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Synthesis of zwitterionic salts via three component reactions of nitrogen-containing heterocycles, acetylenedicarboxylate and cyclic 1,3-dicarbonyl compounds

Er-Yan Xia, Jing Sun, Rong Yao, Chao-Guo Yan *

College of Chemistry & Chemical Engineering, Yangzhou University, Yangzhou 225002, China

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ABSTRACT

A practical synthetic procedure for the preparation of the charge-separated pyridinium–Meldrum acid zwitterionic salts was developed through a unique one-pot three component reaction of pyridine, acetylenedicarboxylate and Meldrum acid. Other nitrogen-containing heterocycles such as *N*-methylimidazole, 2-picoline, quinoline, isoquinoline and other cyclic 1,3-dicarbonyl compounds such as 1,3-cyclopentanedione, 1,3-cyclohexanedione, barbituric acid also took part in the reaction to give corresponding zwitterionic salts in moderate yields, respectively. In one case an unusual isoquinolinium 1,3-cyclopentanedionate was obtained. A feasible explanation is given for this novel one-pot tandem reaction and the formation of different kinds of products.

1. Introduction

The reaction of nucleophiles with activated acetylenes has attracted the attention of organic chemists for a long times, especially from the advantage point of heterocyclic synthesis.[1] In this class of reaction the addition of aprotic nucleophiles to activated acetylenes generated a dipolar zwitterionic intermediate. This kind of zwitterion can have a 1,3 or 1,4 disposition depending upon the nature of the nucleophile. Subsequent interception of the zwitterions with nucleophilic reagents gave versatile compounds.[2] In recent years more interest in this area has been given to the reaction of nitrogen-containing heterocycles with activated acetylenes. The synthetic potential of the addition intermediate derived from the reaction of nitrogen-containing heterocycles with activated acetylenes has been developed greatly especially by study of Nair et al.[3–10] and Yavari and Karimi[11–13] as well as others.[14–17] We thought that the rich and fascinating chemistry that stems from the addition of nucleophilic reagents to the activated acetylenes could be used to design new multicomponent reactions, which are our research interest. Thus we initiated the investigation of three component reactions of nitrogen-containing heterocycles, dimethyl acetylenedicarboxylate and cyclic 1,3-dicarbonyl compounds. In this text we wish to report the preliminarily interesting results of three component reaction and the formation of the zwitterionic salts.

2. Results and discussion

Recently Issa Yavari reported that the 1:1 intermediate generated by the addition of quinoline to dialkyl acetylenedicarboxylates is trapped by 1,3-indanedione to yield cycloaddition products in good yields, while under similar reaction conditions, *N*-methylimidazole, pyridine and 4-picoline produced the 1,4-zwitterionic compounds, respectively.[18–20] These results demonstrated that the properties of nitrogen-containing heterocycles play a determining rule in the reaction. It would be helpful to screen the scope and limitations of this three component reaction. We began our research by examining the reactivity of *N*-methylimidazole. The three component reactions of *N*-methylimidazole (**1a**), dimethyl acetylenedicarboxylate (**2**) with cyclic 1,3-dicarbonyl compounds (**3a**–**3d**) in methylene dichloride proceeds smoothly at room temperature to give the expected 1,4-zwitterionic salts **4a**–**4d** in higher yields in about 2 h. The used cyclic 1,3-dicarbonyl compounds included Meldrum acid (**3a**), 1,3-cyclopentanedione (**3b**), 1,3-cyclohexanedione (**3c**) and *N*,*N*-dimethylbarbituric acid (**3d**) (Scheme 1). The structures of 1,4-zwitterionic salts **4a**–**4d** were fully characterized by IR, ^{1}H, ^{13}C NMR and MS spectra as well as further confirmed by X-ray diffraction determination of one representative compound **4a** (Fig. 1). From Figure 1 it is clearly seen

* Corresponding author. E-mail address: cgyan@yzu.edu.cn.

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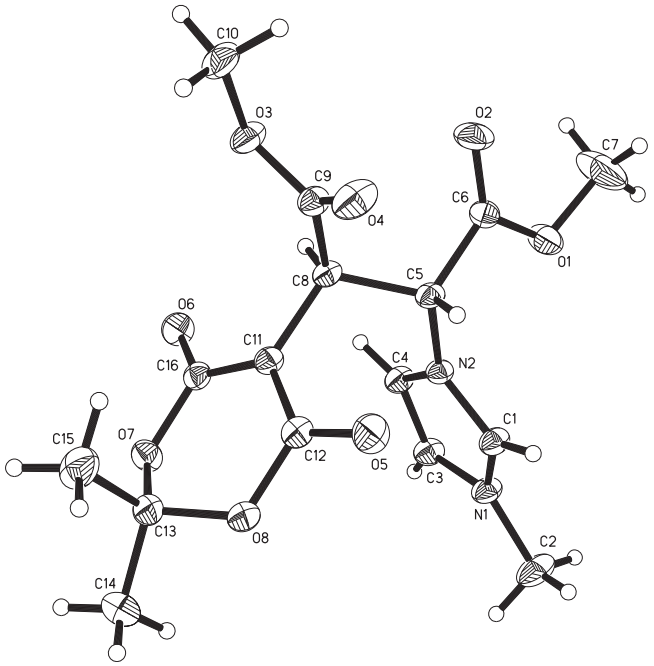
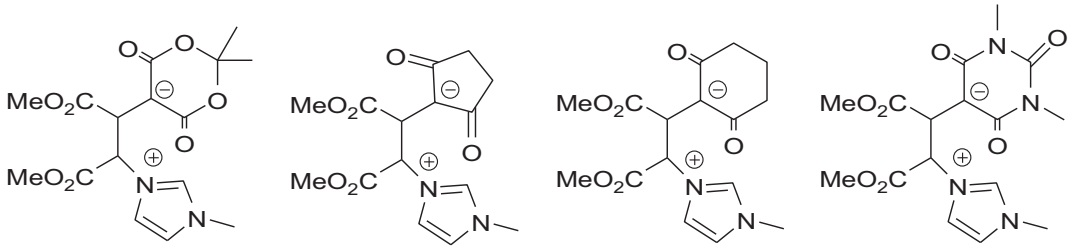


Figure 1. The molecular structure of compound **4a**.

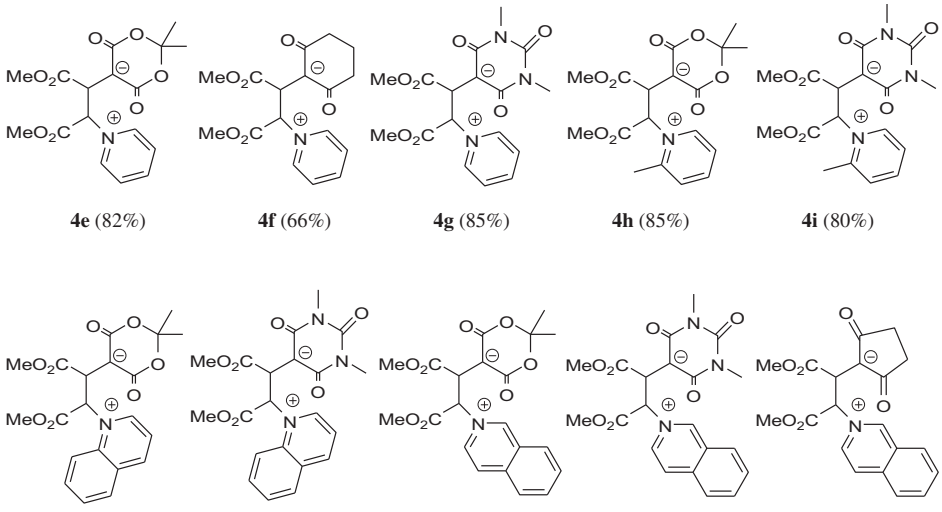
that the formed zwitterionic salt came from all three components of the reaction. The imidazolyl group and Meldrum acid unit exist in the same side of molecule, which cause the positive charge and negative charge are in the shortest distance. The methylene carbon atom in Meldrum acid unit adopts an sp^2 hybrid and the negative charge is delocalized to two carbonyl groups. The charge delocalization increases the stability of the 1,4-zwitterionic salt and makes it could be separated at room temperature. Very recently the synthesis of highly stable unusual charge-separated pyridinium–tetronic acid zwitterions from the reaction of nitrogen-containing heterocycles with dialkyl acetylenedicarboxylates and 3-chlorotetronic acid in EtOH at room temperature is also described (Scheme 1).[21]

Next the reactivity of pyridine, 2-picoline, quinoline and isoquinoline in this three component reaction was also investigated. The reactions were also furnished at room temperature in 2–3 h and the same kind of 1,4-zwitterionic salts **4e**–**4m** were obtained in high yields in most cases (Scheme 2). No any kinds of cycloaddition products were separated. It should be pointed that the 1,4-zwitterionic salts **4e** and **4g** have been described by Yavari's research group.[20] These results clearly demonstrated that this three component reaction has great generality. Quinoline and isoquinoline showed similar reactivity with pyridine. The structures of 1,4-zwitterionic salts **4e**–**4m** were established by IR, ^1H, ^{13}C NMR and MS spectra. The prepared 1,4-zwitterionic salts have high polarity and usually dissolve in water very well. Most NMR spectra are recorded in deuterium water. An interesting phenomenon was found by careful analysis of ^1H NMR spectra of the obtained



4a (85%) **4b** (87%) **4c** (85%) **4d** (83%)

Scheme 1. The synthesized 1,4-zwitterionic salts **4a**–**4d**.

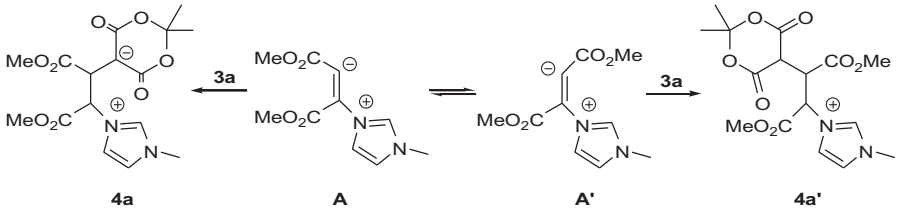


4e (82%) **4f** (66%) **4g** (85%) **4h** (85%) **4i** (80%)

4j (65%) **4k** (70%) **4l** (72%) **4m** (65%) **4n** (68%)

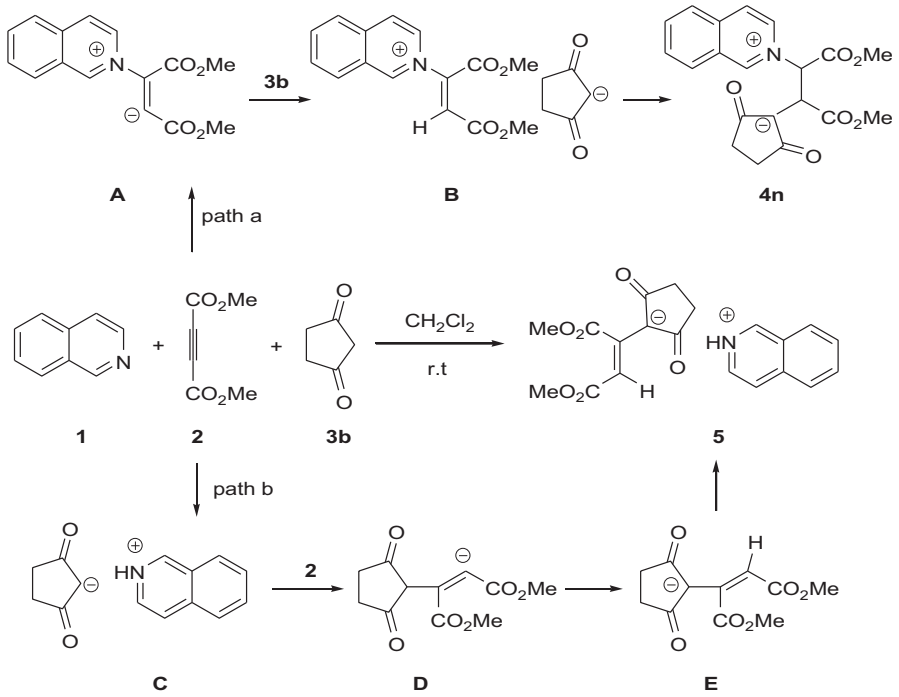
Scheme 2. The synthesized 1,4-zwitterionic salts **4e**–**4m**.

1,4-zwitterionic salts. The ^{1}H NMR spectra of **4a**, **4e**, **4f** and **4j** gave two sets of peaks for each characteristic group, which indicates that two isomers co-existed in the samples of these four products. The ratio of two isomers in each pair can be also determined by calculation of integration areas (**4a**/**4a**′=3:1, **4e**/**4e**′=3:1, **4f**/**4f**′=3:1, **4j**/**4j**′=5:2). These two isomers are obviously diastereomers due to the existence of two chiral carbon atoms in the molecule. In order to explain the formation of two diastereomers a plausible rationalization is tentatively proposed by using the formation of **4a** and **4a**′ as an example, which is illustrated in Scheme 3. The addition of *N*-methylimidazole to dimethyl acetylenedicarboxylates gave a 1,3-zwitterionic intermediate (**A**), which in turn is attacked by Meldrum acid (**3a**) to give the final 1,4-zwitterionic salt **4a**. On the other hand the 1,3-zwitterionic intermediate (**A**) is a *cis* vinyl anion, which could transferred partially to a trans intermediate (A′) by racemization. Then Meldrum acid attacked intermediate (A′) to give the product **4a**′. It is the transformation of intermediates A to A′ caused the formation of the formation of two diastereomers in some cases.



Scheme 3. The formation of two diastereomers **4a** and **4a**′.

Under similar reaction conditions the three component reaction of isoquinoline (**1e**), dimethyl acetylenedicarboxylate (**2**) and 1,3-cyclopentanedione (**3b**) in dry methylene dichloride at room temperature gave an isoquinolinium 1,3-pentanedionate **5** (80%) as main product instead of the expected 1,4-zwitterionic salt (**4n**) (Scheme 4). But when the three component reaction was carried out in methanol the expected 1,4-zwitterionic salt (**4n**) could be prepared in 68% yields. The structure of salts **4n** and **5** were established by spectroscopic data and X-ray determination of single crystal (Figs. 2 and 3). From Figure 3 it clearly seen that the cyclopentanedione connected to C-6 atom of dimethyl fumarate and the C(6)–C(9) bond is a double bond with the bond distance of 1.356 (8) Å, while the C(5)–C(6), C(6)–C(7) and C(9)–C(10) bonds are single bonds with the distances of 1.446(3) Å, 1.507(3) Å and 1.453(3) Å, respectively. The negative charge is on the C-2 carbon atom of cyclopentanedione ring with the existence of the separated isoquinolinium cation. One intramolecular hydrogen bond existed between the N–H and C=O bond with the N–H···O distance at 2.578(2) Å. The anions and cations form well separated columns along the *b*-axis in the stacking structure of the compound (Fig. 4). The H atoms of the cations are hydrogen bonded to the carbonyl oxygen form adjacent anions. These intermolecular hydrogen bonds play an important role in the stabilization of the whole structure, which allows the compound to form a 3D network structure. The formation of isoquinolinium salt **5** indicated that the three component reaction of nitrogen-containing heterocycles, DMAD and reactive methylene compounds has very potential versatility and molecular diversity. Although the mechanistic details of the reactions are not known, we proposed a plausible reaction course for the formation of isoquinolinium salt, which is illustrated in Scheme 2. In this three component reaction there are two reaction paths. On path a isoquinoline added to DMAD to give 1,3-zwitterionic intermediate (A), which in turn is attacked by cyclopentanedione to give another intermediate (B). Then it is attacked by carbanium ion of cyclopentanedione to give the usual 1,4-zwitterionic salt **4n**.[20] But this common reaction did not happen on this case and the reaction proceeded according to path b.



Scheme 4. The proposed mechanism for the formation of salts **4** and **5**.

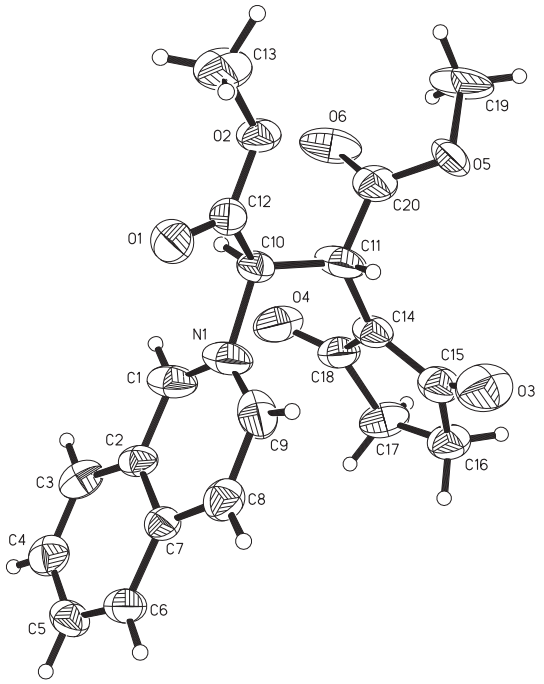


Figure 2. The molecular structure of compound **4n**.

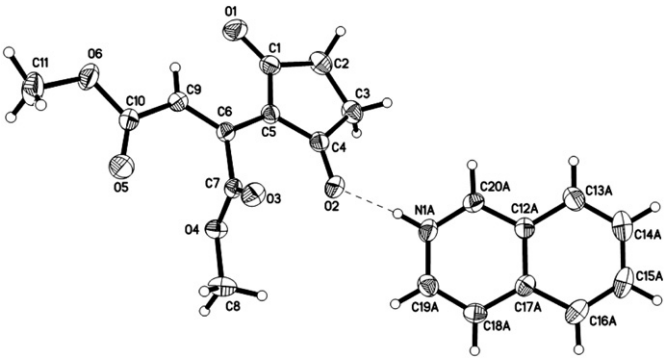


Figure 3. The molecular structure of compound **5**.

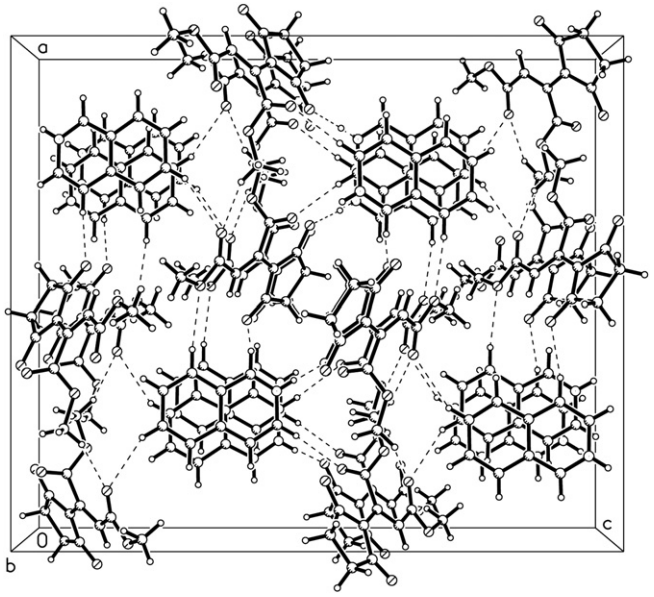


Figure 4. The packing diagram of a unit cell of compound **5** along the *b*-axis.

On reaction path b isoquinoline firstly deprotonated more acidic cyclopentanedione to give a carbanion ion (C), which in turn acted as nucleophile to add to triple bond of DMAD to yield intermediate (D). This intermediate is converted to final product **5** via a 1,3-proton shift process.

In summary we have demonstrated an interesting three component reactions of nitrogen-containing heterocycles, acetylene and cyclic 1,3-dicarbonyl compounds. A series of charge-separated zwitterionic salts are prepared in high yields in very convenient manner. Prominent among the advantages of this new method are novelty, operational simplicity, and good yields. Further expansion of the reaction scope and synthetic applications of this methodology are in progress in our laboratory.

3. Experiment section

3.1. General procedure for the three component reaction

The cyclic amine **1a**–**1e** (2.0 mmol) was added to a stirred solution of dimethyl acetylenedicarboxylate **2** (2.0 mmol) and cyclic 1,3-dicarbonyl compounds **3a**–**3d** (2.0 mmol) in dry methylene dichloride at room temperature. The reaction mixture was then stirred at room temperature for 2–3 h. The resulting precipitates were collected by filtration and washed with a little of CH_2Cl_2 to give the pure products for analysis.

*3.1.1. Compound **4a**.* White solid, 85%, dec 208–210 °C; ^{1}H NMR (600 MHz, D_2O) δ (**4a**): 8.78 (s, 1H, CH), 7.42 (s, 1H, CH), 7.33 (s, 1H, CH), 5.73 (d, J=8.4 Hz, 1H, CH), 4.41 (d, J=8.4 Hz, 1H, CH), 3.79 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.62 (s, 3H, NCH_3), 1.41 (s, 6H, CH_3); (**4a**′): 8.81 (s, 1H, CH), 7.45 (s, 1H, CH), 7.29 (s, 1H, CH), 5.36 (d, J=6.0 Hz, 1H, CH), 4.49 (d, J=6.6 Hz, 1H, CH), 3.81 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.58 (s, 3H, NCH_3), 1.49 (s, 6H, CH_3); ^{13}C NMR (150 MHz, D_2O) δ: 174.1, 173.7, 169.2, 168.8, 168.0, 167.8, 138.1, 137.0, 124.0, 123.0, 122.9, 122.8, 122.2, 103.4, 71.2, 70.5, 62.1, 60.5, 53.9, 53.8, 53.0, 52.9, 44.4, 43.8, 35.8, 24.4, 24.3; IR (KBr) ν: 3424, 3136, 3108, 3070, 2984, 1741, 1717, 1678, 1597, 1434, 1388, 1368, 1265, 1212, 1178, 1116, 1004, 978, 929, 893, 821, 783, 750 cm^{-1}; MS (m/z): 369.42 ($[M+1]^+$) 100%. Anal. Calcd for $C_{16}H_{20}N_2O_8$: C, 52.17; H, 5.47; N, 7.61. Found: C, 52.45; H, 5.72; N, 7.39.

*3.1.2. Compound **4b**.* White solid, 87%, mp 159–160 °C; ^{1}H NMR (600 MHz, D_2O) δ: 8.69 (s, 1H, CH), 7.35 (s, 1H, CH), 7.26 (s, 1H, CH), 5.80 (d, J=6.6 Hz, 1H, CH), 4.21 (d, J=6.6 Hz, 1H, CH), 3.77 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.59 (s, 3H, NCH_3), 2.15 (s, 4H, CH_2); ^{13}C NMR (150 MHz, D_2O) δ: 204.3, 173.0, 173.0, 168.8, 137.1, 123.1, 122.4, 105.7, 60.1, 53.9, 52.9, 41.9, 35.8, 31.7; IR (KBr) ν: 3429, 3063, 2947, 1736, 1716, 1645, 1534, 1435, 1345, 1290, 1173, 1109, 1016, 964, 771 cm^{-1}; MS (m/z): 323.54 ($[M+1]^+$) 100%. Anal. Calcd for $C_{15}H_{19}N_2O_6$: C, 55.72; H, 5.92; N, 8.66. Found: C, 56.03; H, 5.84; N, 8.50.

*3.1.3. Compound **4c**.* Light yellow solid, 85%, mp 134–135 °C; ^{1}H NMR (600 MHz, D_2O) δ: 8.61 (s, 1H, CH), 7.29 (s, 1H, CH), 7.22 (s, 1H, CH), 5.63 (d, J=7.2 Hz, 1H, CH), 4.53 (d, J=7.2 Hz, 1H, CH), 3.74 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.54 (s, 3H, NCH_3), 2.06–2.04 (m, 4H, CH_2), 1.65–1.62 (m, 2H, CH_2); ^{13}C NMR (150 MHz, D_2O) δ: 195.2, 175.2, 174.9, 169.5, 169.1, 124.2, 124.1, 123.2, 122.3, 121.7, 107.0, 106.4, 61.6, 60.4, 53.8, 53.6, 52.7, 52.6, 42.9, 42.8, 42.5, 35.9, 35.8, 34.5, 34.4, 20.7; IR (KBr) ν: 3435, 3103, 3050, 2940, 1732, 1713, 1582, 1499, 1435, 1384, 1285, 1260, 1175, 1114, 1018, 873, 771 cm^{-1}; MS (m/z): 337.50 ($[M+1]^+$) 100%. Anal. Calcd for $C_{16}H_{21}N_2O_6$: C, 56.97; H, 6.27; N, 8.30. Found: C, 57.26; H, 6.51; N, 7.88.

*3.1.4. Compound **4d**.* White solid, 83%, dec 198–199 °C; ^{1}H NMR (600 MHz, D_2O) δ: 8.70 (s, 1H, CH), 7.35 (s, 1H, CH), 7.22 (s, 1H, CH), 5.75 (d, J=6.6 Hz, 1H, CH), 4.62 (d, J=6.6 Hz, 1H, CH), 3.76 (s, 3H,

OCH_3), 3.73 (s, 3H, OCH_3), 3.59 (s, 3H, NCH_3), 3.03 (s, 6H, NCH_3); ^{13}C NMR (150 MHz, D_2O) δ: 174.0, 169.2, 164.0, 154.0, 136.9, 123.2, 123.1, 122.4, 122.3, 82.9, 60.5, 53.8, 52.9, 44.3, 35.8, 27.6; IR (KBr) ν: 3435, 3131, 3071, 2954, 1732, 1678, 1595, 1425, 1380, 1321, 1249, 1172, 1100, 1051, 1007, 983, 888, 806, 780 cm^{-1}; MS (m/z): 381.59 ($[M+1]^+$) 100%. Anal. Calcd for $C_{16}H_{20}N_4O_7$: C, 50.52; H, 5.30; N, 14.73. Found: C, 50.28; H, 5.61; N, 14.56.

3.1.5. Compound ***4e***. Orange solid, 82%, mp 180–182 °C; ^1H NMR (600 MHz, D_2O) δ (**4e**): 8.96 (d, J=6.0 Hz, 2H, CH), 7.98–7.94 (m, 3H, CH), 5.71 (d, J=7.8 Hz, 1H, CH), 4.67 (d, J=7.8 Hz, 1H, CH), 3.74 (s, 3H, OCH_3), 3.55 (s, 3H, OCH_3), 1.48 (s, 6H, CH_3); (**4e′**): 8.75 (d, J=6.6 Hz, 2H, CH), 8.53–8.49 (m, 3H, CH), 6.09 (d, J=9.0 Hz, 1H, CH), 4.61 (d, J=9.0 Hz, 1H, CH), 3.76 (s, 3H, OCH_3), 3.64 (s, 3H, OCH_3), 1.30 (s, 6H, CH_3); ^{13}C NMR (150 MHz, D_2O) δ: 173.6, 173.3, 168.3, 167.9, 167.8, 147.5, 147.3, 146.2, 145.1, 127.3, 103.5, 103.4, 71.5, 70.8, 70.4, 70.2, 54.3, 54.0, 53.1, 53.0, 44.8, 44.0, 24.5, 24.3; IR(KBr) ν: 3426, 3030, 2961, 2902, 1749, 1723, 1596, 1491, 1435, 1403, 1263, 1242, 1215, 1167, 1119, 1070, 1000, 816, 783 cm^{-1}; MS (m/z): 366.42 ($[M+1]^+$) 100%. Anal. Calcd for $C_{17}H_{19}NO_8$: C, 55.89; H, 5.24; N, 3.83. Found: C. 56.27; H, 5.40; N, 4.11.

3.1.6. Compound ***4f***. Yellow solid, 66%, mp 141–142 °C; ^1H NMR (600 MHz, D_2O) δ (**4f**): 8.61 (d, J=6.0 Hz, 2H, CH), 8.47 (t, J=7.8 Hz, 1H, CH), 7.89 (t, J=7.2 Hz, 2H, CH), 6.01 (d, J=8.4 Hz, 1H, CH), 4.78 (d, J=8.4 Hz, 1H, CH), 3.78 (s, 3H, OCH_3), 3.59 (s, 3H, OCH_3), 2.00–1.92 (m, 4H, CH_2), 1.52–1.50 (m, 2H, CH_2); (**4f**): 8.63 (d, J=5.4 Hz, 2H, CH), 8.37 (t, J=7.8 Hz, 1H, CH), 7.85 (t, J=7.2 Hz, 2H, CH), 6.49 (s, 1H, CH), 3.66 (s, 3H, OCH_3), 3.60 (s, 3H, OCH_3), 2.26 (t, J=6.6 Hz, 4H, CH_2), 1.84–1.82 (m, 2H, CH_2); ^{13}C NMR (150 MHz, D_2O) δ: 197.5, 194.2, 191.6, 173.6, 172.6, 170.7, 170.4, 169.7, 168.4, 168.1, 161.7, 145.3, 142.5, 140.2, 140.1, 136.5, 130.8, 127.2, 126.8, 126.2, 110.9, 53.7, 53.0,52.9, 52.5, 52.2, 51.8, 48.8, 36.6, 36.4, 34.5, 33.9, 33.1, 28.0, 20.3, 20.0, 19.9, 19.8, 19.3, 19.2; IR (KBr) ν: 3434, 3133, 3070, 2953, 1743, 1726, 1633, 1580, 1494, 1438, 1390, 1284, 1175, 1127, 1019, 998, 969,853, 792, 768 cm^{-1}; MS (m/z): 334.24 ($[M+1]^+$) 100%. Anal. Calcd for $C_{17}H_{20}NO_6$: C, 61.07; H, 6.03; N, 4.19. Found: C, 59.76; H, 6.40; N, 3.79.

3.1.7. Compound ***4g***. Yellow solid, 85%, mp 180–181 °C; ^1H NMR (600 MHz, D_2O) δ: 8.70–8.69 (m, 2H, CH), 8.46–8.43 (m, 1H, CH), 7.88–7.86 (m, 2H, CH), 6.14 (d, J=7.8 Hz, 1H, CH), 4.84 (d, J=7.8 Hz, 1H, CH), 3.79 (s, 3H, OCH_3), 3.61 (s, 3H, OCH_3), 2.95 (s, 6H, NCH_3); ^{13}C NMR (150 MHz, D_2O) δ: 173.5, 168.2, 163.9, 153.8, 147.2, 145.1, 127.4, 82.6, 70.2, 54.2, 53.1, 44.5, 27.6; IR (KBr) ν: 3430, 3132, 3055, 3032, 2962, 1748, 1722, 1681, 1614, 1573, 1489, 1427, 1386, 1324, 1270, 1239,1176, 1052, 1009, 853, 810, 774 cm^{-1}; MS (m/z): 378.32 ($[M+1]^+$) 100%. Anal. Calcd for $C_{17}H_{19}N_3O_7$: C, 54.11; H, 5.08; N, 11.14. Found: C, 53.75; H, 5.31; N, 10.83.

3.1.8. Compound ***4h***. Light yellow solid, 85%, mp 192–193 °C; ^1H NMR (600 MHz, D_2O) δ: 9.13 (d, J=6.6 Hz, 1H, CH), 8.34–8.31 (m, 1H, CH), 7.86–7.82 (m, 2H, CH), 6.11 (d, J=10.2 Hz, 1H, CH), 4.67 (d, J=9.6 Hz, 1H, CH), 3.68 (s, 3H, OCH_3), 3.49 (s, 3H, OCH_3), 2.83 (s, 3H, CH_3), 1.49 (s, 6H, CH_3); ^{13}C NMR (150 MHz, D_2O) δ: 173.3, 168.0, 167.6, 156.9, 146.4, 144.3, 129.9, 125.4, 103.7, 71.0, 64.2, 54.1, 53.0, 44.3, 24.4, 20.5; IR (KBr) ν: 3637, 3402, 3062, 3008, 2960, 2345, 1758, 1725, 1609, 1513, 1444, 1402, 1319, 1261, 1209, 1166, 1117, 1072, 999, 968, 935, 911, 815, 785 cm^{-1}; MS (m/z): 380.32 ($[M+1]^+$) 100%. Anal. Calcd for $C_{18}H_{21}NO_8$: C, 56.99; H, 5.58; N, 3.69. Found: C, 57.20; H, 5.66; N, 3.83.

3.1.9. Compound ***4i***. Yellow solid, 80%, mp 170–172 °C; ^1H NMR (600 MHz, D_2O) δ: 8.55 (d, J=6.0 Hz, 1H, CH), 8.24 (t, J=7.2 Hz, 1H, CH), 7.76 (d, J=7.8 Hz, 1H, CH), 7.71 (br s, 1H, CH), 6.26 (d, J=10.2 Hz, 1H, CH), 4.91 (d, J=9.6 Hz, 1H, CH), 3.76 (s, 3H, OCH_3), 3.62 (s, 3H, OCH_3), 2.94 (s, 6H, NCH_3), 2.78 (s, 3H, CH_3); ^{13}C NMR (150 MHz, D_2O) δ: 173.8, 168.6, 163.9, 157.0, 153.7, 146.4, 143.7, 130.0, 125.1, 82.4, 64.1, 54.2, 53.9, 53.2, 43.4, 27.5, 20.1; IR (KBr) ν: 3508, 3417, 3046, 2951, 1748, 1670, 1591, 1508, 1436, 1385, 1320, 1268, 1174, 1090, 1052, 1011, 974, 897, 853, 779 cm^{-1}; MS (m/z): 392.24 ($[M+1]^+$) 100%. Anal. Calcd for $C_{18}H_{21}N_3O_7$: C, 55.24; H, 5.41; N, 10.74. Found: C, 55.15; H, 5.80; N, 10.40.

3.1.10. Compound ***4j***. Orange solid, 65%, mp 168–169 °C; ^1H NMR (600 MHz, DMSO-d_6) δ (**4j**): 9.94 (d, J=6.0 Hz, 1H, ArH), 9.29 (d, J=7.8 Hz, 1H, ArH), 8.50 (d, J=9.0 Hz, 1H, ArH), 8.43 (d, J=7.8 Hz, 1H, ArH), 8.21–8.19 (m, 2H, ArH), 8.00–7.98 (m, 1H, ArH), 6.82 (d, J=7.2 Hz, 1H, CH), 4.86 (d, J=6.6 Hz, 1H, CH), 3.77 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 1.00 (s, 6H, CH_3); (**4j′**): 8.92 (br s, 1H, ArH), 8.39 (d, J=8.4 Hz, 1H, ArH), 8.03 (d, J=8.4 Hz, 1H, ArH), 8.00–7.98 (m, 1H, ArH), 7.78 (t, J=7.8 Hz, 1H, ArH), 7.63 (t, J=7.8 Hz, 1H, ArH), 7.56–7.54 (m, 1H, ArH), 3.72 (s, 2H, CH), 3.66 (s, 6H, OCH_3), 1.83 (s, 6H, CH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 164.8, 163.4, 150.4, 147.5, 136.2, 129.6, 128.7, 128.1, 127.9, 126.6, 121.4, 106.4, 99.6, 64.1, 53.5, 52.8, 36.7, 32.9, 26.8, 25.2; IR(KBr) ν: 3440, 3107, 3007, 2955, 1752, 1729, 1598, 1532, 1441, 1403, 1333, 1310, 1263, 1236, 1205, 1108, 1035, 996, 966, 911, 817, 776 cm^{-1}; MS (m/z): 416.42 ($[M+1]^+$) 100%. Anal. Calcd for $C_{21}H_{21}NO_8$: C, 60.72; H, 5.10; N, 3.37. Found: C, 60.53; H, 4.85; N, 3.64.

3.1.11. Compound ***4k***. Yellow solid, 70%, mp 143–144 °C; ^1H NMR (600 MHz, D_2O) δ: 9.71 (d, J=5.4 Hz, 1H, ArH), 8.96 (d, J=7.8 Hz, 1H, ArH), 8.12 (d, J=8.4 Hz, 1H, ArH), 7.99 (d, J=9.6 Hz, 1H, ArH), 7.92–7.88 (m, 2H, ArH), 7.33 (t, J=7.8 Hz, 1H, ArH), 6.62 (d, J=6.6 Hz, 1H, CH), 5.02 (d, J=6.6 Hz, 1H, CH), 3.75 (s, 3H, OCH_3), 3.48 (s, 3H, OCH_3), 2.73 (s, 6H, NCH_3); ^{13}C NMR (150 MHz, D_2O) δ: 173.9, 168.5, 163.2, 153.3, 151.4, 148.9, 139.5, 135.1, 130.7, 129.4, 129.3, 121.0, 116.7, 84.0, 62.8, 54.0, 53.8, 53.0, 44.9, 27.3; IR(KBr) ν: 3430, 3118, 2993, 2951, 1721, 1678, 1584, 1530, 1438, 1341, 1288, 1225, 1176, 1065,1033, 997, 968, 886, 808, 781 cm^{-1}; MS (m/z): 428.16 ($[M+1]^+$) 100%. Anal. Calcd for $C_{21}H_{21}N_2O_8$: C, 59.01; H, 4.95; N, 9.83. Found: C, 58.69; H, 5.41; N, 9.57.

3.1.12. Compound ***4l***. Yellow solid, 72%, mp 196–197 °C; ^1H NMR (600 MHz, DMSO-d_6) δ: 10.10 (br s, 1H, ArH), 8.80 (s, 1H, ArH), 8.55–8.47 (m, 2H, ArH), 8.31–8.26 (m, 2H, ArH), 8.05–8.03 (m, 1H, ArH), 5.96 (br s, 1H, CH), 4.97 (br s, 1H, CH), 3.78 (d, J=6.6 Hz, 3H, OCH_3), 3.56 (d, J=6.6 Hz, 3H, OCH_3), 1.30 (d, J=6.6 Hz, 6H, CH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 173.9, 167.5, 164.5, 152.3, 152.0, 142.1, 137.5, 137.4, 137.0, 135.3, 131.1, 130.9, 128.1, 127.7, 127.1, 126.5, 126.3, 123.9, 120.6, 99.7, 72.0, 67.8, 56.0, 53.3, 52.8, 52.0, 45.3, 36.7, 30.6, 26.8, 25.6, 18.6; IR (KBr) ν: 3422, 3049, 3004, 2955, 1748, 1720, 1675, 1606,1514, 1471, 1441, 1402, 1368, 1336, 1246, 1207, 1167, 1126, 1060, 1024, 1002, 934, 827, 778 cm^{-1}; MS (m/z): 416.48 ($[M+1]^+$) 100%. Anal. Calcd for $C_{21}H_{21}NO_8$: C, 60.72; H, 5.10; N, 3.37. Found: C, 60.68; H, 5.42; N, 3.10.

3.1.13. Compound ***4m***. Yellow solid, 65%, mp 180–181 °C; ^1H NMR (600 MHz, $CDCl_3$) δ: 8.16 (s, 1H, ArH), 7.83 (t, J=7.2 Hz, 1H, ArH), 7.74 (d, J=7.2 Hz, 1H, ArH), 7.69 (d, J=7.8 Hz, 2H, ArH), 7.62 (t, J=7.8 Hz, 1H, ArH), 7.09 (d, J=7.2 Hz, 1H, ArH), 6.05 (d, J=6.6 Hz, 1H, CH), 5.00 (d, J=6.6 Hz, 1H, CH), 3.91 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.02 (s, 6H, NCH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 172.3, 169.5, 168.5, 167.4, 162.3, 161.5, 152.1, 151.7, 148.8, 148.5, 137.5, 136.9, 135.2, 134.2, 130.4, 130.3, 130.0, 129.8, 127.2, 127.1, 126.8, 125.9, 124.0, 102.6, 86.5, 78.5, 69.5, 53.5, 52.0, 50.9, 50.4 44.7, 27.0, 26.8; IR (KBr) ν: 3464, 3073, 2955, 1739, 1682, 1647, 1580, 1432, 1313, 1266, 1192, 1170, 1007, 941, 878, 837, 778 cm^{-1}; MS (m/z): 428.51 ($[M+1]^+$) 100%. Anal. Calcd for $C_{21}H_{21}N_3O_7$: C, 59.01; H, 4.95; N, 9.83. Found: C, 58.70; H, 5.27; N, 9.77.

3.1.14. Compound ***4n***. Yellow solid, 68%, mp 134–136 °C; ^1H NMR (600 MHz, D_2O) δ: 9.46 (s, 1H, ArH), 8.27–8.25 (m, 2H, ArH), 8.19 (d, J=6.6 Hz, 1H, ArH), 8.11–8.07 (m, 2H, ArH), 7.91–7.89 (m, 1H, ArH), 6.26 (d, J=9.0 Hz, 1H, CH), 4.47 (d, J=9.0 Hz, 1H, CH), 3.76 (s, 3H, OCH_3), 3.61 (s, 3H, OCH_3), 1.83 (s, 4H, CH_2); ^{13}C NMR (150 MHz, D_2O) δ: 204.2, 172.5, 168.2, 150.5, 138.2, 138.0, 134.1, 131.7, 130.6, 127.2, 126.9, 125.5, 105.5, 69.5, 57.4, 54.3, 53.2, 48.8, 42.0, 31.5, 16.7;

IR (KBr) ν: 3419, 3073, 2955, 1743, 1645, 1537, 1470, 1436, 1399, 1361, 1313, 1274, 1238, 1165, 1131, 1012, 985, 930, 883, 834, 774 cm^{-1}; MS (m/z): 370.58 ($[M+1]^+$) 100%. Anal. Calcd for $C_{20}H_{19}NO_6$: C, 65.37; H, 5.18; N, 3.79. Found: C, 65.58; H, 5.44; N, 3.56.

3.1.15. Compound ***5***. White solid, 80%, mp 166–168 °C; ^1H NMR (600 MHz, D_2O) δ: 9.46 (s, 1H, ArH), 8.34–8.27 (m, 4H, ArH), 8.11–8.08 (m, 2H, ArH), 7.89 (s, 1H, ArH), 3.74 (s, 3H, OCH_3), 3.56 (s, 3H, OCH_3), 2.22 (s, 4H, CH_2); ^{13}C NMR (150 MHz, D_2O) δ: 205.7, 203.4, 172.6, 169.7, 146.7, 142.6, 138.8, 136.7, 130.9, 130.8, 130.1, 127.4, 127.2, 125.4, 107.2, 52.8, 51.8, 32.4; IR (KBr) ν: 3430,3080, 3026, 2919, 2095, 1730, 1707, 1639, 1554, 1457, 1431, 1356, 1295, 1258, 1235, 1189, 1152, 1111, 1029, 1007, 971, 904, 874, 856, 749 cm^{-1}; MS (m/z): 239.41 ($[M-C_9H_8N]^+$) 100%. Anal. Calcd for $C_{20}H_{19}NO_6$: C, 65.03; H, 5.18; N, 3.79. Found: C, 64.74; H, 5.52; N, 3.60.

4. Supplementary data available

Crystallographic data (**4a**: CCDC 755770; **4i**: CCDC 761762; **4n**: CCDC 761761; **5**: CCDC 755769) have been deposited vat the Cambridge Crystallographic Database Centre.

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