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Synthesis of new malonaldehyde derivatives using 2-heteroaryl-substituted trimethinium salts

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ABSTRACT

A synthetic route for obtaining 2-heteroaryl-substituted zwitterionic malonaldehydes **1c–6c** is described. The synthesis involves the two-fold formylation of heteroarylacetic acids **1a–6a** using the Vilsmeier–Haack reagent, followed by hydrolysis of the intermediate trimethinium salts **1b–6b** with aqueous sodium carbonate. Elemental analysis, IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data confirm the structures of the newly synthesized compounds.

Malonaldehyde (MA) is a highly reactive biochemically important three-carbon dialdehyde (O=CHCH$_2$CH=O ⇆ HOCH=CHCH=O), produced, for example, as one of the end-products of lipid peroxidation.[1] Due to its high reactivity, MA has the ability to form adducts with α-amino acids and biomolecules such as proteins or DNA. Proteins are much more reactive with MA than free amino acids, resulting in a variety of adducts and cross-linked products. MA can also react with DNA bases producing a variety of mutagenic and possibly carcinogenic compounds.[2–13]

There has been a significant interest in the synthesis of various malonaldehyde derivatives.[14–18] In this Letter, we report on the synthesis and structural characterization of six new 2-heteroaryl-substituted zwitterionic malonaldehyde derivatives **lc–6c**. To the best of our knowledge, almost no attention has been paid to the synthesis of such compounds using 2-heteroaryl-substituted trimethinium salts as starting compounds.[18] The structural characterizations were performed using UV/vis absorption, IR, ^{1}H NMR, and ^{13}C NMR spectroscopy, and mass spectrometry.

The new malonaldehyde derivatives **1c–6c** were synthesized using a three-step procedure as shown in Figure 1: (i) synthesis of *N*-heteroaryl acetic acids **1a–6a** via the nucleophilic substitution reaction between the heteroarenes **R1–6** and bromoacetic acid; (ii) synthesis of the corresponding 2-heteroaryl-substituted trimethinium salts **1b–6b** by two-fold Vilsmeier–Haack–Arnold formylation of the *N*-heteroaryl-substituted acetic acids **1a–6a**;[18–22] (iii) synthesis of the zwitterionic malonaldehyde derivatives **1c–6c** by hydrolysis of the 2-heteroaryl substituted trimethinium salts **1b–6b** with aqueous sodium carbonate solution. The application of the Vilsmeier–Haack formylation of aliphatic instead of aromatic substrates was successfully first introduced by Arnold.[15,17,18b] Among the *N*-heteroaryl acetic acids **1a–6a** synthesized and the corresponding trimethinium salts **1b–6b**, compounds **1a–3a** and **1b–3b** are new and their structural characterizations are provided in the experimental section and Supplementary data. Furthermore, all of the zwitterionic malonaldehyde derivatives **1c–6c** are novel and their structures were confirmed by elemental analysis, ^{1}H NMR, ^{13}C NMR, and IR spectroscopy, and by mass spectrometry (see experimental section and the Supplementary data).

In conclusion, six novel zwitterionic malonaldehyde derivatives **1c–6c** were synthesized using 2-heteroaryl-substituted trimethinium salts as starting compounds. These new zwitterionic malonaldehydes are promising candidates for the synthesis of the corresponding heteroaryl-substituted carbo-and heterocycles.

Typical procedure for the synthesis of *N*-heteroaryl acetic acids 1a–6a

Heteroarenes **R1–6** (7.0 mmol) was added to bromoacetic acid (1.00 g, 7.0 mmol) dissolved in MeCN (40 mL). The mixture was refluxed at 60 °C for 7 h. The resulting colorless crystals of **1a–6a** were collected by filtration, recrystallized from 2-propanol, and dried over P_4O_{10} in a desiccator.[19]

Typical procedure for the synthesis of 2-heteroaryl-substituted trimethinium salts 1b–6b

The formylation reagent was prepared by mixing $POCl_3$ (8.30 mL; 0.90 mol) with DMF (16.60 mL, 0.21 mol) at 0 °C and stirring at room temperature for 30 min. The *N*-heteroaryl acetic acid

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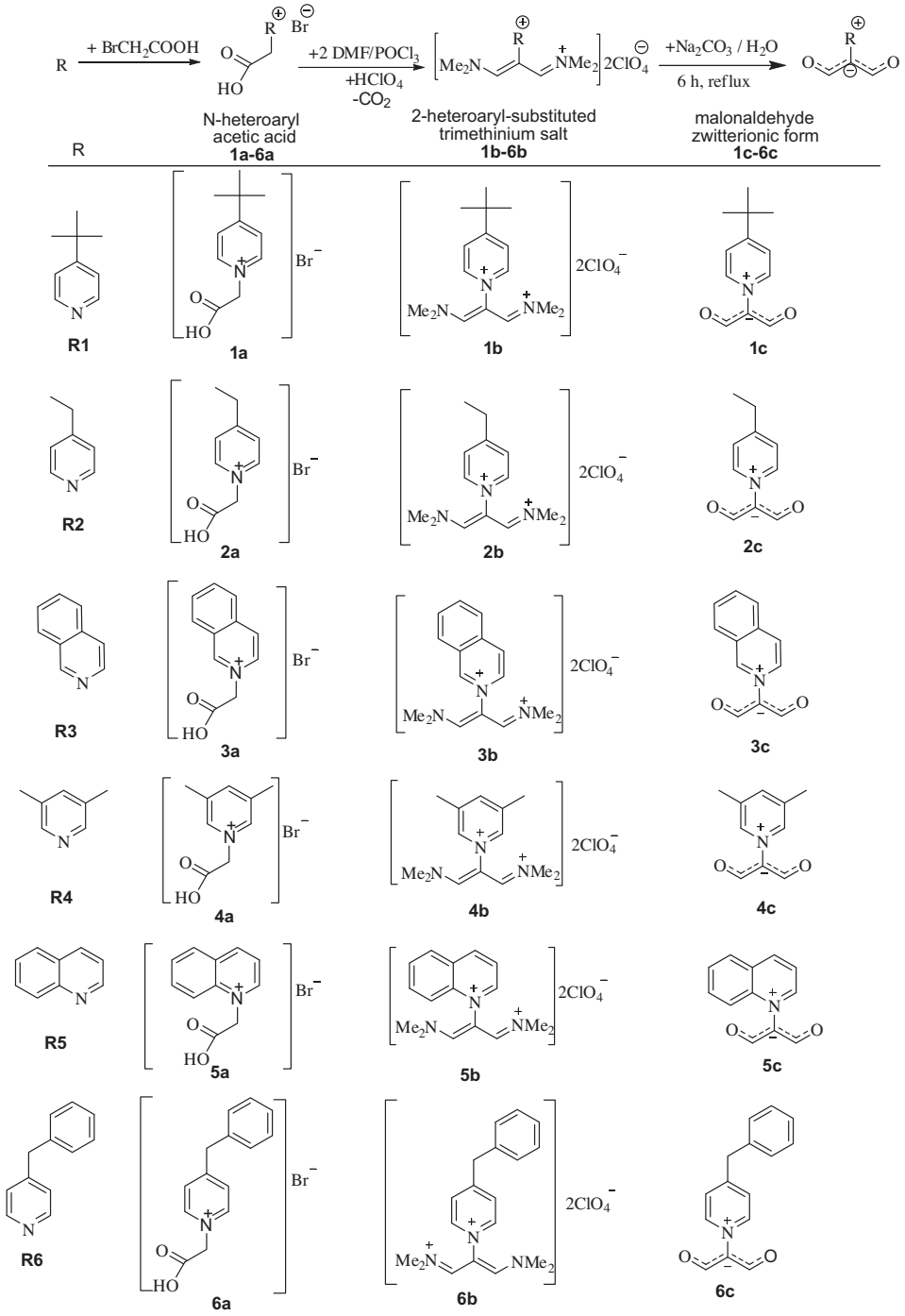

Figure 1. Synthesis of the zwitterionic malonaldehyde derivatives **1c–6c**.

(**1a–6a**) (0.90 mol) was added to this reagent. The mixture was refluxed at 80 °C for 5 h, and then set aside in a refrigerator for 12 h. The solution was diluted with pre-cooled EtOH (100 mL). A solution of $HClO_4$ (70%, 14.60 mL, 0.1 mol) in EtOH (30 mL) was added and the mixture was set aside in a refrigerator for 12 h. The crystals of the trimethinium salt (**1b–6b**) were collected by filtration, washed with Et_2O, and dried over P_4O_{10} in a desiccator.[20–22]

Typical procedure for the synthesis of the zwitterionic malonaldehyde derivatives 1c–6c

A mixture of 2-heteroaryl-substituted trimethinium salt (**1b–6b**) (28.0 mmol) and Na_2CO_3 (5.7 mmol, 0.60 g) dissolved in 40 mL of H_2O was refluxed for 7 h. After cooling to room temperature, the resulting solution was extracted with CH_2Cl_2 (4 × 15 mL) and the combined organic extracts washed with H_2O (2 × 10 mL), dried over $MgSO_4$ and the solvent removed by distillation. The resulting residue (**1c–6c**) was recrystallized from EtOH.

N-(Carboxymethyl)-4-*tert*-butylpyridinium bromide (1a)

Colorless powder; Yield 75%; mp = 221 °C; IR: ν/cm^{-1} = 3437, 1725; ^1H NMR (500 MHz, DMSO-d_6): δ/ppm = 1.35 (s, 9H, CH_3), 5.64 (s, 2H, CH_2), 8.27 (d, J = 7.2 Hz, 2H, *H*-pyridine), 9.05 (d, J = 7.2 Hz, 2H, *H*-pyridine); ^{13}C NMR (DMSO-d_6): δ/ppm = 30.3, 37.2, 60.5, 125.6, 146.3, 168.6, 171.6; MS: m/z = 194 [M^+−Br$^-$];

Anal. Calcd for $C_{11}H_{16}O_2NBr$: C, 48.19; H, 5.88; N, 5.11%; Found: C, 48.02; H, 6.01; N, 4.99%.

1,1,5,5-Tetramethyl-3-(4-*tert*-butylpyridinium)-1,5-diazapentadienium bis(perchlorate) (1b)

Yellow powder; Yield 62%; mp = 250 °C; IR: ν/cm^{-1} = 3121, 2965, 1634, 1091; ^{1}H NMR (500 MHz, DMSO-d_6): δ/ppm = 1.40 (s, 9H, CH_3), 2.36 (s, 6H, NMe_2), 3.36 (s, 6H, NMe_2), 8.01–9.05 (m, 6H, *H*-vinyl and *H*-pyridine); ^{13}C NMR (DMSO-d_6): δ/ppm = 30.2, 37.8, 38.7, 50.6, 108.1, 139.7, 146.9, 151.1, 158.2, 168.65; MS: *m*/*z* = 261 [M^+−2ClO_4^-]; Anal. Calcd for $C_{16}H_{27}N_3(ClO_4)_2$: C, 41.75; H, 5.91; N, 9.13%. Found: C, 42.01; H, 6.21; N, 8.72%.

2-(4-*tert*-Butylpyridinium-1-yl)propane-1,3-dialate (1c)

Yellow powder; Yield 50%; decomposition at 156 °C; IR: ν/cm^{-1} = 3435, 2962, 1587; ^{1}H NMR (500 MHz, DMSO-d_6): δ/ppm = 1.37 (s, 9H, CH_3), 8.07 (d, ^3J = 7.2 Hz, 2H, *H*-pyridine), 8.69 (d, ^3J = 7.2 Hz, 2H, *H*-pyridine), 8.78 (s, 2H, *H*-vinyl); ^{13}C NMR (DMSO-d_6): δ/ppm = 30.0, 36.4, 123.7, 124.1, 144,7, 167.6, 177.5; UV: λ_{max} (DMSO)/nm [ε_{max}/ $M^{-1}cm^{-1}$] = 375 [4726], 270 [14072.1] and 254 [28855]; MS: *m*/*z* = 205 [M^+]; Anal. Calcd for $C_{12}H_{15}N_3O_2N$: C, 70.22; H, 7.37; N, 6.82%. Found: C, 70.30; H, 7.31; N, 6.75%.

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Supplementary data

Supplementary data (materials and measurements and the structural characterization of **2a**, **3a**, **2b**, **3b**, and **2c**–**6c** associated with this article can be found in the supplementary data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.11.046.

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