals, (acetonitrile); ^{1}H-NMR ($CDCl_3$) δ 3.62 (s, 3H, OCH_3), 7.68-8.28 (m, 5H, Ar-H), 8.16 (d, 1H, J= 8.90 Hz), 8.42 (d, 1H, Ar-H, J= 8.92 Hz), 10.95 (s, 1H, CHO); IR (KBr): ν_{max} 3050-3000 cm^{-1}(Ar-CH), 2990-2885 (ali.-CH), 1705 (CO), 1605 (C=N); MS (70 eV): *m/z* (%) 237 (M^+, 8), 221 (18), 208 (14), 192, 178 (100), 160 (38), 86 (14), 76 (18); Analysis: $C_{15}H_{11}NO_2$ (237.267): calc. C, 75.94; H, 4.67; N, 5.90; found: C, 75.81; H, 4.79; N, 6.11.

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