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Synthesis of *N*-[(dialkylamino)methyl]acrylamides and *N*-[(dialkylamino)methyl]methacrylamides from Schiff base salts: useful building blocks for smart polymers†

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The traditional thermal Mannich reaction is unsuitable for preparing polymerizable *N*-methylene amino substituted acrylamides and methacrylamides. Herein we provide a facile multi-gram high yield synthesis of these monomeric precursors to stimuli-responsive polymers by the addition of acrylamides and methacrylamides onto *in situ* generated or freshly isolated methylene Schiff base (iminium) salts. The X-ray crystal structure of the hydrated iminium salt, 1-(hydroxymethyl)azocan-1-ium chloride and monomer·HCl salt (*N*-[(azocan-1-yl)methyl]prop-2-enamide hydrochloride) is described.

Introduction

The three-component Mannich reaction is fundamental, allowing access to β-amino methylated carbonyl compounds.[1,2] *N*-[(Dialkylamino)methyl]acrylamide and methacrylamide analogues are valuable monomeric precursors to smart polymers, with dual functionalities of temperature and pH-responsiveness (Fig. 1), however potential applications have not been realised due to problems with their synthesis.

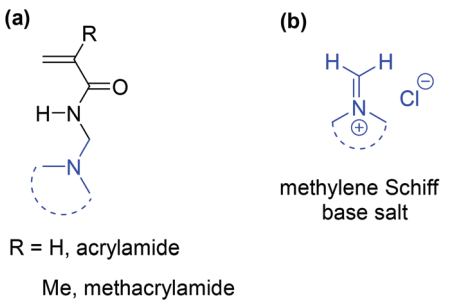
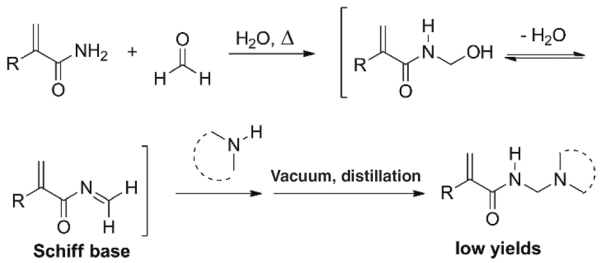


Fig. 1 (a) Synthetic targets and (b) precursors.

Literature routes have used one-pot Mannich condensation of (meth)acrylamide with formaldehyde to generate the Schiff base followed by secondary amine addition (Scheme 1).[3–6] The reaction operates thermally (at ~80 °C), and is inefficient in forming the Schiff base *in situ*, with the elevated temperature resulting in premature polymerization of the monomer and intermediates. The reaction has the added difficulty of monomer isolation, which requires vacuum distillation from the aqueous reaction mixture.

The most widely studied temperature-responsive polymers are those with lower critical solution temperature (LCST) close to physiological temperature, such as poly(*N*-isopropylacrylamide) and poly(*N*,*N*-diethylacrylamide) with LCST of 32–34 °C in water.[7–9] The *N*-dialkyl amino (including saturated nitrogen heterocycle) of substituted acrylamides and methacrylamides can be reversibly ionized allowing for a pH-response that alters polymer hydrophobicity.[9–15] Amphiphilic block copolymers comprising such monomers can self-assemble into a variety of nano-objects for use as stimuli-responsive



Scheme 1 One-pot thermal Mannich reaction route.

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polymersomes for targeted delivery of therapeutics.[11–13] In a recent communication, the synthesis of the selected acrylamides containing *N*-methylene saturated nitrogen heterocycles, and their incorporation into well-defined water-soluble block copolymer polyacrylamides was realised.[14] In this full paper, we expand on the monomer synthesis by providing efficient multi-gram routes to acrylamides and methacrylamides, including those with dialkyl acyclic and large saturated nitrogen heterocyclic rings. The synthesis involves efficient generation of the methylene Schiff base salt, which was characterized in the hydrated form.

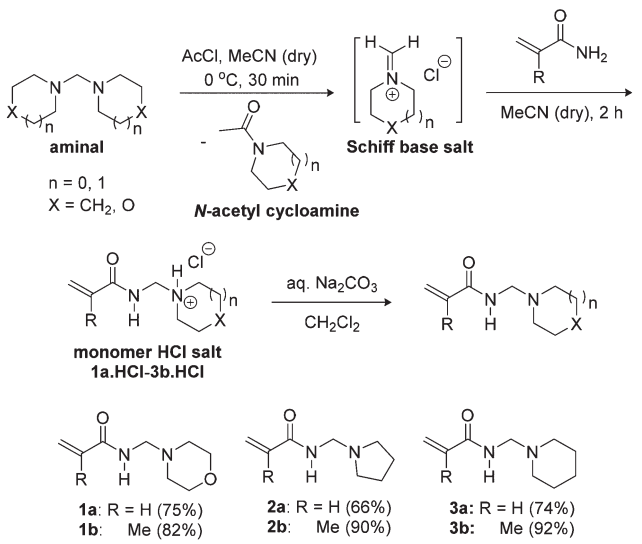
Results and discussion

In contrast to the one-pot thermal Mannich condensation reaction in Scheme 1, our synthesis uses readily accessible aminals made from the condensation of formaldehyde with secondary amines at 0 °C (Scheme 2).[16,17] Böhme pioneered the quaternization of the aminal to generate the Schiff base (iminium) salt, and this procedure using acetyl chloride was followed.[17,18] There are numerous accounts of alkylation and nucleophilic addition onto methylene Schiff base salts,[16–28] including by non-vinylic amides.[27,28] The most utilised is commercial *N*,*N*-dimethylmethyleneiminium iodide or Eschenmoser's salt.[20,29] Inspired by the simplicity and low temperatures, acrylamides and methacrylamides were added onto *in situ* generated methylene Schiff salts to give the monomer hydrochloride salts of morpholine, pyrrolidine and piperidine.

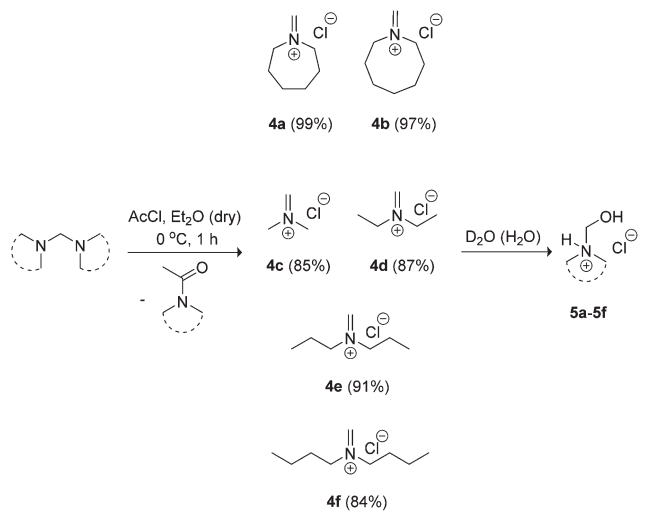
The monomer hydrochloride salts **1a·HCl–3b·HCl** were precipitated upon the addition of diethyl ether to the reaction in acetonitrile, which allowed the separation of the soluble *N*-acetyl cycloamines (Scheme 2). The isolable **1a·HCl–3b·HCl** salts are themselves useful as monomeric building blocks in aqueous solution polymerizations.[14] Basification of the latter allowed the free *N*-[(cycloalkylamino)methyl]acrylamides **1a–3a** to be isolated on a 20–25 g scale in yields of 66–75% with the *N*-[(cycloalkylamino)methyl]methacrylamides **1b–3b** isolated in higher yields of 82–92% and on a ≥30 g scale.

Our *in situ* Schiff base salt approach was not applicable for larger cycloamines (azepane and azocane) and acyclic analogues. Isolation of the methylene Schiff base salts was deemed necessary in these cases due to the poor solubility of their aminals in acetonitrile. Seven and eight-membered heterocyclic base-containing monomers are useful for increased hydrophobicity in the ionisable block segment of amphiphilic copolymers promoting sharper pH-sensitivity of micelles.[11,12] In contrast, linear dialkyl amine-containing polyacrylamides generally have greater water solubility in comparison to heterocyclic amine-containing analogues affording higher LCSTs.[10] Treatment of the aminals with acetyl chloride in diethyl ether at 0 °C allowed access to both larger heterocyclic and acyclic methylene Schiff base salts **4a–4f**, which were more conveniently characterised as *N*-hydroxymethyl hydrochloride salt derivatives **5a–5f** (Scheme 3).

NMR spectra of iminium salts **4a–4f** showed mixtures with their respective hydrated derivatives **5a–5f**. For example, the ^{1}H-NMR spectrum in CD_2Cl_2 gave similar intensity signals for the *exo*-methylene of *N*-methylideneazocan-1-ium chloride (**4b**) at 8.87 ppm and its *N*-hydroxymethyl derivative **5b** *exo*-methylene at 4.74 ppm (Fig. 2a). Upon recrystallization from acetonitrile, the more stable *N*-(hydroxymethyl)azocan-1-ium chloride **5b** was obtained (Fig. 2b). It was thus more convenient to characterize the moisture sensitive methylene Schiff base salts **4a–4f** using NMR in D_2O, as **5a–5f** (Fig. 2c). An exception was *N*,*N*-dibutylmethaniminium chloride (**4f**), which appeared less hygroscopic. The NMR spectrum in CD_2Cl_2 contained only trace amounts of hydrated derivative **5f** (Fig. 3a). The *exo*-methylene at 8.58 ppm in CD_2Cl_2 for the methylene Schiff



Scheme 2 Synthesis of *N*-[(cycloalkylamino)methyl]acrylamides **1a–3a**,[14] and *N*-[(cycloalkylamino)methyl]methacrylamides **1b–3b** using the *in situ* Schiff base salt approach.



Scheme 3 Synthesis of methylene Schiff base salts **4a–4f** characterised by ^{1}H NMR as hydrated derivatives **5a–5f**.

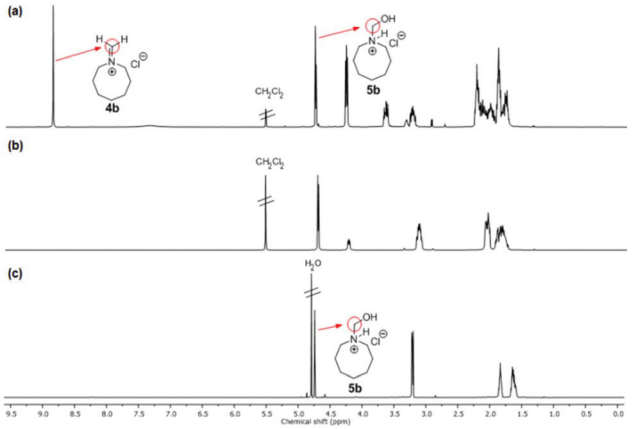


Fig. 2 ^{1}H-NMR spectrum: (a) of the initially isolated mixture containing *N*-methylideneazocan-1-ium chloride (**4b**) and *N*-(hydroxymethyl) azocan-1-ium chloride (**5b**) in CD_2Cl_2 and spectra after recrystallization from MeCN in (b) CD_2Cl_2, and (c) D_2O.

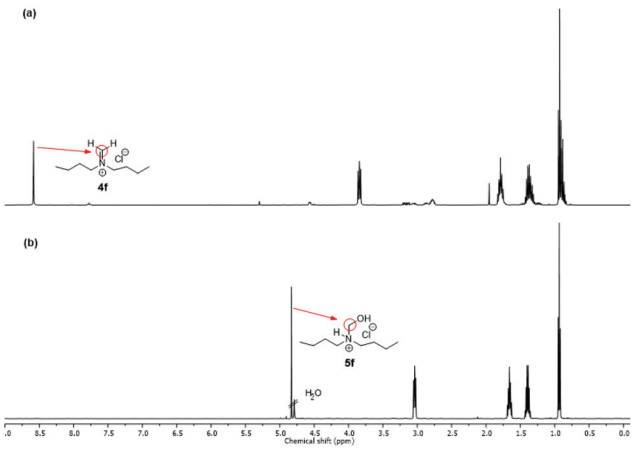


Fig. 3 ^{1}H-NMR spectrum: (a) of *N*,*N*-dibutylmethaniminium chloride (**4f**) in CD_2Cl_2 and (b) of *N*-butyl-*N*-(hydroxymethyl)butan-1-aminium chloride (**5f**) in D_2O.

base was replaced by the *exo*-methylene at 4.83 ppm in D_2O for *N*-butyl-*N*-(hydroxymethyl)butan-1-aminium chloride (**5f** in Fig. 3b).

The X-ray crystal structure of *N*-(hydroxymethyl)azocan-1-ium chloride (**5b**) was obtained (Fig. 4a, Table S1†). The large eight membered ring of **5b** was found to be disordered over two equally populated sites with both the N–H and O–H bonds found to be involved in H-bonding to the chloride counter ion (Fig. 4b). Interestingly, a search of the CCDC database for the R_2NH–CH_2–OH moiety gave only one hit, CSD code DIVDET, which was for a pyrimidine salt of tris(hydroxymethyl) ammonium chloride.[30] The hydroxymethyl hydrochlorides **5a–5f** were however difficult to isolate cleanly due to their susceptibility to decompose to formaldehyde.

Nucleophilic addition of acrylamides or methacrylamides onto the freshly prepared methylene Schiff base salts of azepane and azocane **4a** and **4b** gave the hydrochloride

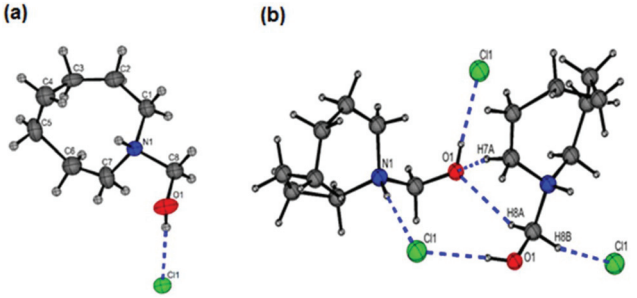
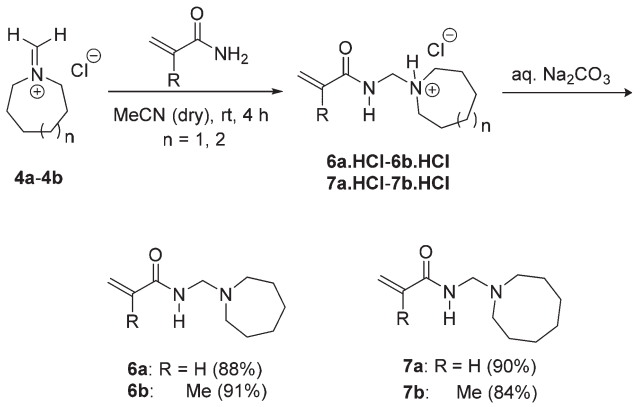


Fig. 4 The X-ray crystal structure of *N*-(hydroxymethyl)azocan-1-ium chloride (**5b**): (a) only one component of the ring disorder shown for clarity and (b) H-bonding interactions (Table S1†).



Scheme 4 Synthesis of seven and eight-membered *N*-[(cycloalkylamino)methyl]acrylamides **6a–7a** and *N*-[(cycloalkylamino)methyl] methacrylamides **6b–7b** from the freshly prepared methylene Schiff base salts.

monomer salts (**6a·HCl**, **6b·HCl**, **7a·HCl** and **7b·HCl**) after precipitation from diethyl ether (Scheme 4). The monomer HCl salts were suspended in dichloromethane and basified to give the monomers **6a–6b** and **7a–7b** in high yields of 84–91% (from **4a–4b**). Attempts to react acrylamide and methacrylamide with an analytically pure sample of *N*-(hydroxymethyl) azocan-1-ium chloride (**5b**) in dried acetonitrile resulted in the isolation of unreacted **5b** and some degradation with the release of formaldehyde. It follows that yields of the monomer from addition onto methylene Schiff base salts were determined by the extent of hydration of the latter substrate.

The X-ray crystal structure of *N*-[(azocan-1-yl)methyl]prop-2-enamide hydrochloride (**7a·HCl**) was obtained with very small fitting errors suggesting that the ring was in the optimal conformation (Fig. 5). The crystal structure showed N–H bonds forming H-bonding interactions with the chloride anions and the oxygen atoms resulting in intermolecular packing with some weaker C–H···Cl and C–H···O (see Fig. S1, S2 and Table S2†).

For the preparation of *N*-dialkyl amino substituted monomers, *N*-[(dialkylamino)methyl]acrylamides **8a–11a** and *N*-[(dialkylamino)methyl]methacrylamides **8b–11b**, freshly pre-

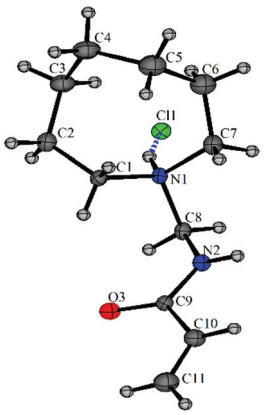
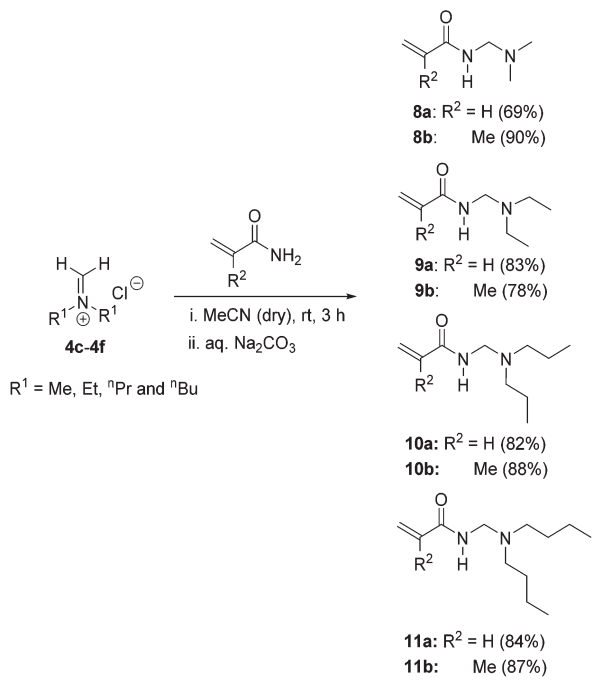


Fig. 5 The X-ray crystal structure of *N*-[(azocan-1-yl)methyl]prop-2-enamide hydrochloride (**7a·HCl**) with one molecule from the asymmetric unit shown.

pared acyclic Schiff base salts **4c–4f** were reacted with acrylamides and methacrylamides in acetonitrile at room temperature (Scheme 5). In this case, the isolation of the *N*-dialkyl amino substituted monomer hydrochloride salts proved difficult due to appreciable solubility in the reaction solvent and attempted precipitation solvents (including diethyl ether). Thus basification of the reaction mixture was preferred and the free monomer bases were isolated in multi-gram quantities (22–49 g) in yields of 69–90% without the isolation of the intermediate salts.



Scheme 5 Synthesis of *N*-[(dialkylamino)methyl]acrylamides **8a–11a** and *N*-[(dialkylamino)methyl]methacrylamides **8b–11b** from the freshly prepared Schiff base salts.

Conclusions

Readily accessible methylene Schiff base (iminium) salts have allowed the preparation of eighteen previously inaccessible acrylamides and methacrylamides containing methylene *N*-amino groups (both heterocyclic and acyclic). Heterocyclic substituted monomer syntheses have the added advantage of allowing the isolation of the monomer hydrochloride salt intermediate useful for polymerizations in water. For the preparation of monomers substituted with azepane, azocane, and acyclic derivatives, the iminium salts should be first isolated, prior to reactions with acrylamides and methacrylamides. Syntheses occur at low or ambient temperatures avoiding premature polymerization of vinyl compounds. Iminium salts are however hygroscopic and X-ray crystal structures of the hydrated eight-membered Schiff base salt, 1-(hydroxymethyl)azocan-1-ium chloride (**5b**), and the related monomer, *N*-[(azocan-1-yl)methyl]prop-2-enamide hydrochloride (**7a·HCl**) are described. Future research will involve controlled radical polymerizations of this new vinyl monomer class to give amphiphilic block copolymers for use as smart stimuli (temperature, pH, CO_2)-responsive materials.

Experimental

General information

Melting points were measured on a Stuart Scientific SMP1 melting point apparatus. Infrared spectra were recorded using a PerkinElmer Spec 1 with ATR attached. ^{1}H NMR spectra were recorded at 400 or 500 MHz and ^{13}C NMR were recorded at 101 or 125 MHz using a 400 MHz JEOL ECX and a 500 MHz Varian instrument respectively. The chemical shifts were recorded in ppm relative to Me_4Si. NMR assignments were supported by DEPT. Deuterated solvents were used for homonuclear lock, and the signals were referenced to the deuterated solvent peaks. 1,4-Dioxane was used as a reference for ^{13}C NMR in D_2O. High resolution mass spectra (HRMS) were recorded using an ESI time-of-flight mass spectrometer (TOFMS) in positive mode. The precision of all accurate mass measurements was better than 5 ppm. All reactions were performed under inert conditions.

Materials

All chemicals were obtained from commercial sources. Aminals, 1,1′-methylenedipyrrolidine,[16] 1,1′-methylenedipiperidine,[17] 1,1′-methylenebis(azepane),[31] *N*,*N*,*N*′,*N*′-tetramethylmethanediamine,[16] *N*,*N*,*N*′,*N*′-tetraethylmethanediamine,[16] and *N*,*N*,*N*′,*N*′-tetrapropyl-methanediamine[31] were readily prepared in high yields from the reaction of formaldehyde (Sigma-Aldrich, 37 wt% in H_2O) with the appropriate secondary amine according to the literature procedures. Distilled aminals were stored under vacuum and dry atmospheres in desiccators at room temperature. Heptamethyleneimine (Sigma-Aldrich, 98%), acetyl chloride (AcCl, Sigma-Aldrich, 98%), acrylamide (Sigma-Aldrich, 97%), and methacrylamide (Sigma-Aldrich, 98%) were

used as received. CH_2Cl_2 (Sigma-Aldrich, ≥99%), $CDCl_3$ (Sigma-Aldrich, 99.8 atom%), D_2O (Sigma-Aldrich, 99.9 atom%), KOH pellets (Sigma-Aldrich, ≥85%), Na_2CO_3 (Sigma-Aldrich, ≥99%), and $MgSO_4$ (Sigma-Aldrich, ≥99.99%) were used as received. The synthesis of *N*-[(morpholin-4-yl)methyl] prop-2-enamide **1a**, 2-methyl-*N*-[(morpholin-4-yl)methyl]prop-2-enamide **1b**, *N*-[(pyrrolidin-1-yl)methyl]prop-2-enamide **2a** and *N*-(piperidin-1-ylmethyl)prop-2-enamide **3a** is included in our recent communication.[14] For Schiff base salt and monomer synthesis all solvents were freshly distilled, and the reactions were carried out using anhydrous solvents using an inert nitrogen atmosphere. Acetonitrile (MeCN, Sigma-Aldrich, ≥99.9%) was freshly distilled over 3 Å molecular sieves and then CaH_2 (Sigma-Aldrich, 95%) and Et_2O (Et_2O, Sigma-Aldrich, ≥99.5%) were freshly distilled over Na wire and benzophenone (Sigma-Aldrich, 95%).

Synthesis of *N*-[(cycloalkylamino)methyl]methacrylamides using the *in situ* Schiff base salt approach

AcCl (14.30 mL, 0.20 mol) was added over 30 min to aminal (0.20 mol) in MeCN (40 mL) at *ca*. 0 °C. Methacrylamide (17.02 g, 0.20 mol) in MeCN (40 mL) was added, and stirred at *ca*. 20 °C for 2 h. Et_2O (200 mL) was added and the hydrochloride salt of the monomer was precipitated, filtered, and dried under vacuum. The hydrochloride salts (**1b·HCl–3b·HCl**) were recrystallized, dried, and characterized. An aqueous solution of Na_2CO_3 (100 mL, 3 M) was added to a suspension of the hydrochloride salt in CH_2Cl_2 (100 mL) and stirred for 30 min. The organic layer was separated, and the aqueous layer was washed with CH_2Cl_2 (4 × 250 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated to dryness to give the monomer, which was recrystallized.

2-Methyl-*N*-[(pyrrolidin-1-yl)methyl]prop-2-enamide hydrochloride (2b·HCl). White solid; mp 131–133 °C (recryst. from MeCN); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.87–1.94 (m, 7H), 3.05–3.41 (m, 4H), 4.49 (d, J 6.7 Hz, 2H), 5.55–5.57 (m, 1H), 5.92–5.94 (m, 1H), 9.33–9.36 (t, J 6.7 Hz, 1H, NH), 10.61–10.94 (brs, 1H, NH); ^{13}C NMR (101 MHz, DMSO-d_6) δ 18.4 (Me), 22.9, 50.4, 56.4, 122.0 (all CH_2), 138.4 (C), 168.8 (C=O).

2-Methyl-*N*-[(pyrrolidin-1-yl)methyl]prop-2-enamide (2b). (30.29 g, 90%), white solid; mp 56–58 °C (recryst. from MeCN); ν_{max} (neat, cm^{-1}) 3215, 2962, 2819, 1655, 1619, 1521 (C=O), 1450, 1362, 1356, 1299, 1208, 1134, 1046; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.75–1.79 (m, 4H), 1.96 (s, 3H), 2.62 (t, J 6.4 Hz, 4H), 4.24 (dd, J 0.7, 6.2 Hz, 2H), 5.33–5.34 (m, 1H), 5.69–5.70 (m, 1H), 6.17–6.31 (brs, 1H, NH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 18.8 (Me), 23.7, 51.0, 58.6, 119.8 (all CH_2), 140.1 (C), 168.7 (C=O); HRMS (ESI) m/z $[M + H]^+$, $C_9H_{17}N_2O$ calcd 169.1341 observed 169.1334.

2-Methyl-*N*-[(piperidin-1-yl)methyl]prop-2-enamide hydrochloride (3b·HCl). White solid; mp 143–145 °C (recryst. from MeCN); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.34–1.76 (m, 6H), 1.91 (s, 3H), 2.82–2.85 (m, 2H), 3.26–3.29 (m, 2H), 4.42 (d, J 6.6 Hz, 2H), 5.56 (s, 1H), 5.92 (s, 1H), 9.13 (t, J 6.6 Hz, 1H, NH), 10.12–10.32 (brs, 1H, NH); ^{13}C NMR (101 MHz, DMSO-d_6) δ 18.4 (Me), 21.2, 22.1, 49.7, 59.1, 121.9 (all CH_2), 138.4 (C), 168.7 (C=O).

2-Methyl-*N*-[(piperidin-1-yl)methyl]prop-2-enamide (3b). (33.54 g, 92%), white solid; mp 67–69 °C (recryst. from MeCN); ν_{max} (neat, cm^{-1}) 3353, 2934, 2852, 1671 (C=O), 1655, 1615, 1453, 1453, 1440, 1368, 1333, 1306, 1158, 1110, 1034; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38–1.44 (m, 2H), 1.54–1.59 (m, 4H), 1.95 (s, 3H), 2.45–2.59 (m, 4H), 4.10 (d, J 6.4 Hz, 2H), 5.34 (s, 1H), 5.71 (s, 1H), 6.29–6.38 (brs, 1H, NH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 18.8 (Me), 24.2, 25.9, 51.6, 62.4, 119.8 (all CH_2), 140.2 (C), 168.9 (C=O); HRMS (ESI) m/z $[M + H]^+$, $C_{10}H_{19}N_2O$ calcd 183.1497 observed 183.1493.

Synthesis of 1,1′-methylenebis(azocane)

Heptamethyleneimine (15.0 g, 0.13 mol) was added over 30 min to formaldehyde (37 wt% in H_2O, 6.2 mL, 0.07 mol) with stirring at *ca*. 0 °C. The solution was stirred overnight at *ca*. 20 °C, after which KOH pellets were added to form a saturated solution, and stirring was continued for 30 min. H_2O (40 mL) was added and the mixture was extracted with Et_2O (4 × 40 mL). The organic layers were combined and washed with H_2O (3 × 20 mL), dried ($MgSO_4$), and evaporated to dryness. Fractional distillation under reduced pressure gave the title compound as a colorless liquid (14.69 g, 88%); bp 138–140 °C (0.25 mmHg); ν_{max} (neat, cm^{-1}) 2915, 2846, 2779, 1657, 1472, 1448, 1358, 1250, 1158, 1094, 1046, 1017; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.51–1.68 (m, 20H), 2.53–2.60 (m, 8H), 3.02 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 26.1, 27.9, 28.2, 52.9, 83.8 (all CH_2); HRMS (ESI) m/z $[M + H]^+$, $C_{15}H_{31}N_2$, calcd 239.2487, observed 239.2312.

Synthesis of *N*,*N*,*N*′,*N*′-tetrabutylmethanediamine

Dibutylamine (68.00 mL, 0.40 mol) was added over 30 min to formaldehyde (37 wt% in H_2O, 15.00 mL, 0.20 mol) with stirring at *ca*. 0 °C. The solution was stirred overnight at *ca*. 20 °C. KOH pellets were added to form a saturated solution, and the drying agent was removed by filtration. Fractional distillation under reduced pressure gave the title compound as a colorless liquid (45.98 g, containing about 10% of suspected (dibutylamino)methanol impurity by ^{1}H NMR); bp 112–114 °C (0.25 mmHg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, J 7.2 Hz, 12H), 1.28 (m, 8H), 1.33–1.41 (m, 8H), 2.42 (t, J 7.3 Hz, 8H), 2.98 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.3 (Me), 20.9, 29.5, 52.0, 75.6 (all CH_2). HRMS (ESI) m/z $[M + H]^+$, $C_{17}H_{39}N_2$ calcd 271.3113 observed 271.3143. The title compound was used without further purification to prepare *N*,*N*-dibutylmethaniminium chloride (**4f**).

Synthesis of Schiff base salts

AcCl (21.33 mL, 0.3 mol) was added over 30 min to a stirred solution of aminal (0.3 mol) in Et_2O (150 mL) at *ca*. 0 °C, and the resulting white precipitate was stirred for an additional 30 min. Et_2O (200 mL) was added and the precipitate was filtered, and dried under vacuum to give the methylene Schiff-base salt (**4a–4f**). Iminium salts **4a–4f** were immediately used

in addition reactions with acrylamides and methacrylamides due to their hygroscopic nature.

1-Methylideneazepan-1-ium chloride (4a) (white solid, 43.85 g, 99%). 1-Methylideneazepan-1-ium chloride (**4a**) (white solid, 43.85 g, 99%) was characterized as *N*-(hydroxymethyl) azepan-1-ium chloride (**5a**)

^{1}H NMR (400 MHz, D_2O) δ 1.63–1.66 (m, 4H), 1.78–1.85 (brs, 4H), 3.17–3.21 (m, 4H), 4.77 (d, J 0.8 Hz, 2H); ^{13}C NMR (101 MHz, D_2O, 1,4-dioxane added) δ 25.2, 26.6, 46.8, 82.4 (all CH_2).

1-Methylideneazocan-1-ium chloride (4b) (white solid, 47.04 g, 97%). 1-Methylideneazocan-1-ium chloride (**4b**) (white solid, 47.04 g, 97%) was characterized as *N*-(hydroxymethyl) azocan-1-ium chloride (**5b**)

^{1}H NMR (500 MHz, D_2O) δ 1.57–1.67 (m, 6H), 1.81–1.86 (m, 4H), 3.21 (t, J 5.8 Hz, 4H), 4.74 (s, 2H); ^{13}C NMR (125 MHz, D_2O, 1,4-dioxane added) δ 23.9, 24.8, 25.2, 45.8, 82.4 (all CH_2).

***N*,*N*-Dimethylmethaniminium chloride (4c)[32] (white solid, 23.85 g, 85%).** *N*,*N*-Dimethylmethaniminium chloride (**4c**)[32] (white solid, 23.85 g, 85%) was characterized as hydroxy-*N*,*N*-dimethylmethanaminium chloride (**5c**)

^{1}H NMR (400 MHz, D_2O) δ 2.79 (s, 6H), 4.56 (s, 2H); ^{13}C NMR (101 MHz, D_2O, 1,4-dioxane added) δ 35.2 (Me), 82.4 (CH_2).

***N*,*N*-Diethylmethaniminium chloride (4d)[33] (white solid, 31.74 g, 87%).** *N*,*N*-Diethylmethaniminium chloride (**4d**)[33] (white solid, 31.74 g, 87%) was characterized as *N*-ethyl-*N*-(hydroxymethyl)ethanaminium chloride (**5d**)

^{1}H NMR (400 MHz, D_2O) δ 1.23 (t, J 7.3 Hz, 6H), 3.00–3.07 (m, 4H), 4.78 (s, 2H); ^{13}C NMR (101 MHz, D_2O, 1,4-dioxane added) δ 11.2 (Me), 42.9, 82.4 (both CH_2).

***N*,*N*-Dipropylmethaniminium chloride (4e)[34,35] (white solid, 40.85 g, 91%).** *N*,*N*-Dipropylmethaniminium chloride (**4e**)[34,35] (white solid, 40.85 g, 91%) was characterized as *N*-(hydroxymethyl)-*N*-propylpropan-1-aminium chloride (**5e**)

^{1}H NMR (400 MHz, D_2O) δ 0.92 (t, J 7.6 Hz, 6H), 1.65 (sext, J 7.6 Hz, 4H), 2.95 (t, J 7.6 Hz, 4H), 4.78 (s, 2H); ^{13}C NMR (101 MHz, D_2O, 1,4-dioxane added) δ 10.8 (Me), 19.7, 49.7, 82.4 (all CH_2).

***N*,*N*-Dibutylmethaniminium chloride (4f)[35] (white solid, 44.78 g, 84%).** *N*,*N*-Dibutylmethaniminium chloride (**4f**)[35] (white solid, 44.78 g, 84%) was characterized as *N*-butyl-*N*-(hydroxymethyl)butan-1-aminium chloride (**5f**)

^{1}H NMR (400 MHz, D_2O) δ 0.93 (t, J 6.0 Hz, 6H), 1.39 (sext, J 6.0 Hz, 4H), 1.66 (quint, J 6.0 Hz, 4H), 3.04 (t, J 6.0 Hz, 4H), 4.83 (s, 2H); ^{13}C NMR (101 MHz, D_2O, 1,4-dioxane added) δ 13.4 (Me), 19.8, 28.2, 47.9, 82.4 (all CH_2).

Synthesis of seven and eight-membered *N*-[(cycloalkylamino)-methyl]acrylamides and *N*-[(cycloalkylamino)methyl] methacrylamides

A solution of acrylamide or methacrylamide (0.03 mol) in MeCN (10 mL) was added to a solution of freshly prepared Schiff base salt **4a** or **4b** (0.04 mol) in MeCN (30 mL) and stirred at *ca*. 20 °C for 4 h. Et_2O (200 mL) was added and the hydrochloride salt of the monomer was precipitated, filtered, and dried under vacuum. The hydrochloride salts (**6a·HCl–6b·HCl** and **7a·HCl–7b·HCl**) were recrystallized, dried, and characterized. An aqueous solution of Na_2CO_3 (15 mL, 3 M) was added to a suspension of the hydrochloride salt in CH_2Cl_2 (20 mL) and left to stir for an additional 30 min and extracted with CH_2Cl_2 (4 × 50 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to dryness to give the corresponding monomers **6a–6b** and **7a–7b**.

***N*-[(Azepan-1-yl)methyl]prop-2-enamide hydrochloride (6a·HCl).** White solid; mp 136–138 °C (recryst. from MeCN); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.55–1.62 (m, 4H), 1.79–1.82 (m, 4H), 3.03–3.09 (m, 2H), 3.23–3.32 (m, 2H), 4.49 (d, J 6.8 Hz, 2H), 5.80 (dd, J 1.9, 10.2 Hz, 1H), 6.26 (dd, J 1.9, 17.2 Hz, 1H), 6.41 (dd, J 10.2, 17.2 Hz, 1H), 9.53 (t, J 6.8 Hz, 1H, NH), 10.46–10.63 (brs, 1H, NH); ^{13}C NMR (101 MHz, DMSO-d_6) δ 22.9, 26.1, 51.3, 59.2, 128.2 (all CH_2), 130.4 (CH), 166.2 (C=O).

***N*-[(Azepan-1-yl)methyl]prop-2-enamide (6a).** (4.81 g, 88%) colourless liquid; bp 134–136 °C (0.25 mmHg); ν_{max} (neat, cm^{-1}) 3278, 2922, 2852, 2852, 1656 (C=O), 1623, 1539, 1452, 1405, 1365, 1309, 1227, 1133, 1080; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52–1.61 (m, 8H), 2.68 (t, J 5.6 Hz, 4H), 4.23 (d, J 6.2 Hz, 2H), 5.61 (dd, J 1.6, 10.2 Hz, 1H), 6.11 (dd, J 10.2, 17.0 Hz, 1H), 6.25 (dd, J 1.6, 17.0 Hz, 1H), 6.31–6.40 (brs, 1H, NH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 26.9, 28.6, 53.1, 62.6, 126.7 (all CH_2), 131.1 (CH), 166.1 (C=O); HRMS (ESI) m/z $[M + H]^+$, $C_{10}H_{19}N_2O$ calcd 183.1497 observed 183.1516.

***N*-[(Azepan-1-yl)methyl]-2-methylprop-2-enamide hydrochloride (6b·HCl).** White solid; mp 88–90 °C (recryst. from THF); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.53–1.64 (m, 4H), 1.79–1.81 (m, 4H), 1.91 (s, 3H), 3.02–3.15 (m, 2H), 3.23–3.30 (m, 2H), 4.46 (d, J 4.3 Hz, 2H), 5.57 (s, 1H), 5.92 (s, 1H), 9.19 (m, 1H, NH), 10.28–10.44 (brs, 1H, NH); ^{13}C NMR (101 MHz, DMSO-d_6) δ 18.4 (Me), 22.8, 26.2, 51.4, 59.7, 122.0 (all CH_2), 138.4 (C), 168.7 (C=O).

***N*-[(Azepan-1-yl)methyl]-2-methylprop-2-enamide (6b).** (5.36 g, 91%) colourless liquid; bp 139–141 °C (0.25 mmHg); ν_{max} (neat, cm^{-1}) 3328, 2923, 2852, 1655, 1616 (C=O), 1526, 1373, 1313, 1201, 1133, 1088, 1020; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.56–1.68 (m, 8H), 1.96 (s, 3H), 2.72 (t, J 5.5 Hz, 4H), 4.24 (d, J 6.1 Hz, 2H), 5.33 (s, 1H), 5.69 (s, 1H), 6.12–6.22 (brs, 1H, NH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 18.8 (Me), 27.0, 28.6, 53.2, 62.7, 119.6 (all CH_2), 140.3 (C), 168.8 (C=O); HRMS (ESI) m/z $[M + H]^+$, $C_{11}H_{21}N_2O$ calcd 197.1654 observed 197.1708.

***N*-[(Azocan-1-yl)methyl]prop-2-enamide hydrochloride (7a·HCl).** White solid; mp 87–89 °C (recryst. from EtOAc); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.43–1.70 (m, 6H), 1.76–1.96 (m, 4H), 3.10–3.16 (m, 2H), 3.22–3.32 (m, 2H), 4.48–4.68 (m, 2H), 5.69 (d, J 10.1 Hz, 1H), 6.25 (d, J 17.1 Hz, 1H), 6.43 (dd, J 10.1, 17.1 Hz, 1H), 9.58–9.67 (m, 1H, NH), 10.25–10.38 (brs, 1H, NH); ^{13}C NMR (101 MHz, DMSO-d_6) δ 22.1, 24.0, 25.1, 48.8, 59.2, 128.2 (all CH_2), 130.4 (CH), 166.2 (C=O).

***N*-[(Azocan-1-yl)methyl]prop-2-enamide (7a).** (5.30 g, 90%) colourless oil; ν_{max} (neat, cm^{-1}) 3328, 2917, 2850, 1657 (C=O), 1624, 1536, 1363, 1232, 1162, 1095, 1060; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50–1.62 (m, 10H), 2.62–2.70 (m, 4H), 4.27 (d,

J 6.0 Hz, 2H), 5.65 (d, *J* 10.2 Hz, 1H), 5.91–6.02 (brs, 1H), 6.10 (dd, *J* 10.2, 17.0 Hz, 1H), 6.28 (d, *J* 17.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 26.1, 27.7, 28.0, 51.6, 62.6, 126.7 (all CH_2), 131.2 (CH), 166.0 (C=O); HRMS (ESI) *m*/*z* $[M + H]^+$, $C_{11}H_{21}N_2O$, calcd 197.1656, observed 197.1654.

***N*-[(Azocan-1-yl)methyl]-2-methylprop-2-enamide hydrochloride (7b·HCl).** White solid; mp 128–130 °C (recryst. from EtOAc); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.46–1.75 (m, 6H), 1.81–1.99 (m, 7H), 3.07–3.18 (m, 2H), 3.23–3.35 (m, 2H), 4.45–4.53 (m, 2H), 5.70 (s, 1H), 5.93 (s, 1H), 9.17–9.27 (brs, 1H, NH), 9.94–10.09 (brs, 1H, NH); ^{13}C NMR (101 MHz, DMSO-d_6) δ 18.4 (Me), 22.2, 24.0, 25.0, 48.9, 59.8, 122.0 (all CH_2), 138.4 (C), 168.6 (C=O).

***N*-[(Azocan-1-yl)methyl]-2-methylprop-2-enamide (7b).** (5.30 g, 84%) colourless oil; ν_{max} (neat, cm^{-1}) 3324, 2918, 2850, 1655, 1618 (C=O), 1523, 1452, 1363, 1201, 1162, 1095, 1060; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49–1.59 (m, 10H), 1.93 (s, 3H), 2.61–2.66 (m, 4H), 4.21 (t, *J* 4.3 Hz, 2H), 5.28 (s, 1H), 5.64 (s, 1H), 6.12–6.26 (brs, 1H, NH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 18.8 (Me), 26.0, 27.7, 28.0, 51.5, 62.7, 119.2 (all CH_2), 140.4 (C), 168.9 (C=O); HRMS (ESI) *m*/*z* $[M + H]^+$, $C_{12}H_{23}N_2O$, calcd 211.1838, observed 211.1810.

Synthesis of *N*-[(dialkylamino)methyl]acrylamides and *N*-[(dialkyl-amino)methyl]methacrylamides

A solution of acrylamide or methacrylamide (0.25 mol) in MeCN (50 mL) was added to a stirred solution of freshly prepared Schiff base salt **4c–4f** (0.25 mol) in MeCN (50 mL) and stirred at *ca*. 20 °C for 3 h. An aqueous solution of Na_2CO_3 (150 mL, 3 M) was added and the solution was stirred for an additional 30 min and extracted with CH_2CL_2 (4 × 250 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to give the corresponding acrylamides **8a–11a** and methacrylamides **8b–11b**.

***N*-[(Dimethylamino)methyl]prop-2-enamide (8a).** (22.11 g, 69%) colourless liquid; bp 64–66 °C (760 mmHg); ν_{max} (neat, cm^{-1}) 3281, 2942, 2827, 2780, 1659 (C=O), 1625, 1536, 1407, 1230, 1029; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.24 (s, 6H), 4.05 (d, *J* 6.4 Hz, 2H), 5.62 (dd, *J* 1.6, 10.2 Hz, 1H), 6.12 (dd, *J* 10.2, 17.0 Hz, 1H), 6.26 (dd, *J* 1.6, 17.0 Hz, 1H), 6.71–6.82 (brs, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 41.8 (Me), 61.5, 126.0 (both CH_2), 130.7 (CH), 166.2 (C=O); HRMS (ESI) *m*/*z* $[M + H]^+$, $C_6H_{13}N_2O$, calcd 129.1028, observed 129.1026.

***N*-[(Dimethylamino)methyl]-2-methylprop-2-enamide (8b).** (32.10 g, 90%) colourless liquid, bp 60–62 °C (0.25 mmHg); ν_{max} (neat, cm^{-1}) 3323, 2942, 2827, 1658 (C=O), 1619, 1523, 1453, 1311, 1196, 1049, 1033; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.92 (s, 3H), 2.23 (s, 6H), 4.03 (d, *J* 6.3 Hz, 2H), 5.30 (s, 1H), 5.66 (s, 1H), 6.31–6.45 (brs, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 18.7, 42.3 (both Me), 62.2, 119.5 (both CH_2), 140.1 (C), 169.0 (C=O); HRMS (ESI) *m*/*z* $[M + H]^+$, $C_7H_{15}N_2O$ calcd 143.1184, observed 143.1180.

***N*-[(Diethylamino)methyl]prop-2-enamide (9a).** (32.39 g, 83%) yellow oil; bp 65–67 °C (0.25 mmHg); ν_{max} (neat, cm^{-1}) 3289, 2969, 2828, 1657 (C=O), 1624, 1536, 1464, 1233, 1206, 1067; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (t, *J* 7.2 Hz, 6H), 2.56 (q, *J* 7.2 Hz, 4H), 4.29 (d, *J* 6.1 Hz, 2H), 5.64 (dd, *J* 1.4, 10.2 Hz, 1H), 5.90–5.99 (brs, 1H), 6.09 (dd, *J* 10.2, 17.0 Hz, 1H), 6.28 (dd, *J* 1.4, 17.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 12.7 (Me), 45.4, 56.9, 126.6 (all CH_2), 131.0 (CH), 166.1 (C=O); HRMS (ESI) *m*/*z* $[M + H]^+$, $C_8H_{17}N_2O$, calcd 157.1341, observed 157.1337.

***N*-[(Diethylamino)methyl]-2-methylprop-2-enamide (9b).** (33.21 g, 78%) colourless liquid, bp 72–74 °C (0.25 mmHg); ν_{max} (neat, cm^{-1}) 3344, 2970, 2827, 1656 (C=O), 1617, 1522, 1455, 1375, 1197, 1066, 1046; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (t, *J* 7.2 Hz, 6H), 1.90 (s, 3H), 2.52 (q, *J* 7.2 Hz, 4H), 4.22 (d, *J* 6.0 Hz, 2H), 5.27 (s, 1H), 5.63 (s, 1H), 6.11–6.21 (brs, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 12.7, 18.8 (both Me), 45.4, 57.3, 119.5 (all CH_2), 140.2 (C), 168.9 (C=O); HRMS (ESI) *m*/*z* $[M + H]^+$, $C_9H_{19}N_2O$ calcd 171.1497, observed 171.1789.

***N*-[(Dipropylamino)methyl]prop-2-enamide (10a).** (37.80 g, 82%) colourless plates, mp 25–26 °C; ν_{max} (neat, cm^{-1}) 3269, 2959, 2930, 1657 (C=O), 1623, 1550, 1457, 1246, 1185, 1069; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.82 (t, *J* 7.4 Hz, 6H), 1.44 (sext, *J* 7.4 Hz, 4H), 2.39 (t, *J* 7.4 Hz, 4H), 4.23 (d, *J* 6.0 Hz, 2H), 5.58 (dd, *J* 1.6, 10.2 Hz, 1H), 6.11 (dd, *J* 10.2, 17.0 Hz, 1H), 6.22 (dd, *J* 1.6, 17.0 Hz, 1H), 6.28–6.39 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.9 (Me), 20.9, 54.0, 58.1, 126.5 (all CH_2), 131.1 (CH), 166.1 (C=O); HRMS (ESI) *m*/*z* $[M + H]^+$, $C_{10}H_{21}N_2O$ calcd 185.1654, observed 185.1663.

***N*-[(Dipropylamino)methyl]-2-methylprop-2-enamide (10b).** (43.62 g, 88%) colourless liquid, bp 86–88 °C (0.25 mmHg); ν_{max} (neat, cm^{-1}) 3316, 2959, 2934, 2873, 1655 (C=O), 1619, 1524, 1456, 1374, 1183, 1075, 1052; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (t, *J* 7.4 Hz, 6H), 1.46 (sext, *J* 7.4 Hz, 4H), 1.93 (s, 3H), 2.42 (t, *J* 7.4 Hz, 4H), 4.22 (d, *J* 6.0 Hz, 2H), 5.29 (s, 1H), 5.65 (s, 1H), 6.02–6.15 (brs, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 11.9, 18.8 (both Me), 20.9, 54.1, 58.5, 119.4 (all CH_2), 140.3 (C), 168.9 (C=O); HRMS (ESI) *m*/*z* $[M + H]^+$, $C_{11}H_{23}N_2O$ calcd 199.1810, observed 199.1800.

***N*-[(Dibutylamino)methyl]prop-2-enamide (11a).** (44.56 g, 84%) colourless liquid, bp 124–126 °C (0.25 mmHg); ν_{max} (neat, cm^{-1}) 3281, 3069, 2957, 2863, 1658 (C=O), 1625, 1542, 1456, 1459, 1366, 1180, 1071; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, *J* 7.3 Hz, 6H), 1.24–1.33 (m, 4H), 1.40–1.47 (m, 4H), 2.45 (t, *J* 7.5 Hz, 4H), 4.26 (d, *J* 6.0 Hz, 2H), 5.63 (dd, *J* 1.5, 10.2 Hz, 1H), 5.88–6.00 (brs, 1H), 6.10 (dd, *J* 10.2, 17.0 Hz, 1H), 6.27 (dd, *J* 1.5, 17.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.1 (Me), 20.7, 30.0, 51.9, 58.3, 126.7 (all CH_2), 131.0 (CH), 166.0 (C=O); HRMS (ESI) *m*/*z* $[M + H]^+$, $C_{12}H_{25}N_2O$ calcd 213.1967, observed 213.1952.

***N*-[(Dibutylamino)methyl]-2-methylprop-2-enamide (11b).** (49.21 g, 87%) colourless liquid, bp 133–135 °C (0.25 mmHg); ν_{max} (neat, cm^{-1}) 3325, 2957, 2931, 2872, 1625 (C=O), 1525, 1456, 1374, 1296, 1179, 1083, 1034; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, *J* 7.4 Hz, 6H), 1.25–1.34 (m, 4H), 1.40–1.47 (m, 4H), 1.95 (s, 3H), 2.46 (t, *J* 7.4 Hz, 4H), 4.24 (d, *J* 5.9 Hz, 2H), 5.32 (s, 1H), 5.66 (s, 1H), 5.98–6.06 (brs, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.1, 18.8 (both Me), 20.7, 30.0, 51.9, 58.6, 119.4 (all CH_2), 140.4 (C), 168.9 (C=O); HRMS (ESI) *m*/*z* $[M + H]^+$, $C_{13}H_{27}N_2O$ calcd 227.2123, observed 227.2129.

X-ray crystallographic studies

Single crystal X-ray diffraction data were collected using an Oxford Diffraction Xcalibur system operated using the CrysAlisPro software[36] and the data collection temperature was controlled at 150 K using a Cryojet system from Rigaku Oxford Diffraction. The crystals were hygroscopic and were first coated in cold paraffin oil before being transferred to the cold stream on the diffractometer. The crystal structures were solved using ShelxT version 2014/5,[37] and refined using ShelxL version 2017/1[38] both of which were operated within the Oscail software package.[39]

Crystal refinement data for 1-(hydroxymethyl)azocan-1-ium chloride (5b). Colourless crystals, $C_8H_{18}ClNO$, M = 179.68, monoclinic, space group $P2_1/c$, a = 11.3190(18), b = 10.9194(16), c = 7.7658(10) Å, α = 90, β = 90.269(13), γ = 90°, V = 959.8(2) Å^3, Z = 4, T = 150.0(1) K, ρ_{calcd} = 1.243 g cm^{-3}, refinement of 147 parameters on 2345 independent reflections out of 7528 measured reflections (R_{int} = 0.0709) led to R_1 = 0.0857 ($I > 2\sigma(I)$), wR_2 = 0.2182 (all data), and S = 1.119 with the largest difference peak and hole of 0.396 and −0.398 e Å^{-3}.

Crystal refinement data for *N*-[(azocan-1-yl)methyl]prop-2-enamide hydrochloride (7a·HCl). Colourless needle crystals, $C_{11}H_{21}ClN_2O$, M = 232.75, triclinic, space group $P\bar{1}$, a = 10.1121(7), b = 10.4420(6), c = 12.0205(14) Å, α = 95.695(8), β = 91.086(8), γ = 97.671(5)°, V = 1251.02(19) Å^3, Z = 4, T = 150.0(1) K, ρ_{calcd} = 1.236 g cm^{-3}, refinement of 271 parameters on 4487 independent reflections out of 7456 measured reflections (R_{int} = 0.0638) led to R_1 = 0.0684 ($I > 2\sigma(I)$), wR_2 = 0.2128 (all data), and S = 0.979 with the largest difference peak and hole of 0.852 and −0.705 e Å^{-3}.

Crystallographic data for compounds **5b** and **7a·HCl** have been deposited with the Cambridge Crystallographic Data Centre with deposition numbers CCDC 1819145 and 1819144 respectively.†

Conflicts of interest

There are no conflicts to declare.

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