Monatshefte für Chemie 135, 833–838 (2004)
DOI 10.1007/s00706-003-0139-5

Monatshefte für Chemie
Chemical Monthly
Printed in Austria

Synthesis and Photochemistry of Novel 3,5-Diacetyl-1,4-dihydropyridines. II [1]

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Received September 23, 2003; accepted September 29, 2003
Published online February 5, 2004

Summary. In continuation of previous work some novel 3,5-diacetyl-1,4-dihydropyridine derivatives were synthesized and their photochemical behavior was studied under oxygen and argon atmosphere. Oxidation of the dihydropyridine ring and formation of pyridine derivatives was the result of the reaction. The presence of oxygen affects not only on the rate of oxidation, but also the formation of some unidentified by-products was observed on irradiation under this atmosphere.

Keywords. Aromatization; 1,4-Dihydropyridines; Heterocycles; Photochemistry; Photooxidation.

Introduction

Recently we have reported on the synthesis and photochemistry of novel 3,5-diacetyl-1,4-dihydropyridines **1a**–**1e** [1]. These results indicated that besides the presence or absence of oxygen atmosphere, the type and nature of the 4-substituent has an effect on the rate or type of reaction. Two types of reactions have been observed: oxidation with retention and with expulsion of the 4-substituent.

Our experience with the photochemistry of 1,4-dihydropyridine-3,5-diesters, known as *Hantzsch* esters [2], showed also such dependence of the reaction on both factors [3, 4]. In continuation of our recent work, we synthesized some other novel 3,5-diacetyl-1,4-dihydropyridines **1f**–**1l** and investigated their photochemical behavior under oxygen and argon atmosphere. The aim of this work was to study the effect of various substituents in position 4 on the rate or type of reaction.

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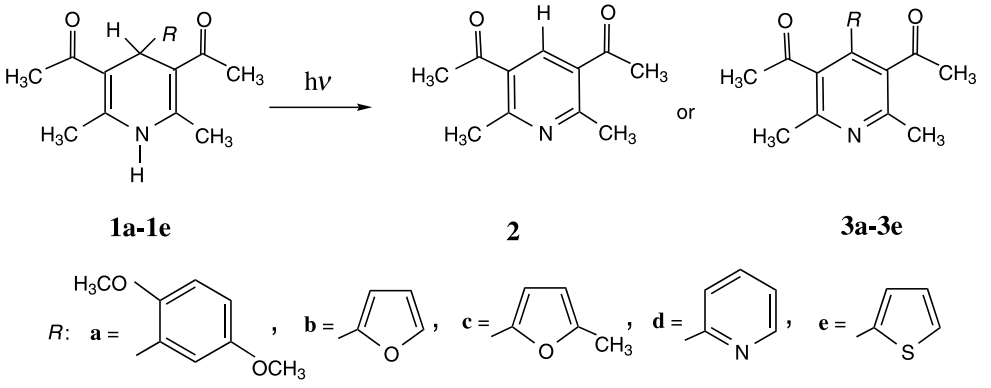
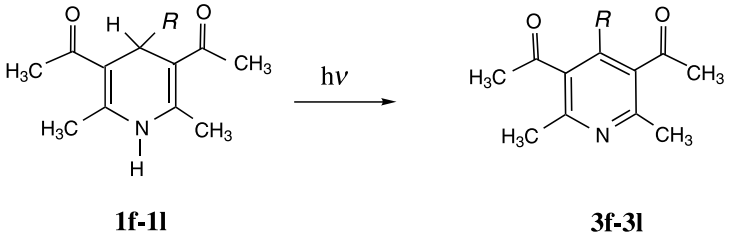


Scheme 1

Results and Discussion

A $15 \cdot 10^{-3}\,M$ solution of **1f–1l** in chloroform was irradiated under oxygen and argon atmosphere until total disappearance of starting material. The results are summarized in Table 1.

As shown in Table 1, only the product with retention of the 4-substituent was obtained under both atmospheres, except for **1f**. In this case, reaction under oxygen atmosphere resulted in the formation of an unidentified salt, may be the pyridinium salt. This is supported by the fact, that the isolated yield of products is lower in the reaction under oxygen atmosphere than under argon atmosphere. The presence of oxygen could induce a radical reaction and formation of HCl in chloroform solution, which leads to the formation of the pyridinium salt. Therefore we should obtain a higher yield of product in reaction under argon atmosphere. Another interesting result is that the irradiation time under oxygen is shorter than under argon atmosphere, except for **1h**. This should be due to the involvement of the triplet excited state of **1h** and quenching of this excited state by the presence of oxygen.



R: **f:** CH_3 **g:** C_6H_5 **h:** 4-ClC_6H_4 **i:** 2-$CH_3OC_6H_4$

j: 3-$CH_3OC_6H_4$ **k:** 4-$CH_3OC_6H_4$ **l:** 3-$NO_2C_6H_4$

Scheme 2

Table 1. Irradiation of dihydropyridines **1f–1l** under oxygen and argon atmosphere

	O_2		Ar	
	Product (yield/%)[a]	Time/h[b]	Product (yield/%)[a]	Time/h[b]
1f	–	7	**3f** (60)	13.5
1g	**3g** (85)	8	**3g** (92)	13.5
1h	**3h** (86)	12	**3h**(94)	10
1i	**3i** (82)	8	**3i** (85)	10
1j	**3j** (85)	8.25	**3j** (90)	11
1k	**3k** (61)	10	**3k** (90)	12
1l	**3l** (50)	26	**3l** (81)	49

[a] Isolated yield; [b] The irradiation times are given after total disappearance of the starting material

IR, ^{1}H NMR, and UV data allowed the structural assignments of the photoproducts **3f–3l**. A comparison of the IR spectra of educts and products showed the disappearance of the NH band and a shift of the CO vibration to higher frequency due to oxidation and aromatization of the ring, which cause a decrease in the conjugation of the CO group with the C=C bonds. ^{1}H NMR spectra showed the loss of the NH and C_4–H signals and aromatization of ring. Due to the missing conjugation of the CO group with the pyridine ring, the signals of the methyl groups in positions 2 and 6 are shifted upfield and the protons of the acetyl groups are shifted downfield in comparison with the starting materials. Also, a comparison of the UV spectra did not show any strong absorption above 300 nm, which indicates aromatization of the ring and formation of pyridine derivatives.

Experimental

All melting points were determined with a Stuart Scientific SMP 2. IR: Shimadzu IR-435; ^{1}H NMR: Bruker AW 80 (80 MHz); UV: Shimadzu UV-160; Mass spectra: Micromass Platform II: EI mode (70 eV). Elemental analyses: Euro EA CHNS Analysator; the results agreed favourably with the calculated values. Preparative thin layer chromatography (PLC) was carried out on $20\times20\,cm^2$ plates coated with a 1 mm layer of Merck silica gel PF_{254}. Column chromatography: Merck silica gel 60, 70–230 mesh ASTM.

All irradiations were performed using a 400 W high-pressure Hg-vapour lamp from NARVA with cooling of samples in Duran glass ($\lambda \geq 280$ nm) by running cold H_2O. Ar (99.99%) or O_2 (99.99%) was bubbled through the solutions during irradiation.

General Procedure for the Preparation of 3,5-Diacetyl-1,4-dihydropyridines

A mixture of 0.05 mol of freshly distilled acetyl acetone, 0.025 mol of the corresponding aldehyde, and $30\,cm^3$ of conc. NH_3 (in the case of **1f** NH_3 gas was used) in $15\,cm^3$ of C_2H_5OH was refluxed for the time given. The solvent was evaporated, the precipitate was washed with cold diethyl ether, and recrystallized from ethanol.

3,5-Diacetyl-2,4,6-trimethyl-1,4-dihydropyridine (**1f**, $C_{12}H_{17}NO_2$)

Refluxed for 4 h, yield 32%, yellow crystals, mp 150–152°C; IR (KBr): $\bar{\nu} = 3280$ (NH), 1665 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 0.9$ (d, $J = 7.2$ Hz, 4-CH_3), 2.3 (s, 2- and 6-CH_3, 3- and 5-$COCH_3$), 3.8

(q, 4-H), 6.3 (brd s, NH) ppm; EI-MS: m/z (%) = 208 [M^++1] (11), 207 [M^+] (52), 192 [M^+–CH_3] (100), 176 [M^+–2CH_3–H] (20), 164 [M^+–CH_3CO] (37), 150 [M^+–CH_3–CH_2CO] (66), 149 [M^+–CH_3–CH_3CO] (65), 106 [M^+–CH_3–2CH_3CO] (57), 43 [CH_3CO^+] (64); UV ($CHCl_3$): λ (log ε) = 368 (3.82), 250 (3.98) nm.

3,5-Diacetyl-2,6-dimethyl-4-phenyl-1,4-dihydropyridine (**1g**, $C_{17}H_{19}NO_2$)

Refluxed for 3 h, yield 31%, yellow crystals, mp 169–170°C; IR (KBr): $\bar{\nu}$ = 3280 (NH), 1665 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 2.2 (s, 2- and 6-CH_3), 2.25 (s, 3- and 5-$COCH_3$), 5.05 (s, 4-H), 6.7 (brd s, NH), 7.1 (s, C_6H_5) ppm; EI-MS: m/z (%) = 270 [M^++1] (7), 269 [M^+] (39), 268 [M^+–H] (43), 254 [M^+–CH_3] (13), 226 [M^+–CH_3CO) (39), 192 [M^+–C_6H_5–CH_3CO–CH_3] (16), 106 [M^+–C_6H_5–2CH_3CO] (15), 43 [CH_3CO^+] (56); UV ($CHCl_3$): λ (log ε) = 367 (3.55), 254 (3.88) nm.

3,5-Diacetyl-4-(4-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine (**1h**, $C_{17}H_{18}NO_2Cl$)

Refluxed for 3 h, yield 26%, yellow crystals, mp 140–141°C; IR (KBr): $\bar{\nu}$ = 3300 (NH), 1670 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 2.2 (s, 2- and 6-CH_3), 2.3 (s, 3- and 5-$COCH_3$), 5.2 (s, 4-H), 5.9 (brd s, NH), 7.3 (s, C_6H_4) ppm; EI-MS: m/z (%) = 305 [M^{+37}Cl] (67), 303 [M^{+35}Cl] (89), 288 [M^+–CH_3) (75), 262 [M^+(^{37}Cl)–CH_3CO] (73), 260 [M^+(^{35}Cl)–CH_3CO] (89), 192 [M^+–C_6H_4Cl] (100), 149 [M^+–C_6H_4Cl–CH_3CO] (81), 134 [M^+–C_6H_4Cl–CH_3CO–CH_3] (88), 106 [M^+–C_6H_4Cl–2CH_3CO] (72) 43 [CH_3CO^+] (81); UV ($CHCl_3$): λ (log ε) = 368 (3.79), 252 (4.14) nm.

3,5-Diacetyl-4-(2-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine (**1i**, $C_{18}H_{21}NO_3$)

Refluxed for 3.25 h, yield 30%, yellow crystals, mp 172–173°C; IR (KBr): $\bar{\nu}$ = 3280 (NH), 1670 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 2.2 (s, 2- and 6-CH_3, 3- and 5-$COCH_3$), 3.75 (s, OCH_3), 5.3 (s, 4-H), 6.1 (brd s, NH), 6.8–7.1 (m, C_6H_4) ppm; EI-MS: m/z (%) = 300 [M^++1] (4), 299 [M^+] (11), 297 [M^+–2H] (16), 284 [M^+–CH_3] (110), 268 [M^+–OCH_3] (85), 192 [M^+–$C_6H_4OCH_3$] (100), 150 [M^+–$C_6H_4OCH_3$–CH_2CO] (61), 134 [M^+–$C_6H_4OCH_3$–CH_3CO–CH_3] (36), 107 [$C_6H_4OCH_3^+$] (22), 43 [CH_3CO^+] (73); UV ($CHCl_3$): λ (log ε) = 348 (3.84), 252 (4.03) nm.

3,5-Diacetyl-4-(3-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine (**1j**, $C_{18}H_{21}NO_3$)

Refluxed for 3 h, yield 29%, yellow crystals, mp 196–198°C; IR (KBr); $\bar{\nu}$ = 3260 (NH), 1660 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 2.3 (s, 2- and 6-CH_3), 2.4 (s, 3- and 5-$COCH_3$), 3.8 (s, OCH_3), 5.2 (s, 4-H), 6.1 (brd s, NH), 6.7–7.3 (m, C_6H_4) ppm; EI-MS: m/z (%) = 300 [M^++1] (50), 299 [M^+] (82), 284 [M^+–CH_3] (64), 256 [M^+–CH_3CO] (83), 241 [M^+–CH_3CO–CH_3] (16), 192 [M^+–$C_6H_4OCH_3$] (100), 149 [M^+–$C_6H_4OCH_3$–$COCH_3$] (76), 134 [M^+–$C_6H_4OCH_3$–$COCH_3$–CH_3] (85), 106 [M^+–$C_6H_4OCH_3$–2$COCH_3$] (69), 92 [$C_6H_4O^+$] (42), 43 [CH_3CO^+] (85); UV ($CHCl_3$): λ (log ε) = 366 (3.81), 252 (4.10) nm.

3,5-Diacetyl-4-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine (**1k**, $C_{18}H_{21}NO_3$)

Refluxed for 7 h, yield 33%, yellow crystals, mp 175–176°C; IR (KBr): $\bar{\nu}$ = 3300 (NH), 1660 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 2.2 (s, 2- and 6-CH_3), 2.25 (s, 3- and 5-$COCH_3$), 3.7 (s, OCH_3), 5.0 (s, 4-H), 6.5 (brd s, NH), 6.7–7.15 (m, C_6H_4) ppm; EI-MS: m/z (%) = 300 [M^++1] (9), 299 [M^+] (45), 298 [M^+–H] (56), 284 [M^+–CH_3] (19), 256 [M^+–CH_3CO] (63), 240 [M^+–CH_3CO–CH_3–H] (23), 192 [M^+–$C_6H_4OCH_3$] (100), 149 [M^+–$C_6H_5OCH_3$–CH_3CO] (20), 106 [M^+–C_6H_5–2CH_3CO] (15), 43 [CH_3CO^+] (12); UV ($CHCl_3$): λ (log ε): 368 (3.66), 253 (4.13) nm.

3,5-Diacetyl-4-(3-nitrophenyl)-2,6-dimethyl-1,4-dihydropyridine (**1l**, $C_{17}H_{18}N_2O_4$)

Refluxed for 2.75 h, yield 45%, yellow crystals, mp 210–211°C; IR (KBr): $\bar{\nu} = 3300$ (NH), 1670 (CO) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 2.25$ (s, 2- and 6-CH_3), 2.4 (s, 3- and 5-$COCH_3$), 5.25 (s, 4-H), 6.35 (brd s, NH) 7.2–8.0 (m, C_6H_4) ppm; EI-MS: m/z (%) = 314 [M^+] (4), 297 [M^+–OH] (17), 271 [M^+–CH_3CO] (17), 192 [M^+–$C_6H_4NO_2$] (100), 149 [M^+–$C_6H_4NO_2$–CH_3CO] (16), 134 [M^+–$C_6H_4NO_2$–CH_3CO–CH_3] (13), 43 [CH_3CO^+] (65); UV ($CHCl_3$): λ (log ε) = 348 (3.74), 254 (4.31) nm.

General Procedure for the Irradiation of Dihydropyridines

A 0.015 *M* solution of **1f–1l** in chloroform was irradiated under Ar or O_2 atmosphere until total disappearance of dihydropyridines was observed (TLC; the corresponding irradiation times are given in Table 1). When the reaction was complete, the product was purified by chromatography.

3,5-Diacetyl-2,4,6-trimethylpyridine (**3f**, $C_{12}H_{15}NO_2$)

Column chromatography, petroleum ether/ethyl acetate (3/2), yield 60%, white crystals, mp 58–59°C; IR (KBr): $\bar{\nu} = 1700$ (CO) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 2.05$ (s, 4-CH_3), 2.35 (s, 2- and 6-CH_3), 2.4 (s, 3- and 5-$COCH_3$) ppm; EI-MS: m/z (%) = 205 [M^+] (10), 190 [M^+–CH_3] (24), 162 [M^+–CH_3CO] (8), 147 [M^+–CH_3–CH_3CO] (2), 120 [M^+–CH_3CO–CH_2CO] (21), 105 [M^+–CH_3CO–CH_2CO–CH_3] (5), 44 [CH_3COH^+] (100), 43 [CH_3CO^+] (64); UV ($CHCl_3$): λ (log ε): 272 (3.51) nm.

3,5-Diacetyl-2,6-dimethyl-4-phenylpyridine (**3g**, $C_{17}H_{17}NO_2$)

PLC, petroleum ether/ethyl acetate (5/3), yield 85%, mp 185–186°C; IR (KBr): $\bar{\nu} = 1690$ (CO) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.8$ (s, 2- and 6-CH_3), 2.5 (s, 3- and 5-$COCH_3$), 7.1–7.6 (m, C_6H_5) ppm; EI-MS: m/z (%) = 268 [M^++1] (8), 267 [M^+] (39), 252 [M^+–CH_3] (47), 224 [M^+–CH_3CO] (9), 210 [M^+–CH_2CO–CH_3] (63), 209 [M^+–CH_3CO–CH_3] (4), 191 [M^+–C_6H_5] (2), 181 [M^+–2CH_3CO] (5), 167 [M^+–CH_3CO–CH_2CO–CH_3] (12), 43 [CH_3CO^+] (100); UV ($CHCl_3$): λ (log ε): 252 (3.96) nm.

3,5-Diacetyl-4-(4-chlorophenyl)-2,6-dimethylpyridine (**3h**, $C_{17}H_{16}NO_2Cl$)

The solvent was evaporated and the residue was washed with cold ethanol, yield 86%, mp 174–175°C; IR (KBr): $\bar{\nu} = 1695$ (CO) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.95$ (s, 2- and 6-CH_3), 2.6 (s, 3- and 5-$COCH_3$), 7.1–7.5 (m, C_6H_4) ppm; EI-MS: m/z (%) = 303 [$M^+{}^{37}Cl$] (83), 301 [$M^+{}^{35}Cl$] (97), 288 [$M^+(^{37}Cl)$–CH_3] (88), 286 [$M^+(^{35}Cl)$–CH_3] (98), 260 [$M^+(^{37}Cl)$–CH_3CO] (16), 258 [$M^+(^{35}Cl)$–CH_3CO] (46), 246 [$M^+(^{37}Cl)$–CH_2CO–CH_3] (79), 244 [$M^+(^{35}Cl)$–CH_2CO–CH_3] (94), 163 [M^+–C_6H_4Cl–CH_3CO] (16), 139 (100), 113 [$C_6H_4{}^{37}Cl$] (36), 111 [$C_6H_4{}^{35}Cl$] (8), 43 [CH_3CO^+] (86); UV ($CHCl_3$): λ (log ε) = 248 (4.24) nm.

3,5-Diacetyl-4-(2-methoxyphenyl)-2,6-dimethylpyridine (**3i**, $C_{18}H_{19}NO_3$)

Column chromatography, petroleum ether/ethyl acetate (3/2), yield 82%, white crystals, mp 142–143°C; IR (KBr): $\bar{\nu} = 1695$ (CO) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.9$ (s, 2- and 6-CH_3), 2.5 (s, 3- and 5-$COCH_3$), 3.7 (s, OCH_3), 6.8–7.4 (m, C_6H_4) ppm; EI-MS: m/z (%) = 298 [M^++1] (15), 297 [M^+] (45), 282 [M^+–CH_3] (24), 267 [M^+–2CH_3] (10), 266 [M^+–CH_3O] (39), 264 [M^+–CH_3OH–H] (30), 249 [M^+–CH_3OH–H–CH_3] (24), 224 [M^+–CH_3CO–2CH_3] (28), 196 [M^+–2CH_3CO–CH_3] (16), 132 [M^+–$C_6H_5OCH_3$–CH_3CO–CH_3] (15), 57 [$CH_2COCH_3{}^+$] (100), 44 [CH_3COH^+] (67), 43 [CH_3CO^+] (88); UV ($CHCl_3$): λ (log ε) = 250 (3.82) nm.

3,5-Diacetyl-4-(3-methoxyphenyl)-2,6-dimethylpyridine (**3j**, $C_{18}H_{19}NO_3$)

Column chromatography, petroleum ether/ethyl acetate (3/1), yield 85%, white crystals, mp 111–113°C; IR (KBr): $\bar{\nu} = 1690$ (CO) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.9$ (s, 2- and 6-CH_3), 2.6 (s, 3- and 5-$COCH_3$), 3.8 (s, OCH_3), 6.7–7.6 (m, C_6H_4) ppm; EI-MS: m/z (%) = 299 [M^++2] (13), 298 [M^++1] (66), 297 [M^+] (83), 282 [M^+–CH_3] (76), 264 [M^+–CH_3OH–H] (81), 254 [M^+–CH_3CO] (63), 240 [M^+–CH_2O–CH_3] (84), 211 [M^+–2CH_3CO] (29), 197 [M^+–CH_3CO–CH_2CO–CH_3] (61), 196 [M^+–2CH_3CO–CH_3] (37), 132 [M^+–$C_6H_5OCH_3$–CH_3CO–CH_3] (100), 44 [CH_3COH^+] (67), 43 [CH_3CO^+) (88); UV ($CHCl_3$): λ (log ε) = 249 (3.71) nm.

3,5-Diacetyl-4-(4-methoxyphenyl)-2,6-dimethylpyridine (**3k**, $C_{18}H_{19}NO_3$)

PLC, petroleum ether/ethyl acetate (5/2), yield 61%, white crystals, mp 164–165°C; IR (KBr): $\bar{\nu} = 1700$ (CO) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.85$ (s, 2- and 6-CH_3), 2.45 (s, 3- and 5-$COCH_3$), 3.8 (s, OCH_3), 6.8–7.2 (m, C_6H_4) ppm; EI-MS: m/z (%) = 298 [M^++1] (66), 297 [M^+] (100), 282 [M^+–CH_3] (96), 266 [M^+–CH_3O] (8), 264 [M^+–CH_3OH–H] (45), 254 [M^+–CH_3O] (44), 240 [M^+–CH_2O–CH_3] (94), 211 [M^+–2CH_3CO] (18), 196 [M^+–2CH_3CO–CH_3] (23), 132 [M^+–$C_6H_5OCH_3$–CH_3CO–CH_3] (21), 57 [$CH_2COCH_3^+$] (11), 44 [CH_3COH^+] (13), 43 [CH_3CO^+] (66); UV ($CHCl_3$): λ (log ε) = 274 (4.08) nm.

3,5-Diacetyl-4-(3-nitrophenyl)-2,6-dimethylpyridine (**3l**, $C_{17}H_{16}N_2O_4$)

PLC, petroleum ether/ethyl acetate (3/2), yield 50%, mp 126–127°C; IR (KBr): $\bar{\nu} = 1700$ (CO) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.9$ (s, 2- and 6-CH_3), 2.5 (s, 3- and 5-$COCH_3$), 7.5–8.2 (m, C_6H_4) ppm; EI-MS: m/z (%) = 313 [M^++1] (7), 312 [M^+] (30), 297 [M^+–CH_3] (91), 295 [M^+–OH] (90), 294 [M^+–H_2O] (5), 282 [M^+–NO] (6), 269 [M^+–CH_3O] (6), 266 [M^+–NO_2] (9), 251 [M^+–NO_2–CH_3] (8), 236 [M^+–NO_2–2CH_3] (37), 223 [M^+–NO_2–$COCH_3$] (19), 208 [M^+–NO_2–$COCH_3$–CH_3] (17), 165 [M^+–NO_2–2$COCH_3$–CH_3] (11), 44 [CH_3COH^+] (16), 43 [CH_3CO^+] (83), 42 [CH_2CO^+] (100); UV ($CHCl_3$): λ (log ε) = 253 (4.06) nm.

Acknowledgments

We are grateful to the Isfahan University Research Council for partial support to this work. *H. R. Memarian* is indebted to the German Academic Exchange Service (DAAD) for a scholarship during July–August 2002.

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