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An efficient preparation and some reactions of 2-dimethylaminomethylene-1,3-bis(dimethylimonio)propane diperchlorate

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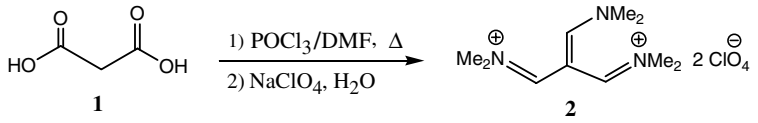
Abstract—An alternative preparation of 2-dimethylaminomethylene-1,3-bis(dimethylimonio)propane diperchlorate from malonic acid is described along with its application to the synthesis of 2,4,6-trisubstituted phenols and 2-(*N*-(2,2-diformylethenyl)-amino)pyridine.

If one examines the literature of vinamidinium salts,[1] their potential utility as three-carbon building blocks for a wide array of carbocycles and heterocycles becomes apparent. Vinamidinium salts can regioselectively incorporate an appended substituent onto a new ring system, making them attractive starting materials for the synthesis of new medicinal[2] agents. The regenerative character of vinamidinium salts has been demonstrated in both electrophilic reactions such as halogenation, nitration and Vilsmeier type alkylations,[3] and in nucleophilic reactions with amines and carbon nucleophiles.

The nucleophilic reactions have been the most exploited and have led to the synthesis of some polycyclic aromatic and heterocyclic compounds.[4–6] Vinamidinium salts have been used to alkylate the activated methylenes of various nitriles,[6,7] however, there are few reports on the alkylation of other types of activated methylene compounds.[8,9]

We now report, that 2-dimethylaminomethylene-1,3-bis(dimethylimonio)propane diperchlorate **2** can be prepared in excellent yield (92%) from commercially available and inexpensive malonic acid under Vilsmeier–Haack conditions and was precipitated as the perchlorate. Compound **2** has been previously prepared from α-bromoacetic acid[10] and phosphonoacetic acid[11] in yields of 60% under the same conditions. We obtained the vinamidinium salt **2** by the reaction of malonic acid with phosphorus oxychloride and *N*,*N*-dimethylformamide at 90 °C until carbon dioxide evolution ceased[12] (approximately 6 h). When the aqueous sodium perchlorate was added to the corresponding vinamidinium salt precipitated (Scheme 1).

This preparation of 2-iminiovinamidinium salt **2** from malonic acid has distinct advantages over the bromoacetic acid method since the reaction is less exothermic and so is easier to control. In addition, malonic acid is less irritant than bromoacetic acid.



1 2

Scheme 1.

Keywords: 2-Iminiovinamidinium salt; β-Keto-esters; 2-Aminopyridine; Condensation; Cyclisation; Bifunctional phenol; α,β-Unsaturated dialdehyde.
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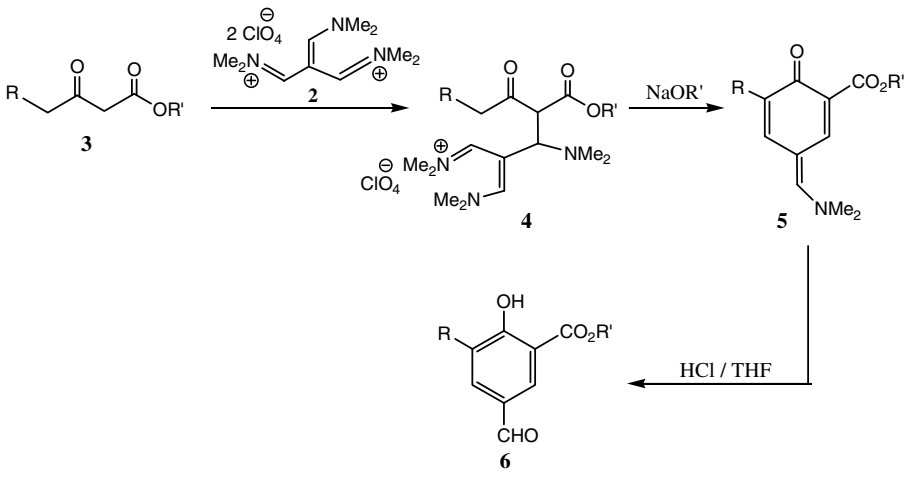


Scheme 2.

Table 1. Condensation of various β-keto-esters with 2-iminiovinamidinium salt **2**

β-Keto-ester	R	R′	Product[a]	Yield (%)
3a	H	CH_3	**6a**	83
3b	H	C_2H_5	**6b**	80
3c	C_2H_5	CH_3	**6c**	78
3d	C_2H_5	C_2H_5	**6d**	82
3e	*n*-C_3H_7	C_2H_5	**6e**	74
3f	*n*-C_4H_9	C_2H_5	**6f**	73

[a] All products were characterised from their ^{1}H NMR, ^{13}C NMR and mass spectroscopic data.[15]

With the desired salt in hand, we next condensed it with various β-keto-esters (Scheme 2).

When vinamidinium salt **2** was treated with enolates generated in situ by reaction of sodium alkoxide with β-keto-esters[13] **3** at 80 °C for 4 h, the desired phenols[14] **6** were isolated in good yields after hydrolysis with 1 N HCl in THF at room temperature. The results are shown in Table 1.

When salt **2** was reacted with 2-aminopyridine in ethanol, 2-(*N*-(2,2-diformylethenyl)amino)pyridine **8** was produced unexpectedly[14] in 81% yield. This presumably happens because the intermediate 4-hydroxy(4*H*)pyrido[1,2-*a*]pyrimidine-3-carbaldehyde **7** is water sensitive and ring-opens to an aldehyde (Scheme 3). The structure of **8** was confirmed by X-ray analysis and is depicted in Figure 1.[15]

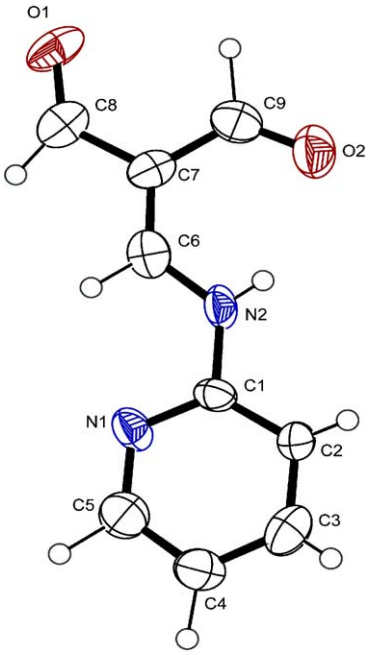
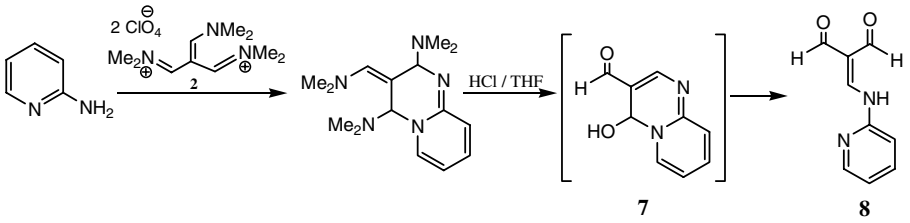


Figure 1. ORTEP view of compound **8**.

In conclusion, we have found that 2-dimethylaminomethylene-1,3-bis(dimethylimonio)propane diperchlorate **2** can be prepared in excellent yield from commercially available malonic acid. This salt undergoes annulation reactions with β-keto-esters **3** to provide 2,4,6-trisubsti-



Scheme 3.

tuted phenols **6** in satisfactory yields and also reacts with 2-aminopyridine to give 2-(*N*-(2,2-diformylethenyl)-amino)pyridine **8**.

Acknowledgements

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12. *Preparation of 2-dimethylamino-1,3-bis(dimethylimonio)-propane bis-perchlorate* **2** *from malonic acid*: $POCl_3$ (4.3 mL, 50.6 mmol) was added over 15 min to DMF (7 mL, 91 mmol) and the mixture was allowed to react for 30 min. To the resulting solution, malonic acid (1.56 g, 15 mmol) was added and the mixture was heated at 90 °C for 6 h until gas evolution ceased. The reaction mixture was cooled in an ice-water bath and poured into 40 mL of ice-water containing 3.7 g of sodium perchlorate monohydrate. The resulting tan solid was removed by filtration and dried at room temperature in vacuo to yield 5.2 g (91%) of a solid, mp 222–223 °C (literature[12] mp 222 °C); ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.33 (s, 9H), 3.50 (s, 9H), 8.40 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 43.3, 49.1, 91.2, 164.8.
13. β-Keto-esters **3c**–**f** were prepared by condensation of acid chlorides with the appropriate lithium enolates of methyl or ethyl acetate. For details, see: Heathcock, C. H.; Stafford, J. A. *J. Org. Chem.* **1992**, *57*, 2566–2568.
14. *Preparation of phenols* **6a**–**e**: *General procedure*:
To a 250 mL flame-dried flask containing NaOR′ (11 mmol) and 80 mL of R′OH, β-keto-ester **3** (3.5 mmol) in R′OH was added, followed by 'vinamidinium' bis-perchlorate **2** (3.5 mmol). Then, the mixture was heated at 80 °C for 4 h. The reaction was monitored by TLC. After cooling to room temperature, the solvent was removed and THF (10 mL) and 1 N HCl (8 mL) were added with stirring for 2 h. The mixture was neutralised with saturated aqueous $NaHCO_3$ and extracted with three portions of chloroform. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated. The crude reaction mixture was purified by flash column chromatography (80% hexane–20% ethyl acetate).
Condensation of iminiovinamidinium salt **2** *with 2-aminopyridine*:
A mixture of vinamidinium salt **2** (0.3 g, 0.78 mmol) and 2-aminopyridine (0.12 g, 1.28 mmol) in ethanol (15 mL) was refluxed for 10 h. After cooling to room temperature, the ethanol was removed and THF (2 mL) and 1 N HCl (2 mL) were added. The mixture was allowed to stir at room temperature for 2 h, then neutralised with saturated aqueous $NaHCO_3$ solution and extracted with three portions of CH_2Cl_2. After drying the combined organic extracts over $MgSO_4$ and concentrating in vacuo, the residue was purified by chromatography on silica gel [SiO_2; $CHCl_3$] to give 0.11 g (81% yield) of dialdehyde **8**.
15. Selected spectroscopic data:
Compound **6a**: white solid: mp 66–68 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.01 (s, 3H), 7.01 (d, $J = 8.7$ Hz, 1H), 8.01 (d, $J = 8.7$ Hz, 1H), 8.39 (d, $J = 2.1$ Hz, 1H), 9.88 (s, 1H), 11.37 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.8, 112.6, 118.8, 128.6, 133.9, 135.7, 166.4, 169.9, 190.0. Anal. Calcd for $C_9H_8O_4$: C, 60.00; H, 4.48; O, 35.52%. Found: C, 59.98; H, 4.36; O, 35.48%. Mass *m*/*z* (EI, 30 ev): M^+ 180.
Compound **6c**: white solid: mp 83–85 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.18 (t, $J = 7.3$ Hz, 3H), 2.61 (q, $J = 7.3$ Hz, 2H), 3.85 (s, 3H), 7.88 (s, 1H), 8.17 (s, 1H), 9.90 (s, 1H), 10.12 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 22.7, 52.6, 116.6, 126.1, 126.7, 128.8, 132.0, 164.2, 169.0, 189.4. Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81; O, 30.74. Found: C, 63.42; H, 5.72; O, 30.74%. Mass *m*/*z* (EI, 30 ev): M^+ 208.
Compound **6e**: white solid: mp 92–94 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90 (t, $J = 7.5$ Hz, 3H), 1.32 (t, $J = 6.8$ Hz, 3H), 1.59 (m, 2H), 2.73 (t, $J = 7.2$ Hz, 2H), 4.26 (q, $J = 6.8$ Hz, 2H), 7.79 (s, 1H), 8.15 (s, 1H), 9.92 (s, 1H), 10.10 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8, 14.2, 23.1, 31.8, 60.7, 116.4, 126.0, 126.7, 128.5, 131.9, 164.2, 168.9, 191.6. Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.82; O, 27.09. Found: C, 65.98; H, 6.70; O, 27.09%. Mass *m*/*z* (EI, 30 ev): M^+ 236.
Compound **8**: yellow solid: mp 140–141 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.98 (d, $J = 8.1$ Hz, 1H), 7.10–7.14 (m, 1H), 7.67–7.73 (m, 1H), 8.35 (dd, $J_1 = 4.8$ Hz, $J_2 = 1.2$ Hz, 1H), 8.81 (d, $J = 10.8$ Hz, 1H), 9.57 (s, 1H), 9.94 (s, 1H), 12.17 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 113.5, 113.8, 122.0, 139.5, 149.4, 149.7, 152.0, 189.3, 191.8. Anal. Calcd for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90; O, 18.16%. Found: C, 61.34; H, 4.51; N, 15.88; O, 18.14%. Mass *m*/*z* (EI, 30 ev): M^+ 176. Crystallographic data for structure **8** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 297480. Copies of the data can be obtained, free of charge, on application to CCDC, 12, Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or email: deposit@ccdc.cam.ac.uk].