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A Simple Synthesis of Stable 1,4-Diionic Pyridinium Betaines

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Summary. Protonation of the reactive intermediate produced in the reaction between pyridine and dialkyl acetylenedicarboxylates by strong CH-acids such as *N*,*N′*-dimethylbarbituric acid, *Meldrum*'s acid, or indane-1,3-dione leads to a vinylpyridinium cation which undergoes an addition reaction with the enolate anion of the CH-acid to produce stable 1,4-diionic pyridinium betaines in good yields.

Keywords. Acetylenic esters; Pyridine; CH-Acids; Nitrogen betaines.

Introduction

The addition reaction between electron-deficient acetylenic compounds and nitrogen-containing heterocycles has been extensively investigated [1]. The reaction of pyridine with dimethyl acetylenedicarboxylate (*DMAD*) yields the zwitterionic compound **1** 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 **2** and **3** were obtained [8]. 6,6-Dimethyl-5,7-dioxaspiro[2,5]octane-4,8-dione (**4**) has been found to react at room temperature with pyridine to yield the yellow betaine product **5** by *Danishefsky* [9, 10] (Scheme 1). The rates and equilibria constants for the nucleophilic cleavage of spiro-activated cyclopropane systems have been studied [11, 12].

We report the results of the reaction between pyridine and dialkyl acetylenedicarboxylates **6** in the presence of strong CH-acids such as *N*,*N′*-dimethylbarbituric acid, *Meldrum*'s acid, or indane-1,3-dione (see Scheme 2).

Results and Discussion

The above three-component reaction leads to stable 1,4-diionic nitrogen betaines **8** in 75–92% yields. **8a–g** are stable solids whose structures are fully supported by elemental analyses and spectroscopic data. The mass spectra of the 1:1:1 adducts exhibited fairly weak molecular ion peaks as well as peaks related to pyridine and alkyl residues.

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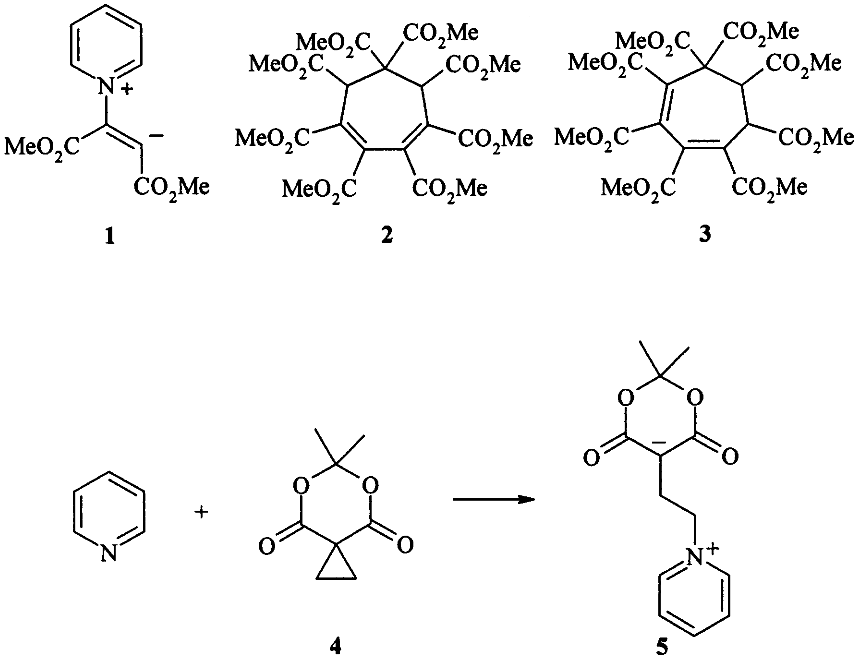
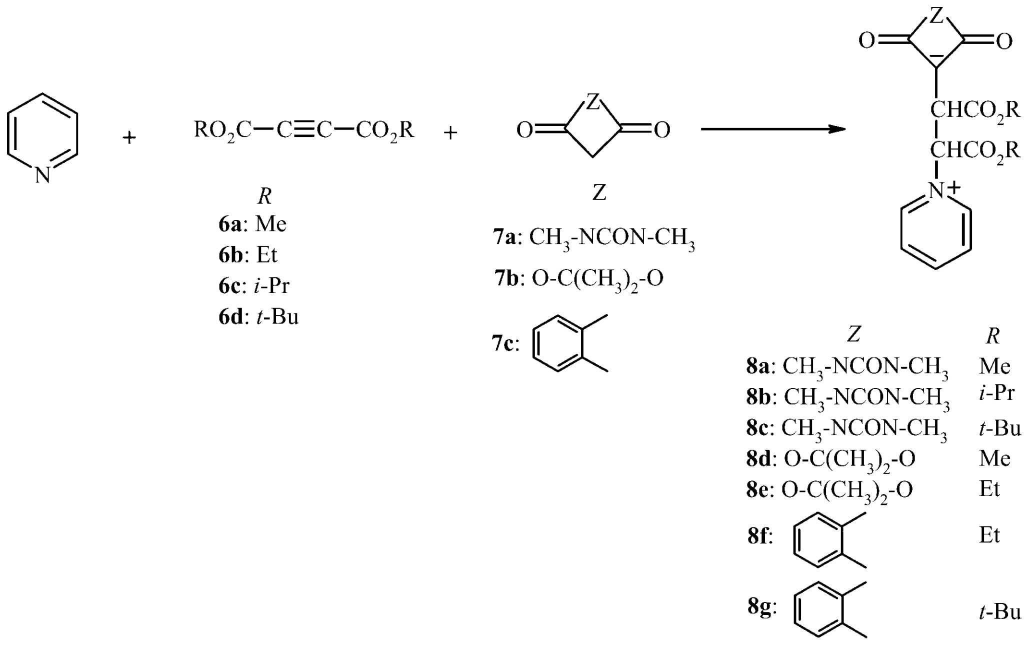
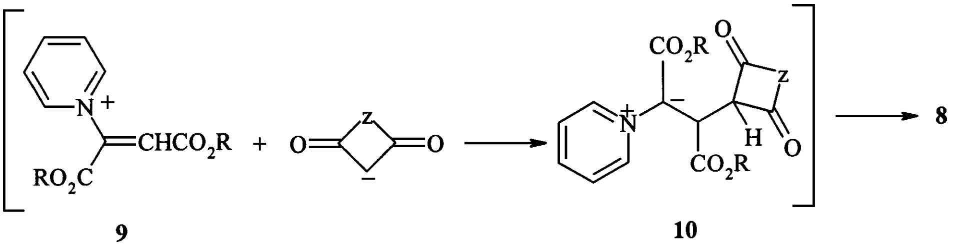


Scheme 1

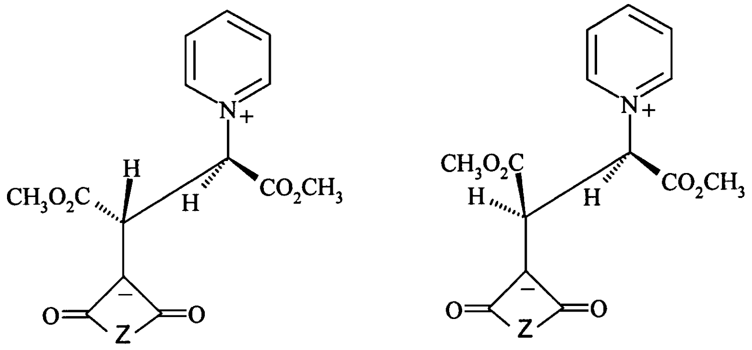


Scheme 2

On the basis of the well established chemistry of pyridine [1–4] it is reasonable to assume that the betaines **8** result from initial addition of pyridine to the acetylenic ester and subsequent protonation of the reactive 1:1 adduct, followed by an attack of the carbon atom of the anion of the CH-acid to vinylpyridinium cation **9**



Scheme 3



(2*S*,3*R*)-**8** or (2*R*,3*S*)-**8** (2*R*,3*R*)-**8** or (2*S*,3*S*)-**8**

Scheme 4

to generate the nitrogen ylide **10**, which apparently isomerizes under the reaction conditions employed to produce the 1,4-diionic compound **8** (Scheme 3).

NMR spectroscopy was employed to distinguish **8** from the primary product **10**. The ^{1}H NMR of each isolated product showed two methine proton signals at about 4.5–5.0 and 5.5–6.5 ppm (doublets, $^3J_{HH} = 6–10$ Hz). The protons of the pyridine moiety displayed signals at 7.5–9.0 ppm.

Compound **8** has two stereogenic centers, and therefore two diastereomers are expected (Scheme 4). When *Meldrum*'s acid was used as CH-acid, the ^{1}H NMR spectrum of the crude product showed both stereoisomers in a nearly 2:1 ratio. However, the ^{1}H NMR spectra of the crude reaction mixtures obtained from *N*,*N*′-dimethylbarbituric acid and indane-1,3-dione were consistent with the presence of only one diastereomer (see Experimental).

In conclusion, the reaction of pyridine with acetylenic esters in the presence of CH-acids, such as *Meldrum*'s acid, *N*,*N*′-dimethylbarbituric acid, or indane-1,3-dione provides a simple one-pot entry into the synthesis of stable 1,4-diionic compounds of potential interest. The present method carries the advantage that the reaction is performed under neutral conditions and the substances can be mixed without any activation or modification.

Experimental

Melting points were measured on an Electrothermal 9100 aparatus. Elemental analyses (C, H, N) were performed using a Heraeus CHN–O-Rapid analyzer; the obtained values agreed favourably with the calculated ones. IR spectra were measured on a Shimadzu IR-460 spectrometer, ^{1}H and ^{13}C NMR spectra on a Bruker DRX-500 Avance spectrometer at 500.1 and 125.8 MHz in $CDCl_3$ or *DMSO*-d_6 using *TMS* as internal standard. All chemicals were purchased from Fluka (Buchs, Switzerland) and used without further purification.

Dimethyl-2-(N,N′-dimethylbarbituric acid-5-yl-5-ylide)-3-pyridinium-1,4-butanedioate (**8a**; $C_{17}H_{19}N_3O_7$); *general procedure*

To a stirred solution of 0.28 g dimethyl acetylenedicarboxylate (2 mmol) and 0.31 g *N*,*N′*-dimethylbarbituric acid (2 mmol) in 10 cm^3 CH_2Cl_2, a mixture of 0.26 g pyridine (4 mmol) in 5 cm^3 CH_2Cl_2 was added dropwise at -5°C over 2 min. After 24 h the solvent was removed under reduced pressure, and the solid residue was washed with $3\times10\,cm^3$ cold diethyl ether to produce **8a** as a pale yellow powder.

Yield: 0.62 g (92%); m.p.: 182–185°C; IR (KBr): $\nu_{max}=1730$ (C=O, ester), 1670 (N_2C=O), 1566 (NC=O) cm^{-1}; MS: m/z (%) = 266 (26), 239 (30), 207 (15), 181 (32), 156 (12), 79 (100), 52 (68); ^1H NMR (500 MHz, *DMSO*-d_6): $\delta=2.9$ (6H, s, 2 NMe), 3.6 (3H, s, OMe), 3.8 (3H, s, OMe), 4.8 (1H, d, $^3J_{HH}=7.9$ Hz, CH–N^+), 6.3 (1H, d, $^3J_{HH}=7.9$ Hz, CH), 8.0 (2H, m, H-3,5 of pyridine), 8.6 (1H, t, $^3J_{HH}=7.7$ Hz, H-4 of pyridine), 8.9 (2H, d, $^3J_{HH}=6.1$ Hz, H-2,6 of pyridine) ppm; ^{13}C NMR (125 MHz, *DMSO*-d_6): $\delta=27.3$ (2 NMe), 40.5 (CH), 52.4 and 52.5 (2 OMe), 70.6 (CH–N^+), 79.2 (*C*$(CO)_2$), 127.1, 146.3 and 147.1 (carbons of pyridine), 153.0 (N–CO–N), 162.4 (NCO), 168.3 and 173.0 (2 CO_2Me) ppm.

Diisopropyl-2-(N,N′-dimethylbarbituric acid-5-yl-5-ylide)-3-pyridinium-1,4-butanedioate (**8b**; $C_{21}H_{27}N_3O_7$)

Pale yellow powder; yield: 0.76 g (88%); m.p.: 135–137°C; IR (KBr): $\nu_{max}=1718$ (C=O, ester), 1668 (N_2C=O), 1570 (NC=O) cm^{-1}; MS: m/z (%) = 267 (30), 235 (39), 225 (45), 208 (32), 180 (52), 79 (96), 43 (100); ^1H NMR (500 MHz, $CDCl_3$): $\delta=1.1$ (3H, d, $^3J_{HH}=5.8$ Hz, Me of isopropyl), 1.2 (6H, d, $^3J_{HH}=5.8$ Hz, 2 Me of isopropyl), 1.4 (3H, d, $^3J_{HH}=5.8$ Hz, Me of isopropyl), 3.1 (6H, s, 2 NMe), 4.9 (1H, d, $^3J_{HH}=7.5$ Hz, CH–N^+), 5.0 (1H, septet, $^3J_{HH}=5.8$ Hz, CH of isopropyl), 5.1 (1H, septet, $^3J_{HH}=5.8$ Hz, CH of isopropyl), 6.7 (1H, d, $^3J_{HH}=7.5$ Hz, CH), 7.8 (2H, m, H-3,5 of pyridine), 8.3 (1H, t, $^3J_{HH}=7.6$ Hz, H-4 of pyridine), 8.9 (2H, d, $^3J_{HH}=6.1$ Hz, H-2,6 of pyridine) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=21.5$, 21.6 and 21.8 (4 Me of isopropyl), 27.4 (2 NMe), 45.1 (CH), 71.8 (CH–N^+), 68.9 and 71.7 (CH of isopropyl), 80.7 (*C*$(CO)_2$), 125.9, 145.1, and 146.7 (carbons of pyridine), 153.0 (N–CO–N), 163.2 (NCO), 167.4 and 171.9 (2 CO of ester groups) ppm.

Di-tert-butyl-2-(N,N′-dimethylbarbituric acid-5-yl-5-ylide)-3-pyridinium-1,4-butanedioate (**8c**; $C_{23}H_{31}N_3O_7$)

Pale yellow powder; yield: 0.74 g (80%); m.p.: 153–154°C; IR (KBr): $\nu_{max}=1716$ (C=O, ester), 1667 (N_2C=O), 1572 (NC=O) cm^{-1}; MS: m/z (%): 271 (30), 253 (32), 235 (15), 208 (11), 180 (20), 79 (29), 57 (100); ^1H NMR (500 MHz, $CDCl_3$): $\delta=1.9$ (9H, s, *t*-Bu), 1.5 (9H, s, *t*-Bu), 3.1 (6H, s, 2 NMe), 4.8 (1H, d, $^3J_{HH}=8.0$ Hz, CH–N^+), 6.6 (1H, d, $^3J_{HH}=8.0$ Hz, CH), 7.8 (2H, m, H-3,5 of pyridine), 8.3 (1H, t, $^3J_{HH}=7.7$ Hz, H-4 of pyridine), 8.9 (2H, d, $^3J_{HH}=6.1$ Hz, H-2,6 of pyridine) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=27.4$ (2 NMe), 27.8 (3 Me of *t*-Bu), 28.0 (3 Me of *t*-Bu), 45.7 (CH), 72.7 (CH–N^+), 76.9 and 77.4 (2 O–C(*t*-Bu)), 85.0 (*C*$(CO)_2$), 125.8, 144.9 and 146.7 (carbons of pyridine), 153.6 (N–CO–N), 163.2 (N–CO), 167.0 and 171.3 (2 CO of ester groups) ppm.

Dimethyl-2-(isopropylidenemalonate-5-yl-5-ylide)-3-pyridinium-1,4-butanedioate (**8d**; $C_{17}H_{19}NO_8$)

Pale yellow powder; yield: 0.58 g (80%); m.p.: 135–137°C; IR (KBr): $\nu_{max}=1736$ (C=O, ester), 1586 (C=O) cm^{-1}; MS: m/z (%) = 156 (27), 125 (15), 79 (95), 59 (41), 43 (100); major isomer (66%):

^{1}H NMR (500 MHz, *DMSO*-d$_6$): $\delta = 1.3$ (6H, s, 2 Me), 3.5 (3H, s, OMe), 3.8 (3H, s, OMe), 4.7 (1H, d, $^3J_{HH} = 6.1$ Hz, CH–N$^+$), 5.9 (1H, d, $^3J_{HH} = 6.1$ Hz, CH), 8.1 (2H, m, H-3,5 of pyridine), 8.6 (1H, t, $^3J_{HH} = 7.7$ Hz, H-4 of pyridine), 9.1 (2H, d, $^3J_{HH} = 6.1$ Hz, H-2,6 of pyridine) ppm; ^{13}C NMR (125 MHz, *DMSO*-d$_6$): $\delta = 25.6$ (2 Me), 45.3 (CH), 52.0 and 53.2 (2 OMe), 67.5 (C(Me)$_2$), 72.0 (CH–N$^+$), 99.7 (*C*(CO)$_2$), 126.5, 145.5 and 146.9 (carbons of pyridine), 164.5 (CO of ring), 167.4 and 173.8 (2 CO$_2$Me) ppm; minor isomer (44%): ^{1}H NMR (500 MHz, *DMSO*-d$_6$): $\delta = 1.4$ (6H, s, 2 Me), 3.6 (3H, s, OMe), 3.7 (3H, s, OMe), 4.5 (1H, d, $^3J_{HH} = 9.5$ Hz, CH–N$^+$), 6.2 (1H, d, $^3J_{HH} = 9.5$ Hz, CH), 8.1 (2H, m, H-3,5 of pyridine), 8.6 (1H, t, $^3J_{HH} = 7.7$ Hz, H-4 of pyridine), 8.9 (2H, d, $^3J_{HH} = 6.1$ Hz, H-2,6 of pyridine) ppm; ^{13}C NMR (125 MHz, *DMSO*-d$_6$): $\delta = 25.4$ (2 Me), 43.8 (CH), 51.8 and 53.5 (2 OMe), 67.2 (C(Me)$_2$), 72.3 (CH–N$^+$), 99.8 (*C*(CO)$_2$), 127.2, 146.6, and 146.8 (carbons of pyridine), 164.6 (CO of ring), 167.7 and 172.1 (2 CO$_2$Me) ppm.

Diethyl-2-(isopropylidenemalonate-5-yl-5-ylide)-3-pyridinium-1,4-butanedioate
(**8e**; $C_{19}H_{23}NO_8$)

Pale yellow powder; yield: 0.68 g (86%); m.p.: 172–174°C; IR (KBr): $\nu_{max} = 1730$ (C=O, ester), 1590 (C=O) cm^{-1}; MS: m/z (%) = 394 (M$^+$ + 1, 2), 256 (25), 211 (40), 183 (52), 156 (50), 138 (97), 79 (100), 43 (28); major isomer (66%): ^{1}H NMR (500 MHz, CDCl$_3$): $\delta = 1.2$ (3H, t, $^3J_{HH} = 7.3$ Hz, CH$_3$ of Et), 1.3 (3H, t, $^3J_{HH} = 7.3$ Hz, CH$_3$ of Et), 1.6 (6H, s, 2 Me), 4.1–4.4 (4H, m, 2 OCH$_2$), 4.9 (1H, d, $^3J_{HH} = 6.3$ Hz, CH–N$^+$), 5.7 (1H, d, $^3J_{HH} = 6.3$ Hz, CH), 7.8 (2H, m, H-3,5 of pyridine), 8.4 (1H, t, $^3J_{HH} = 7.6$ Hz, H-4 of pyridine), 9.1 (2H, d, $^3J_{HH} = 6.1$ Hz, H-2,6 of pyridine) ppm; ^{13}C NMR (125 MHz, CDCl$_3$): $\delta = 14.0$ and 14.1 (CH$_3$ of ester groups), 25.5 (2 Me), 46.7 (CH), 61.6 and 63.0 (2 OCH$_2$), 72.0 (CH–N$^+$), 77.2 (C(Me)$_2$), 101.7 (*C*(CO)$_2$), 126.0, 145.7, and 147.5 (carbons of pyridine), 166.7 (CO), 167.4, and 173.4 (2 CO$_2$Et) ppm; minor isomer (44%): ^{1}H NMR (500 MHz, CDCl$_3$): $\delta = 1.1$ (3H, t, $^3J_{HH} = 7.1$ Hz, CH$_3$ of Et), 1.4 (3H, t, $^3J_{HH} = 7.1$ Hz, CH$_3$ of Et), 1.5 (6H, s, 2 Me), 4.1–4.4 (4H, m, 2 OCH$_2$), 4.8 (1H, d, $^3J_{HH} = 8.5$ Hz, CH–N$^+$), 6.3 (1H, d, $^3J_{HH} = 8.5$ Hz, CH), 7.9 (2H, m, H-3,5 of pyridine), 8.3 (1H, t, $^3J_{HH} = 7.6$ Hz, H-4 of pyridine), 8.8 (2H, d, $^3J_{HH} = 6.1$ Hz, H-2,6 of pyridine) ppm; ^{13}C NMR (125 MHz, CDCl$_3$): $\delta = 13.9$ and 14.1 (CH$_3$ of ester groups), 25.6 (2 Me), 45.1 (CH), 61.5 and 63.5 (2 OCH$_2$), 72.5 (CH–N$^+$), 77.2 (C(Me)$_2$), 101.7 (*C*(CO)$_2$), 126.8, 145.8, and 147.4 (carbons of pyridine), 166.6 (CO), 167.5 and 172.5 (2 CO$_2$Et) ppm.

Diethyl-2-(indane-1,3-dione-2-yl-2-ylide)-3-pyridinium-1,4-butanedioate (**8f**; $C_{22}H_{21}NO_6$)

Pale yellow powder; yield: 0.62 g (78%); m.p.: 145–147°C; IR (KBr): $\nu_{max} = 1719$ (C=O, ester), 1537 (C=O, ketone) cm^{-1}; MS: m/z (%) = 395 (M$^+$, 3), 270 (25), 243 (10), 170 (68), 114 (15), 79 (100), 52 (72); ^{1}H NMR (500 MHz, *DMSO*-d$_6$): $\delta = 1.1$ (3H, t, $^3J_{HH} = 7.1$ Hz, CH$_3$ of Et), 1.2 (3H, t, $^3J_{HH} = 7.3$ Hz, CH$_3$ of Et), 4.0–4.4 (4H, m, 2 OCH$_2$), 4.5 (1H, d, $^3J_{HH} = 9.9$ Hz, CH–N$^+$), 6.5 (1H, d, $^3J_{HH} = 9.9$ Hz, CH), 6.9 (2H, m, CH of C$_6$H$_4$), 7.1 (2H, m, CH of C$_6$H$_4$), 7.9 (2H, m, H-3,5 of pyridine), 8.5 (1H, t, $^3J_{HH} = 7.6$ Hz, H-4 of pyridine), 8.9 (2H, d, $^3J_{HH} = 6.1$ Hz, H-2,6 of pyridine) ppm; ^{13}C NMR (125 MHz, *DMSO*-d$_6$): $\delta = 14.2$ and 14.6 (CH$_3$ of ester groups), 42.6 (CH), 60.8 and 63.1 (2 OCH$_2$), 70.9 (CH–N$^+$), 97.5 (*C*(CO)$_2$), 117.4, 129.7, and 140.1 (carbons of C$_6$H$_4$), 127.2, 146.4, and 147.2 (carbons of pyridine), 167.6 and 171.2 (2 CO$_2$Et), 188.1 (CO, ketone) ppm.

Di-tert-butyl-2-(indane-1,3-dione-2-yl-2-ylide)-3-pyridinium-1,4-butanedioate
(**8g**; $C_{26}H_{29}NO_6$)

Pale yellow powder; yield: 0.68 g (75%); m.p.: 183–184°C; IR (KBr): $\nu_{max} = 1708$ (C=O, ester), 1524 (C=O, ketone) cm^{-1}; MS: m/z (%) = 452 (M$^+$ + 1, 2), 261 (20), 243 (22), 170 (21), 79 (54), 57 (100); ^{1}H NMR (500 MHz, CDCl$_3$): $\delta = 1.2$ (9H, s, *t*-Bu), 1.5 (9H, s, *t*-Bu), 4.5 (1H, d, $^3J_{HH} = 8.7$ Hz, CH–N$^+$), 6.6 (1H, d, $^3J_{HH} = 8.7$ Hz, CH), 7.1 (4H, m, CH of C$_6$H$_4$), 7.7 (2H, m, H-3,5 of pyridine), 8.2 (1H, t, $^3J_{HH} = 7.6$ Hz, H-4 of pyridine), 8.9 (2H, d, $^3J_{HH} = 6.1$ Hz, H-2,6 of pyridine) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 27.9$ and 28.3 (CH_3 of *t*-Bu), 43.7 (CH), 72.5 ($CH{-}N^+$), 81.5 and 85.4 (2 $OC(Me)_3$), 97.2 ($C(CO)_2$), 117.7, 129.6, and 139.4 (carbons of C_6H_4), 126.2, 145.2, and 146.1 (carbons of pyridine), 166.6 and 170.5 (2 CO_2(*t*-Bu)), 190.1 (CO, ketone) ppm.

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