

Reaction of Electrophilic Allyl Halides with Amines: A Reinvestigation

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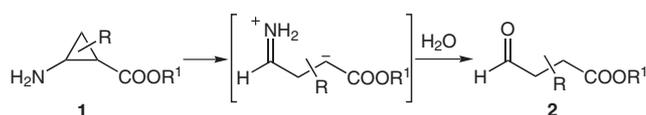
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Dedicated to Professor Dieter Hoppe on the occasion of his 65th birthday

Abstract: The Michael-induced ring closure (MIRC) of amines with 2-bromoalkylidenemalonates has been reinvestigated and the reaction products with primary amines have been identified as (2-iminoethyl)malonates and not 2-aminoalkylidenemalonates as previously reported. The (2-iminoethyl)malonates are formed by ring opening of the intermediate unstable 2-aminocyclopropane-1,1-dicarboxylates (β -ACCs) and were characterized spectroscopically and via chemical transformation.

Key words: Michael additions, ring closure, cyclopropanes, ring opening, imines

Recently, we described the synthesis of 2-(diphenylmethylideneamino)- and 2-azidocyclopropane-1,1-dicarboxylates via Michael-induced ring closure (MIRC) of diphenylmethylideneamine and azide, respectively, to 2-bromoalkylidenemalonates.¹ The former cyclopropanes are protected derivatives of 2-aminocyclopropanecarboxylates (β -ACCs) **1**, which are one of the most conformationally constrained classes of β -amino acid derivatives and find applications in the field of β -peptide chemistry and synthetic organic chemistry.² However, an appropriate N-protecting group has to be introduced during the synthesis of β -ACCs to inhibit their ring opening to γ -oxocarboxylates **2**, due to the 1,2-push-pull substitution on the cyclopropane ring (Scheme 1).³ From earlier research, it has been reported that treatment of dimethyl 2-bromo-2-methylpropylidenemalonate **3a** with primary and secondary amines gave rise to the formation of the formal substitution products, i.e. 2-aminoalkylidenemalonates **4**,⁴ while the reaction of diethyl 2-bromoethylidenemalonate with proline benzyl ester afforded the corresponding aminocyclopropane.⁵ More recently, it has been described that primary amines give the corresponding Michael adducts in the reaction with diethyl 2,2,2-trichloroethylidenemalonate.⁶ The divergent reactivity of amines with dimethyl 2-bromo-2-methylpropylidenemalonate as compared to the reactivity of other N-nucleophiles with related electrophilic allyl halides,^{1,5,7} prompted us to reinvestigate this reaction in order to get better mechanistic insights.



Scheme 1

Reinvestigation of the reaction of electrophilic allyl halides **3** with amines established that indeed formal substitution products **4a–c** were cleanly formed with secondary amines, but that products generated on treatment with primary amines were not the substitution products **4** as identified in our earlier report (Table 1 and Scheme 2).⁴ Careful analysis of the spectra and chemical transformation showed the presence of an imino function. The major reaction products (79–100% yield) were identified as (2-iminoethyl)malonates **5**. From the reactions with isopropylamine, γ -lactams **6a,d,e** and **7a,d** were identified as minor side-products based on ¹H NMR and MS analysis of the reaction mixtures. After the reaction of allyl bromide **3a** with benzhydrylamine, some signals were present in the ¹H NMR spectrum of the reaction mixture corresponding to the presence of about 19% of aziridine **8c** [δ = 1.17, 1.26 (2 \times s, 2 \times 3 H), 2.17 (d, J = 9.63 Hz, 1 H), 3.10 (s, 3 H), 3.17 (d, J = 9.63 Hz, 1 H), 3.71 (s, 3 H), 4.22 (s, 1 H)]. A rapid chromatography over a plug of silica gel was performed to obtain the pure aldimine **5c**, while avoiding hydrolysis to the corresponding aldehyde **10**. The unsaturated γ -lactam **6c** was also isolated in 11% yield, resulting from the acid-catalyzed ring opening of aziridine **8c** to the corresponding allyl amine **4** [R^4 = (Ph)₂CH, R^5 = H] and further lactamization.

Spectral analysis allows the discrimination between substitution products **4** and aldimines **5**. Obviously, the aldimines **5a–e** have a malonate methine function, not present in the corresponding substitution products **4**. This malonate CH-function resonates at δ = 3.67–3.88 ppm in the ¹H NMR spectrum (CDCl₃), close to the signal of the two methoxy groups (δ = 3.57–3.70 ppm). This CH-proton of **5a** and **5b** was not detected during the first investigation⁴ since it did not give a resolved resonance signal in the ¹H NMR spectra obtained with a 60 MHz apparatus. This, together with the unavailability of ¹³C NMR explains the incorrect characterization. However, a clear difference exists in the chemical shift of the aldimine proton of **5** (δ = 7.51–7.86 ppm) and the olefinic proton of **4** (δ = 6.88–6.97 ppm). In the latter compounds the two methoxy

Table 1 Reaction of 2-Bromoalkylidenemalonates **3** with Two Equivalents of Amine in Diethyl Ether at Reflux Temperature

Substrate	Amine	Time (h)	Yield (%) ^a	Ratio of reaction products (%) ^{b,c}					
				3	5	4	6	7	8
3a	<i>i</i> -PrNH ₂	3	94	–	83 (72)	–	9	8	–
3a	<i>t</i> -BuNH ₂	12	96	–	100	–	–	–	–
3a	(Ph) ₂ CHNH ₂	5	100	2	79 (78)	–	(11) ^d	–	19
3b	<i>i</i> -PrNH ₂	10	95	–	86 (20)	–	6	8	–
3c	<i>i</i> -PrNH ₂	16	81	–	82 (53)	–	18	–	–
3a	(CH ₂) ₄ NH	5	82	–	–	100 ^e (53) ^f	–	–	–
3a	(CH ₂) ₅ NH	6	100	9	–	91 ^e (46) ^f	–	–	–
3a	(O(CH ₂) ₄)NH	4	100	13	–	87 ^e (19) ^f	–	–	–

^a Crude yield of aldimine **5** or allyl amine **4**.

^b Based on integration of ¹H NMR of reaction crude.

^c Parentheses indicate isolated yields.

^d γ -Lactam **6c** was formed from aziridine **8c** during purification via chromatography (silica gel).

^e Traces of aldehyde **10** and other unidentified side-products were observed in the reaction crude.

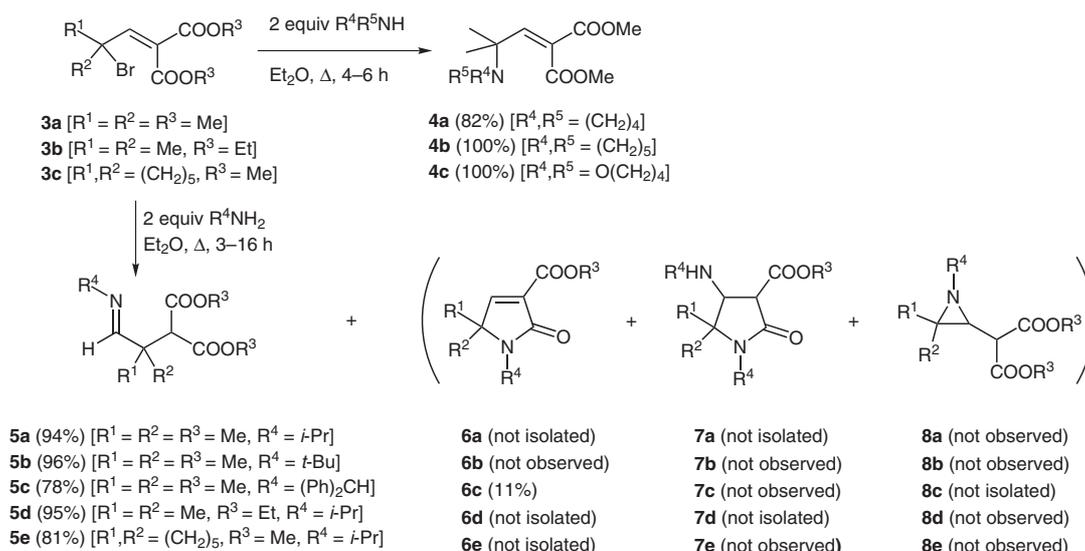
^f Acid–base extraction afforded the analytically pure amines **4**, but the yield dropped due to losses in the aqueous phase.

groups give two separate signals in ¹H NMR. Also in the IR spectra, a distinction can be made between the aldimine function (1660–1666 cm⁻¹) and the C=C bond (1641–1645 cm⁻¹).

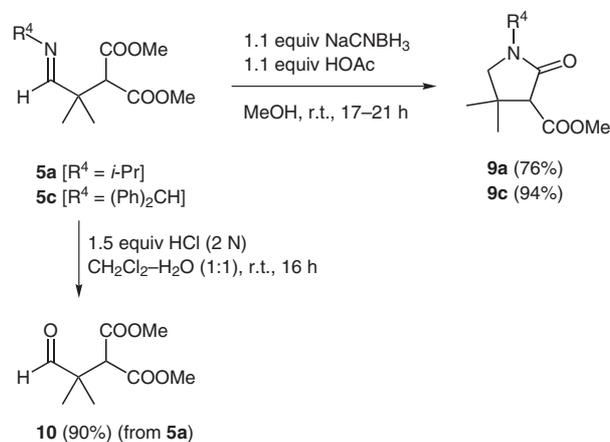
Besides spectroscopic evidence for the characterization of the aldimines **5**, chemical transformation also allowed to confirm their structure (Scheme 3). From our experience in the reduction of 2-(diphenylmethylideneamino)cyclopropane-1,1-dicarboxylates to 3-(alkoxycarbonyl)pyrrolidin-2-ones via the intermediate γ -iminodicarboxylates **5**,^{1a} it was expected that treatment of the aldimines **5** with sodium cyanoborohydride would give the corresponding γ -lactams. Indeed, 3-(methoxycarbonyl)pyrrolidin-2-ones **9a** and **9c**^{1a} were formed in good to excellent yields from reduction of aldimines **5a** and **5c** with sodium cy-

anoborohydride in methanol at room temperature. The aldimine structure of compounds **5** was further proven by the hydrolysis of **5a** to the known aldehyde **10**.⁸

The formation of the aldimines **5** and 2-aminoalkylidenemalonates **4** can be explained via a single mechanistic scheme (Scheme 4). Both primary and secondary amines give 1,4-addition to the 2-bromoalkylidenemalonates **3** to afford the adducts **11**. With primary amines, a further ring closure via C-alkylation occurs to the corresponding 2-aminocyclopropane-1,1-dicarboxylates **12**. The latter β -ACC derivatives are however not stable and undergo ring opening spontaneously to the iminium enolates **13**, which suffer proton transfer to form the stable aldimines **5**. With secondary amines, the addition products **11** probably undergo further N-alkylation to the aziridinium compounds

**Scheme 2**

14 which are prone to ring opening to the stable allyl amines **4**. It is clear that with the primary amines minor pathways are present, either via compounds **14** or through ring opening of β -ACCs **12**, which lead to the formation of aziridine **8c** and γ -lactams **6** and **7**. With the secondary amines, it is also reasonable that cyclopropanes **12**, in equilibrium with the ring-opened compounds **13**, are minor intermediates leading to allyl amines **4** via aziridinium enolates **15**.



Scheme 3

In conclusion, while secondary amines afforded, as already described, 2-aminoalkyldenemalonates upon reaction with 2-bromoalkyldenemalonates, primary amines efficiently yielded 2-(iminoethyl)malonates. The latter compounds are suitably functionalized for further transformations to γ -amino acid derivatives and N-heterocyclic compounds.

^1H NMR spectra (300 MHz) and ^{13}C NMR spectra (75 MHz or 68 MHz) were recorded on a Jeol Eclipse FT 300 NMR spectrometer or a Jeol JNM-EX 270 NMR spectrometer. IR spectra were recorded

on a Perkin–Elmer Spectrum One spectrophotometer. Mass spectra were recorded on an Agilent 1100 Series mass spectrometer using a direct inlet system (ES, 4000V). Melting points were measured with a Büchi B-540 apparatus and are uncorrected. Elemental analyses were measured with a Perkin–Elmer 2400 Elemental Analyzer. Flash chromatography was performed with silica gel (particle size 0.035–0.070 mm, pore diameter ca. 6 nm) using a glass column. The boiling range of petroleum ether used was 40–60 °C.

Synthesis of 2-(Iminoethyl)malonates **5** and 2-Aminoalkyldenemalonates **4**; General Procedure

To a solution of 2-bromoalkyldenemalonate **3**⁹ (2 mmol) in anhyd Et_2O (5 mL) was added the primary or secondary amine (4 mmol). The reaction mixture was stirred at reflux for 3–16 h. The reaction mixture was diluted with anhyd Et_2O , filtered and concentrated to give the aldimines **5** as light yellow oils, except for aldimine **5c** and lactam **6c** (white crystals), which were obtained by column chromatography (silica gel, PE–EtOAc, 3:7), or allyl amines **4a,b** (clear oils) and **4c** (white crystals). Analytically pure samples of the aldimines **5a,d,e** were obtained by high-vacuum distillation (**5a** and **5d**) or Kugelrohr distillation (**5e**) as clear oils. Analytically pure samples of the allyl amines **4** were obtained by acid–base extraction (aq 2 N HCl– Et_2O –NaOH– CH_2Cl_2 or Et_2O).

Dimethyl [(2E)-2-(N-Isopropylimino)-1,1-dimethylethyl]-malonate (**5a**)

Bp 76–82 °C/0.8 mmHg.

IR (NaCl): 1757, 1736, 1666 cm^{-1} .

^1H NMR (300 MHz, CDCl_3): $\delta = 1.09$ (d, $J = 6.33$ Hz, 6 H), 1.25 (s, 6 H), 3.28 (sept, $J = 6.33$ Hz, 1 H), 3.70 (s, 6 H), 3.75 (s, 1 H), 7.65 (s, 1 H).

^{13}C NMR (75 MHz, CDCl_3): $\delta = 23.8$ ($4 \times \text{CH}_3$), 40.5, 52.0, 58.6, 60.7, 165.8, 168.8.

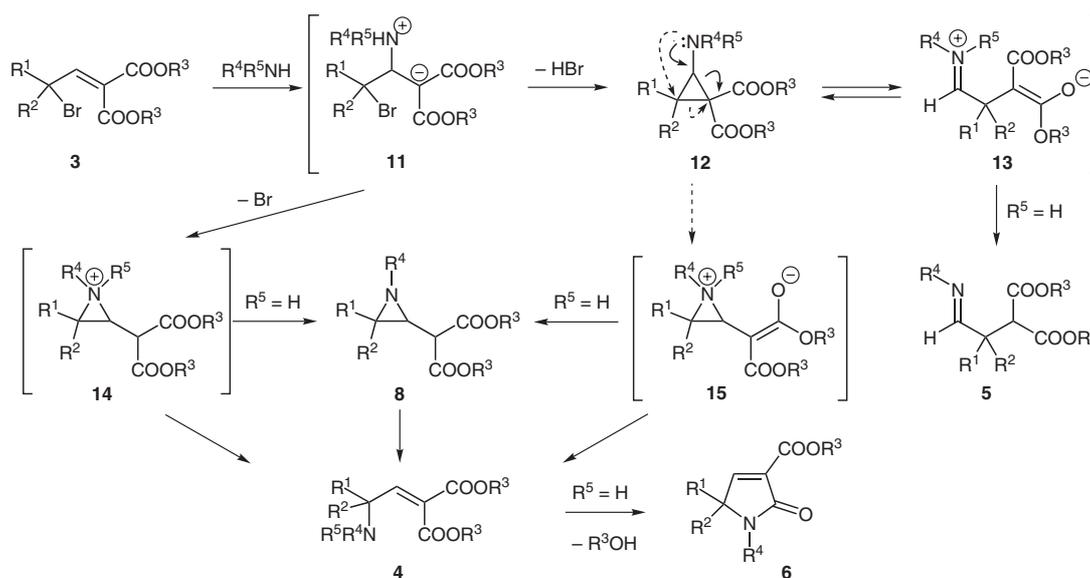
MS (ES, +ve mode): m/z (%) = 244 (100) [$\text{M} + \text{H}^+$].

Anal. Calcd for $\text{C}_{12}\text{H}_{21}\text{NO}_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.09; H, 8.59; N, 5.67.

Dimethyl [(2E)-2-(N-tert-Butylimino)-1,1-dimethylethyl]-malonate (**5b**)

IR (NaCl): 1758, 1736, 1666 cm^{-1} .

^1H NMR (300 MHz, CDCl_3): $\delta = 1.10$ (s, 9 H), 1.23 (s, 6 H), 3.70



Scheme 4

(s, 6 H), 3.80 (s, 1 H), 7.51 (s, 1 H).

^{13}C NMR (75 MHz, CDCl_3): δ = 23.8, 29.4, 40.8, 51.9, 56.2, 58.4, 162.1, 169.1.

MS (ES, +ve mode): m/z (%) = 258 (100) [M + H⁺].

Anal. Calcd for $\text{C}_{13}\text{H}_{23}\text{NO}_4$: C, 60.68; H, 9.01; N, 5.44. Found: C, 60.80; H, 9.12; N, 5.22.

Dimethyl {(2E)-2-[N-(Diphenylmethyl)imino]-1,1-dimethylethyl}malonate (5c)

R_f = 0.71 [PE–EtOAc (3:7)].

IR (NaCl): 1757, 1736, 1666 cm^{-1} .

^1H NMR (300 MHz, CDCl_3): δ = 1.30 (s, 6 H), 3.57 (s, 6 H), 3.88 (s, 1 H), 5.34 (s, 1 H), 7.17–7.32 (m, 10 H), 7.82 (s, 1 H).

^{13}C NMR (75 MHz, CDCl_3): δ = 23.8, 41.3, 52.0, 58.4, 77.1, 126.8, 127.5, 128.3, 143.7, 168.7, 168.9.

MS (ES, +ve mode): m/z (%) = 368 (100) [M + H⁺].

Anal. Calcd for $\text{C}_{22}\text{H}_{29}\text{NO}_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 71.78; H, 6.98; N, 3.70.

Methyl 1-(Diphenylmethyl)-5,5-dimethyl-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxylate (6c)

Mp 192.2–193.2 °C; R_f = 0.46 [PE–EtOAc, (3:7)].

IR (KBr): 1745, 1676, 1629 (w) cm^{-1} .

^1H NMR (300 MHz, CDCl_3): δ = 1.43 (s, 6 H), 3.83 (s, 3 H), 5.64 (s, 1 H), 7.19–7.39 (m, 10 H), 7.79 (s, 1 H).

^{13}C NMR (68 MHz, CDCl_3): δ = 24.3, 52.2, 60.3, 63.1, 127.3, 128.2, 128.7, 128.8, 139.7, 161.5, 162.5, 164.6.

MS (ES, +ve mode): m/z (%) = 693 (15) [2 × M + Na⁺], 336 (90) [M + H⁺], 167 (100).

Anal. Calcd for $\text{C}_{21}\text{H}_{21}\text{NO}_3$: C, 75.20; H, 6.31; N, 4.18. Found: C, 75.12; H, 6.42; N, 4.10.

Diethyl [(2E)-2-(N-Isopropylimino)-1,1-dimethylethyl]malonate (5d)

Bp 65–70 °C/0.4 mmHg.

IR (NaCl): 1753, 1732, 1666 cm^{-1} .

^1H NMR (300 MHz, CDCl_3): δ = 1.09 (d, J = 6.33 Hz, 6 H), 1.25 (s, 6 H), 1.26 (t, J = 7.15 Hz, 6 H), 3.28 (sept, J = 6.33 Hz, 1 H), 3.71 (s, 1 H), 4.17 (q, J = 7.15 Hz, 4 H), 7.68 (s, 1 H).

^{13}C NMR (75 MHz, CDCl_3): δ = 14.1, 23.8, 23.9, 40.4, 59.0, 60.8, 61.0, 166.1, 168.4.

MS (ES, +ve mode): m/z (%) = 272 (100) [M + H⁺].

Anal. Calcd for $\text{C}_{14}\text{H}_{25}\text{NO}_4$: C, 61.97; H, 9.29; N, 5.16. Found: C, 61.88; H, 9.41; N, 5.07.

Dimethyl {1-[(E)-N-Isopropylimino)methyl]cyclohexyl}malonate (5e)

Kugelrohr distillation: T_{oven} = 80–95 °C/0.01 mbar.

IR (NaCl): 1754, 1737, 1660 cm^{-1} .

^1H NMR (300 MHz, CDCl_3): δ = 1.13 (d, J = 6.33 Hz, 6 H), 1.16–1.62 (m, 8 H), 1.97–2.08 (m, 2 H), 3.35 (sept, J = 6.33 Hz, 1 H), 3.67 (s, 1 H), 3.69 (s, 6 H), 7.86 (s, 1 H).

^{13}C NMR (75 MHz, CDCl_3): δ = 22.2, 23.9, 25.6, 32.5, 43.3, 52.1, 60.5, 61.6, 165.4, 168.3.

MS (ES, +ve mode): m/z (%) = 284 (100) [M + H⁺].

Anal. Calcd for $\text{C}_{15}\text{H}_{25}\text{NO}_4$: C, 63.58; H, 8.89; N, 4.94. Found: C, 63.80; H, 8.78; N, 5.12.

Dimethyl (2-Methyl-2-pyrrolidin-1-ylpropylidene)malonate (4a)^d

IR (NaCl): 1735, 1644 cm^{-1} .

^1H NMR (300 MHz, CDCl_3): δ = 1.24 (s, 6 H), 1.67 (m, 4 H), 2.54 (m, 4 H), 3.76 (s, 3 H), 3.77 (s, 3 H), 6.97 (s, 1 H).

^{13}C NMR (75 MHz, CDCl_3): δ = 23.2, 23.4, 46.1, 51.9, 52.4, 56.0, 126.3, 154.5, 164.9, 167.0.

MS (ES, +ve mode): m/z (%) = 256 (100) [M + H⁺].

Anal. Calcd for $\text{C}_{13}\text{H}_{21}\text{NO}_4$: C, 61.16; H, 8.29; N, 5.49. Found: C, 60.90; H, 8.41; N, 5.42.

Dimethyl (2-Methyl-2-piperidin-1-ylpropylidene)malonate (4b)^d

IR (NaCl): 1734, 1645 cm^{-1} .

^1H NMR (300 MHz, CDCl_3): δ = 1.19 (s, 6 H), 1.38 (m, 2 H), 1.51 (m, 4 H), 2.42 (m, 4 H), 3.77 (s, 3 H), 3.82 (s, 3 H), 6.93 (s, 1 H).

^{13}C NMR (75 MHz, CDCl_3): δ = 22.7, 24.8, 26.1, 47.7, 51.9, 52.4, 58.9, 125.8, 155.8, 164.9, 166.8.

MS (ES, +ve mode): m/z (%) = 270 (100) [M + H⁺].

Anal. Calcd for $\text{C}_{14}\text{H}_{23}\text{NO}_4$: C, 62.43; H, 8.61; N, 5.20. Found: C, 62.30; H, 8.72; N, 5.09.

Dimethyl (2-Methyl-2-morpholin-4-ylpropylidene)malonate (4c)^d

Mp 77.3–77.7 °C.

IR (KBr): 1727, 1641 cm^{-1} .

^1H NMR (300 MHz, CDCl_3): δ = 1.22 (s, 6 H), 2.50 (dd, J = 4.68 Hz, 4 H), 3.65 (dd, J = 4.68 Hz, 4 H), 3.77 (s, 3 H), 3.84 (s, 3 H), 6.88 (s, 1 H).

^{13}C NMR (75 MHz, CDCl_3): δ = 22.5, 46.9, 52.0, 52.5, 58.6, 67.0, 126.3, 154.1, 164.7, 166.8.

MS (ES, +ve mode): m/z (%) = 272 (100) [M + H⁺].

Anal. Calcd for $\text{C}_{13}\text{H}_{21}\text{NO}_5$: C, 57.55; H, 7.80; N, 5.16. Found: C, 57.39; H, 7.83; N, 5.10.

Methyl 1-Isopropyl-4,4-dimethyl-2-oxopyrrolidine-3-carboxylate (9a) and Methyl 1-Benzhydryl-4,4-dimethyl-2-oxopyrrolidine-3-carboxylate (9c)^{1a}

To a mixture of aldimine **5a** or **5c** (1 mmol) and MeOH (1 mL) were added NaCNBH_3 (0.07 g, 1.1 mmol) and AcOH (0.07 mL, 1.1 mmol). The reaction mixture was stirred at r.t. for 17–21 h. The reaction mixture was poured into aq NaOH (0.5 N, 10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). After drying of the organic layer (MgSO_4), filtration and evaporation, the pure pyrrolidin-2-ones **9a** (0.16 g, 76%) and **9c** (0.32 g, 94%)^{1a} were obtained. An analytically pure sample of **9a** (clear oil) could be obtained upon flash column chromatography (silica gel, Et_2O); R_f = 0.35 (Et_2O).

IR (NaCl): 1736, 1686 cm^{-1} .

^1H NMR (300 MHz, CDCl_3): δ = 1.10 (s, 3 H), 1.13 (d, J = 7.15 Hz, 3 H), 1.15 (d, J = 7.15 Hz, 3 H), 1.21 (s, 3 H), 2.96 (d, J = 9.36 Hz, 1 H), 3.05 (s, 1 H), 3.25 (d, J = 9.36 Hz, 1 H), 3.72 (s, 3 H), 4.41 (sept, J = 6.88 Hz, 1 H).

^{13}C NMR (75 MHz, CDCl_3): δ = 19.57, 19.64, 22.7, 28.7, 36.6, 42.6, 52.0, 53.9, 61.1, 169.3, 169.6.

MS (ES, +ve mode): m/z (%) = 214 (100) [M + H⁺].

Anal. Calcd for $\text{C}_{11}\text{H}_{19}\text{NO}_3$: C, 61.95; H, 8.98; N, 6.57. Found: C, 61.72; H, 9.09; N, 6.44.

Dimethyl (1,1-Dimethyl-2-oxoethyl)malonate (10)

To a mixture of aldimine **5a** (122 mg, 0.5 mmol) and H₂O (1 mL) and CH₂Cl₂ (1 mL) was added aq HCl (2 N, 0.4 mL). The reaction mixture was stirred at r.t. overnight and extracted with CH₂Cl₂ (3 × 3 mL). After drying of the organic layer (MgSO₄), filtration and evaporation, the aldehyde **10** (91 mg, 90%) was obtained. ¹H NMR data were in good agreement with reported data.⁸

¹H NMR (300 MHz, CDCl₃): δ = 1.24 (s, 6 H), 3.75 (s, 6 H), 3.78 (s, 1 H), 9.62 (s, 1 H).

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