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Three compounent reaction of isoquinoline with strong cyclic CH-acids in presence of dimethylacetylene dicarboxylate

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Abstract: Protonation of highly reactive 1, 4-zwitterionic intermediate produced in the reaction between Isoquinoline or 2, 4-dimethyl pyridine and dimethylacetylene dicarboxylate by strong cyclic CH-acids such as *N,N'*-dimethylbarbitoric acid, meldrum's acid or 1,3-indanedione leads to a vinyl cation which undergoes an addition reaction with the enolate anion of the CH-acid to produce stable 1, 4-diionic betaines in good yields.

Keywords: Strong cyclic CH-acids; Acetylenic ester; Isoquinoline; 1,4-Diionic betaines.

Introduction

The addition reaction between nitrogen-containing heterocycles and electron-deficient acetylenic compounds has been extensively investigated [1]. The reaction of pyridine with dimethylacetylene dicarboxylate (DMAD) yields the zwitterionic compound, which can be trapped by various electrophiles [1-8]. When the reaction of pyridine and *DMAD* was carried out in the presence of a CH-acid such as dimethyl malonate, cyclohepta-1, 3-diene derivatives were obtained [8]. 6, 6-Dimethyl-5,7-dioxaspiro-[2,5]-octane-4,8-dione has been found to react at room temperature with pyridine to yield the yellow betaine product by *Danishefsky* [9-10]. The rates and equilibria constants for the nucleophilic cleavage of spiro-activated cyclopropane systems have been studied [11-12].

The reactions of pyridine or imidazole and DMAD have been studied in the presence of a CH-acid such as N, N'-dimethylbarbitoric acid or Meldrum's acid [13-14]. Also the reactions of pyridine or isoquinoline and DMAD have been studied in the presence of 1, 1, 1, 5, 5, 5-hexafluoropantane-2, 4-dione [15].

We report the results of the reaction between isoquinoline or 2, 4-dimethyl pyridine and dimethylacetylene dicarboxylate in the presence of strong cyclic acids such as barbitoric acid, N, N'-dimethylbarbitoric acid, meldrum's acid, or 1,3-indanedione (Scheme 1).

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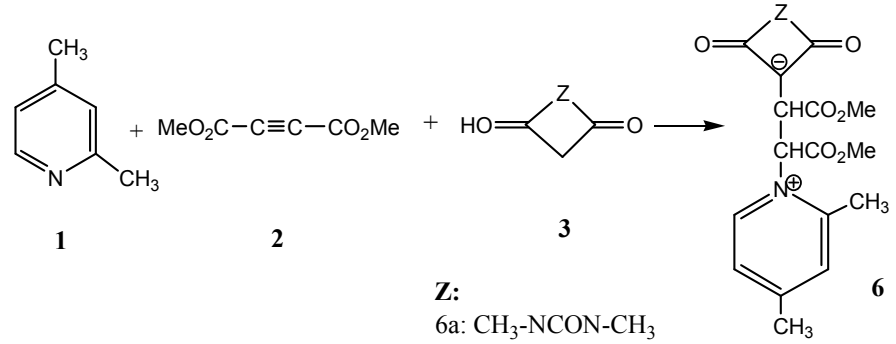
Results and Discussion

The above three-component reaction leads to stable 1,4-diionic nitrogen betaines **6** and **7** in 80-91% yields. **6a-c** and **7a-d** are stable solids and their structures are fully characterized by elemental analyses and spectroscopic data.

On the basis of the well established chemistry of pyridine [1-4], it is reasonable to assume that the betaines **6** and **7** result from the initial addition of 2,4-dimethyl pyridine or isoquinoline to the acetylenic ester and subsequent protonation of the reactive 1:1 adduct, followed by an attack of carbon atom of the anion of the strong cyclic CH-acid to vinylcationes **4** to generate the nitrogen yield **5**, which apparently isomerizes under the reaction conditions employed to produce the 1,4-diionic compounds **6** and **7** (Scheme 2).

The NMR spectroscopy was employed to distinguish compounds **6** and **7** from the primary product **5**. The ^{1}H NMR of each isolated product showed two methine proton signals at about 3.5-6.5 ppm (doublets, $^3J_{HH}$ = 5-10 H_Z). The protons of the pyridine and isoquinoline moiety displayed signals at 7.5-9.0 ppm.

Compounds 6 and 7 have two stereogenic centers and therefore two diastereomers are expected (scheme 3). When *meldrum's* acid or barbitoric acid was used as CH-acid, with isoquinoline, ^{1}H NMR spectra of the crude product showed both stereoisomers in a nearly 2:1 ratio.



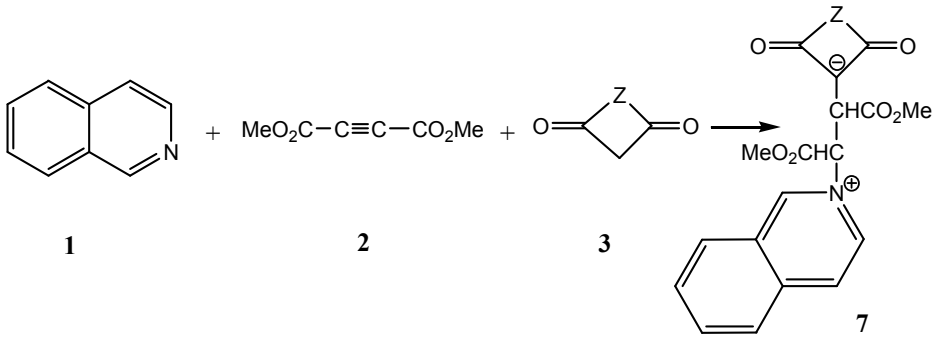
1 **2** **3** **6**

Z:

6a: CH_3-NCON-CH_3

6b: O-C$(CH_3)_2$-O

6c:



1 **2** **3** **7**

Z:

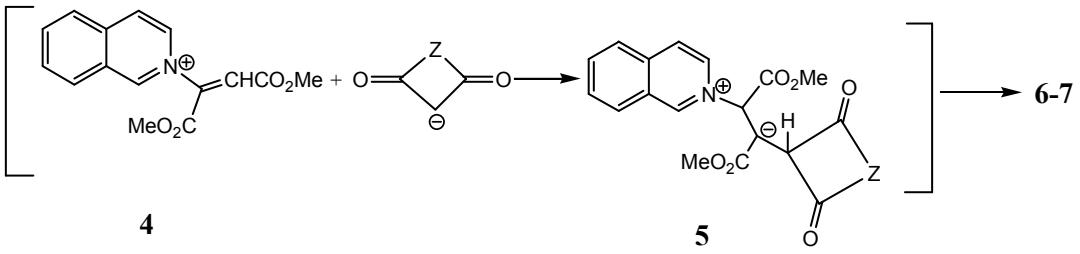
7a: CH_3-NCON-CH_3

7b: O-C$(CH_3)_2$-O

7c:

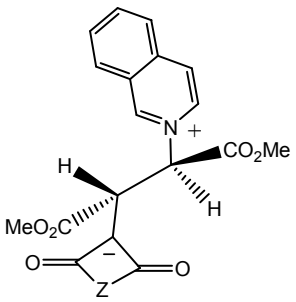
7d: HN-CO-NH

Scheme 1

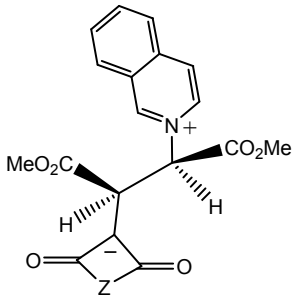


4 **5** **6-7**

Scheme 2



(2S,3R) or (2R,3S)



(2R,3R) or (2S,3S)

Scheme 3

However, the ^{1}H NMR spectra of the crude reaction mixtures obtained from *meldrum's* acid and 2, 4-dimethylpyridine, N, N-dimethyl barbitoric acid and 2, 4-dimethylpyridine or 1, 3-indanedione and 2, 4-dimethylpyridine, were consistent with the presence of only one diastereomer. Also, the ^{1}H NMR spectra of the crude reaction mixtures obtained from N, N'-dimethyl barbitoric acid or 1, 3-indanedione and isoquinoline, the ^{1}H NMR spectra showed both diastereomers.

The ^{1}H NMR spectra of compound **6a** exhibited five singlet sharp resonances due to the methyl (δ=2.54, 2.95 ppm), 3.11 (2 N-CH_3), methoxy (δ = 3.69 and 3.81 ppm) and displayed signals for vicinal methine protons at δ = 5.05 and 6.58, which appear as two sets of doublets with $^3J_{HH}$ values of 9.72 Hz and 9.73 Hz. The protons of the pyridine displayed one singlet signal at δ = 7.39 and two doublets at δ = 7.41 and 8.36 ppm with $^3J_{HH}$ values of 6.5 and 6.5 Hz. The ^{13}C NMR spectra of **6a** showed 18 distinct resonances in agreement with the proposed structure.

The ^{1}H NMR spectrum of **7a, major,** exhibited three single sharp resonances due to the methyl (δ=3.03, 6 H), methoxy (δ = 3.71 and 3.92 ppm) and displayed signals for vicinal methine at δ = 4.99 and 6.05 ppm, which appear as two sets of doublets with $^3J_{HH}$ values of 7.04 Hz. The ^{1}H NMR spectrum of **7a, minor,** exhibited three single sharp resonances due to the methyl (δ = 2.97, 6 H ppm), methoxy (δ = 3.75 and 3.94 ppm) and displayed signals for vicinal methine at δ = 5.16 and 5.61, which appear as two sets of doublets with $^3J_{HH}$ values of 5.88 Hz.. The ^{13}C NMR spectrum of **7a** showed 21 distinct resonances in agreement with the proposed structure. The ^{1}H and ^{13}C NMR spectra of **7b-d** were similar to those of **7a** except for methyl, methoxy, methine and aromatic protons and carbons, which exhibited characteristic signals with appropriate chemical shifts.

In conclusion, the reaction of isoquinoline or 2, 4-dimethylpyridine with acetylenic ester in the presence of CH-acids provides a simple one-pot entry into the synthesis of stable 1,4-diionic-compounds **6** and **7**.

Experimental

All melting points were measured on an Electro thermal 9100 apparatus. Elemental analyses for C, H and N were performed using a Heraeus CHN-O-Rapid analyzer. IR spectra were measured on a Shimadzu IR-460 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz on a Bruker Avance DPX-300 spectrometer instrument with $CDCl_3$ or D_2O as solvent. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. The reagents and solvents used in this work were obtained from Fluka (Buchs, Switzerland) and used without further purification.

Typical procedure for the preparation of **6a:**

To a magnetically stirred solution of dimethylacetylene dicarboxylate (0.28 g, 2 mmol) and N, N-dimethyl barbitoric acid (o.30g, 2 mmol) in 10 mL CH_2Cl_2, was added dropwise 2, 4-dimethylpyridine (0.22 g, 2 mmol) in 10 mL of CH_2Cl_2, at -5ºC over 4 min. After 24 h the solvent was removed under reduced pressure and the solid residue was washed with 3×10 mL cold diethyl ether to produce **6a** as a Pale yellow powder.

6a: 2-[3-(2, 4-Dimethylpyridinium-1-yl)-1, 4-dimethoxy-1, 4-dioxobutane-2-yl]-1, 3-dioxo-1, 3-dihydro-1*H*-inden-2-ide

$C_{19}H_{24}N_3O_7$, Pale yellow powder from Et_2O, yield: 0.79g (90%); m.p.: 130-131ºC; IR: (KBr) (ν_{max}/cm^{-1}): 1746, and 1674 (C=O), 1640 and 1593(C=C), cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$); δ = 2.54 and 2.95 (6 H, 2 s, 2

CH_3 of pyridine), 3.10 (6 H, s, 2 N-CH_3), 3.69 (3 H, s, OCH_3), 3.81 (3 H, s, OCH_3), 5.05 (1 H, d, $^3J_{HH}$ = 9.7 Hz, CH), 6.57 (1 H, d, $^3J_{HH}$ = 9.7 Hz, CH-N^+), 7.39-8.38 (3H, pyridine); ^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 21.2 and 22.5 (2 CH_3 of pyridine), 27.7 and 31.3 (2 N-*Me*), 44.3 (*C*H), 53.1 and 54.3 (2 O*Me*), 65.3 (*C*H-N^+), 80.2 [*C*$^-$(CO)$_2$], 125.6, 129.7, 144.6, 153.9 and 156.1 (C of pyridine), 159.6 (C=O of ring), 163.7 (2 C=O of ring), 168.9 and 173.5 (2 C=O of ester). Ms, *m/z* (%): 406 (M^+, 1), 299 (4), 238 (12), 129 (26), 128 (100), 107 (25), 75 (10), 63 (28); Anal. Calc. for $C_{19}H_{24}N_3O_7$ (406.45); C, 56.14; H, 5.96 %; Found: C, 56.19; H, 5.97 %.

6b: 5-[2-(2, 4-dimethylpyridinium-1-yl)-1, 4-dimethoxy-1, 4-dioxobutan-5-yl]-1, 3-dimethyl-2, 4, 6-trioxohexanhydro-1*H*-pyridin-5-ide

$C_{22}H_{22}NO_6$, Pale yellow powder from Et_2O, yield: 0.76g (80%); m.p.: 124-125ºC; IR: (KBr) (ν_{max}/cm^{-1}): 1719, and 1674 (C=O), 1640 and 1593(C=C), cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$); δ = 2.54 and 2.95 (6 H, 2 s, 2 CH_3 of pyridine), 3.69 (3 H, s, OCH_3), 3.81 (3 H, s, OCH_3), 5.05 (1 H, d, $^3J_{HH}$ = 7.5 Hz, CH), 6.57 (1 H, d, $^3J_{HH}$ =7.5 Hz, CH-N^+), 7.39-8.38 (protons of aromatic); ^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 21.2 and 22.5 (2 CH_3 of pyridine), 44.3 (CH), 53.1 and 54.3 (2 O*Me*), 65.4 (*C*H-N^+), 80.2 [*C*$^-$(CO)$_2$], 125.6, 129.7, 144.6, 153.9 and 156.1 (C of aromatic), 165.3 and 167.6 (2 C=O of ester), 196.9 and 197.9 (2 C=O of ring) ppm. MS, *m/z* (%): 396 (M^+, 4), 286 (2), 226 (4), 129 (100), 107 (25); Anal. Calc. for $C_{22}H_{22}NO_6$ (396.39); C, 66.65; H, 5.60 %; Found: C, 66.67; H, 5.62 %.

6c: 5-[2-(2, 4-dimethylpyridinium-1-yl)-1, 4-dimethoxy-1, 4-dioxobutan-5-yl]-2, 2-dimethyl-4, 6-dioxo-1, 3-dioxan-5-ide

$C_{19}H_{24}NO_8$, Pale yellow powder from Et_2O, yield: 0.79g (90%); m.p.: 157-158ºC; IR: (KBr) (ν_{max}/cm^{-1}): 1736 (C=O), 1574 (C=C), cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$); δ=1.32 (6 H, s, 2 Me), 2.54 and 2.95 (6 H, 2 s, 2 CH_3 of pyridine), 3.69 (3 H, s, OCH_3), 3.81 (3 H, s, OCH_3), 5.12 (1 H, d, $^3J_{HH}$ = 7.5Hz, CH), 6.42 (1 H, d, $^3J_{HH}$ =7.5Hz, CH-N^+), 7.39-8.38 (3 H, of pyridine); ^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 21.2 and 22.5 (2 *C*H$_3$ of pyridine), 44.3 (*C*H), 53.09 and 54.28 (2 O*Me*), 65.34 (*C*H-N^+), 67.51 [*C*(Me)$_2$], 80.14 [*C*$^-$(CO)$_2$], 125.6, 129.7, 144.6, 153.9 and 156.1 (C of pyridine), 159.6 (C=O of ring), 163.7 (2 C=O of ring), 168.9 and 173.5 (2 *C*OOMe), ppm. MS, *m/z* (%): 394 (M^+, 4), 107 (6), 129 (100), 63 (22), 51 (34); Anal. Calc. for $C_{19}H_{24}NO_8$ (394.43); C, 57.85; H, 6.08 %; Found: C, 57.89; H, 6.12 %.

7a: Dimethyl-2-(N, N'-dimethylbarbituricacid-5-yl-5-ylide)-3-isoquinolinium-1, 4-butanedioate

$C_{21}H_{22}N_3O_7$, Pale yellow powder from Et_2O, yield: 0.78g (90%); m.p.: 147-148ºC; IR: (KBr)(ν_{max}/cm^{-1}): 1746, 1730 and 1674 (4 C=O), 1647 and 1589 (C=C), cm^{-1}; **major isomer** (68%): ^{1}H NMR (300 MHz, $CDCl_3$); δ =3.03 (6 H, s, 2 N-CH_3), 3.71 (3 H, *s*, OCH_3), 3.92 (3 H, *s*, OCH_3), 4.99 (1 H, *d*, $^3J_{HH}$ = 5.8Hz, CH), 5.72 (1 H, *d*, $^3J_{HH}$ = 5.8Hz, CH-N^+), 7.07-8.33 (7 H, m, isoquinoline) ppm; ^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 28.1 (2 N-*Me*), 47.3 (*C*H), 53.19 and 54.13 (2 O*Me*), 70.58 (*C*H-N^+), 80.92 [*C*$^-$(CO)$_2$], 126.00, 126.78, 129.5, 129.8, 135.6, 136.4, and 137.7 (9 C of isoquinoline), 152.8 (C=O of ring), 164.9 (2 C=O of ring), 169.6 and 172.5 (2 *C*OOMe) ppm; **minor isomer** (32%): ^{1}H NMR (300 MHz, $CDCl_3$); δ = 2.97 (6H, s, 2N-CH_3), 3.72 (3 H, *s*, OCH_3), 3.91 (3 H, *s*, OCH_3), 5.16 (1 H, *d*, $^3J_{HH}$ =7.2Hz, CH), 6.09 (1 H, *d*, $^3J_{HH}$ = 7.2Hz, CH-N^+), 7.07-8.33 (7 H, m, isoquinoline) ppm; ^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 27.6 (2 N-*Me*), 46.9 (CH), 53.1 and 53.9 (2 O*Me*), 72.6 (CH-N^+), 80.9 [*C*$^-$(CO)$_2$], 123.5, 127.1, 131.5, 131.8, 137.7 (9 C of isoquinoline), 153.3 (C=O of ring), 163.3 (2 C=O of ring), 168.1 and 174.7 (2 *C*OOMe) ppm; Ms, *m/z* (%): 428 (M^+, 4), 239 (5), 129 (100), 128 (22), 75 (6), 63 (28), 51 (32); Anal. Calc. for $C_{21}H_{22}N_3O_7$ (428.45); C, 58.86; H, 5.19 %; Found: C, 58.89; H, 5.21 %.

7b: Dimethyl-2-(isopropylidenemalonate-5-yl-5-ylide)-3-isoquinolinium-1, 4-butanedioate

$C_{21}H_{22}NO_8$, Pale yellow powder from Et_2O, yield: 0.76g (88%); m.p.: 168-169ºC; IR: (KBr) (ν_{max}/cm^{-1}): 1747, 1721 and 1648 (4 C=O ester), 1603 (C=C), cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$); δ = 0.57 (6 H, *s*, 2 CH_3), 2.80 and 2.95 (6 H, *s*, 2 OCH_3), 3.95 (1 H, *d*, $^3J_{HH}$ =5.8Hz, CH), 4.79 (1 H, *d*, $^3J_{HH}$ = 5.8Hz, CH-N^+), 6.94-8.97 (7 H, *m*, isoquinoline); ^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 25.9 (2 Me), 47.2 (CH), 53.2and 53.9 (2 OMe), 68.9 [*C*(2Me)], 72.3 (*CH*-N^+), 102.1 [*C*$^-$(CO)$_2$], 121.9, 124.1, 127.3, 127.5, 131.3, 131.8, 136.9, 137.7 and 138.2 (9C of isoquinoline), 166.6 (C=O of ring), 168.3 and 174.7 (2C=O of ester) ppm. MS, *m/z* (%): 416 (M^+, 1), 226 (4), 156 (28), 129 (27), 125 (34), 69 (60), 59 (100); Anal. Calc. for $C_{21}H_{22}NO_8$ (416.34); C, 60.58; H, 5.34; %; Found: C, 60.61; H, 5.36 %.

7c: Dimethyl-2-(indan-1, 3-dione-2-yl-2-ylide)-3-isoquinolinium-1, 4-butanedioate

$C_{24}H_{20}NO_6$, Pale yellow powder from Et_2O, yield: 0.72g (80%); m.p: 127-128ºC; IR: (KBr) (ν_{max}/cm^{-1}): 1740 and 1709 (4 C=O), 1637 and 1587 (C=C), cm^{-1}; **major**

isomer (65%): ^{1}H NMR (300 MHz, $CDCl_3$); δ = 3.61 (3 H, *s*, OCH_3), 3.99 (3 H, *s*, OCH_3), 5.94 (1 H, *d*, $^3J_{HH}$ = 7.8Hz, CH), 6.43 (1 H, *d*, $^3J_{HH}$ = 7.8Hz, CH-N^+), 6.80-7.98 (11H, m, isoquinoline) ppm; ^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 45.4 (*C*H), 51.8 and 53.8 (2 O*Me*), 90.9 (*C*H-N^+), 110.2 [*C*$^-$$(CO)_2$], 123.5-149.6 (C of aromathic), 165.2 and 167.6 (2 C=O of ester), 196.9 and 197.9 (2 C=O of ring) ppm; **minor isomer** (35 %): ^{1}H NMR (300 MHz, $CDCl_3$); δ = 3.61 (3 H, s, OCH_3), 3.99 (3 H, s, OCH_3), 5.53 (1 H, d, $^3J_{HH}$ = 5.5Hz, CH), 5.73 (1 H, d, $^3J_{HH}$ = 5.5Hz, CH-N^+), 6.80-7.98 (11 H, m, isoquinoline); ^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 45.4 (CH), 57.4 and 58.8 (2 O*Me*), 90.9 (*C*H-N^+), 110.2 (*C*$^-$$[CO)_2$], 123.5-149.8 (C of aromathic), 165.5 and 167.6(2 C=O of ester), 196.9 and 197.9 (2 C=O of ring). ppm. Ms, *m/z* (%): 418 (M^+, 1), 228 (2), 156 (28), 129 (100), 69 (58); Anal. Calc. for $C_{24}H_{20}NO_6$ (418.45); C, 68.88; H, 4.53 %; Found: C, 68.91; H, 4.56 %.

7d: Dimethyl-2-(barbituricacid-5-yl-5-ylide)-3-isoquinolinium-1, 4-butanedioate

$C_{19}H_{18}N_3O_7$, Pale yellow powder from Et_2O, yield: 0.70g (80%); m.p.: 150-151ºC; IR: (KBr) (ν_{max}/cm^{-1}): 1752 and 1692 (4 C=O), 1590 (C=C), cm^{-1}; **major isomer** (68%): ^{1}H NMR (300 MHz,); δ = 3.68 (3H, *s*, OCH_3), 3.89 (3 H, *s*, OCH_3), 4.95 (1 H, *d*, $^3J_{HH}$ = 6.5Hz, CH), 5.82 (1 H, *d*, $^3J_{HH}$ = 6.5Hz, CH-N^+), 8.00-9.76 (7 H, m, isoquinoline) ppm; ^{13}C NMR (75.46 MHz, C_2D_6O): δ = 47.41 (CH), 53.1 and 53.3 (2 O*Me*), 70.9 (*C*H-N^+), 72.2 [*C*$^-$$(CO)_2$], 124.2-138.1 (9 C of isoquinoline), 154.2, 165.5 (3 C=O of ring), 167.7 and 168.2 (2 *C*OOMe of ester) ppm; **minor isomer** (32%): ^{1}H NMR (300 MHz, C_2D_6O); δ=3.72 (3 H, *s*, OCH_3), 3.88 (3 H, *s*, OCH_3), 4.99 (1 H, *d*, $^3J_{HH}$ = 8.8Hz, CH), 6.37 (1 H, *d*, $^3J_{HH}$ = 8.8Hz, CH-N^+), 8.00-9.76 (7 H, m, isoquinoline); ^{13}C NMR (75.46 MHz, C_2D_6O): δ= 43.55 (CH), 52.1 (2 O*Me*), 70.9 (*C*H-N^+), 72.1 [*C*$^-$$(CO)_2$], 124.2-138.1(9C of isoquinoline), 154.2, 165.5 (3 C=O of ring), 167.7 and 168.2 (2*C*OOMe of ester). ppm. Ms, *m/z* (%): 400 (M^+, 4), 231 (5), 129 (100), 75 (18), 51 (24); Anal. Calc. for $C_{19}H_{18}N_3O_7$ (400.39); C, 56.99; H, 4.54 %; Found: C, 57.11; H, 4.56 %.

References

[1] Acheson, R. M.; Elmore, N. F. *Advances in Heterocyclic Chemistry*, **1978**, *23*, 263 and the references cited therein.

[2] Acheson, R. M.; Woolard, J. *J. Chem. Soc. Perkin Trans I*, **1975**, 438.

[3] Acheson, R. M.; Taylor, G. A. *J. Chem. Soc*., **1959**, 186.

[4] Acheson, R. M.; Taylor, G. A. *J. Chem. Soc.*, **1960**, 1691.

[5] Acheson, R. M.; Taylor, G. A. *J. Chem. Soc.* **1960**, 1641.

[6] Diels, O.; Meyer, R. *Annalen*, **1934**, *513*, 129.

[7] Crabtree, A.; Johnson, A. W.; Tebby, J. C. *J. Chem. Soc.* **1961**, 3497.

[8] Bamfiled, P.; Crabtree, A.; Johnson, A. W. *J. Chem. Soc.* **1965**, 4355.

[9] Danishefsky, S.; Singh, R. K. *J. Am. Chem. Soc.* **1975**, *97*, 3239

[10] Danishefsky, S.; Singh, R. K. *J. Org. Chem.* **1975**, *40*, 3807.

[11] McKinney, M. M.; Kremer, K. G.; Aicher, T. *Tetrahedron Lett*. **1984**, *25*, 5477

[12] Ohkata, K.; Nagai, T.; Tamaru, A.; Hannafusa, T. *J. Chem. Soc. Perkin Trans,* **1986**, 43

[13] Bagher Teimouri, M. B.; Bazhrany, R. *J. Chem. Res.* **2005,** 50-53.

[14] Yavari, I.; Anary-Abbasinejad, M.; Alizadeh, A. *Monatsh. Chem.* **2002**, *133*, 1331-1336

[15] Shaabani, A.; Bazgir, A.; Tavasoli-Rad, F.; Bijanzadeh, H. R.; Razmara, F. *J. Chem. Res.* **2004**, *2*, 131-134**.**