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Highly reactive α-bromoacrylate monomers and Michael acceptors obtained by Cu(II)Br_2-dibromination of acrylates and instantaneous E2 by a ligand†

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Depending on the order of their addition to the reaction mixture, acrylates can undergo SET-LRP or dibromination by Cu(II)Br_2 and spontaneously dehydrohalogenate to provide the corresponding highly reactive α-bromoacrylate monomer and Michael acceptor.

Depending on the combination of a solvent, ligand, and initiator, Cu(0)-catalyzed radical polymerization can proceed by a single-electron transfer living radical polymerization (SET-LRP) mechanism or by a combination of SET-LRP and atom transfer radical polymerization (ATRP) mechanisms.[1] Water,[2] hydrogenated and fluorinated protic, dipolar aprotic, other polar solvents[3] and monomers[4] as well as their homogeneous[5] and biphasic mixtures[6] that mediate the disproportionation of Cu(I)X into Cu(0) and Cu(II)X_2 mediate SET-LRP together with suitable ligands,[7] monomers and initiators.[8] Solvents that do not mediate the disproportionation of Cu(I)X into Cu(0) and Cu(II)X_2 are usually nonpolar solvents such as toluene.[9] The classic polar solvent that does not mediate this disproportionation is acetonitrile.[10] When these non-disproportionating solvents are employed in Cu(0)-catalyzed radical polymerization, the early stages of polymerization proceed by an SET-LRP mechanism, and subsequently, as Cu(I)X accumulates, the mechanism of the reaction may change from SET-LRP to ATRP.[1a,b] When non-polar solvents or even polar non-disproportionating solvents are employed, the resulting polymers have poor chain-end functionality.[9,10] Nonpolar solvents exhibit poor solubility for Cu(II)X_2, and the mechanism of ATRP requires bimolecular termination to create the equilibrium concentration of Cu(II)X_2 required to establish the persistent radical effect.[11] Therefore, it is not surprising that the resulting polymer chain ends exhibit poor functionality.[9,10] Consequently, SET-LRP represents the method of choice when a quantitative or near quantitative chain end functionality is in demand.[12] Homogeneous and biphasic mixtures of different solvents, including water, have been employed to remediate the poor chain-end functionality attained in non-disproportionating solvents and develop new SET-LRP methodologies.[1b] Mixtures of the non-disproportionating solvent acetonitrile with DMSO and with water in biphasic systems have been employed to access SET-LRP with acetonitrile as a solvent.[5a,b,10] In all the cases, the mixture is prepared by mixing a ligand with a monomer, initiator, and eventually Cu(II)X_2 in this order before degassing the reaction mixture and placing it in contact with the Cu(0) wire,[13] powder/nanopowder[14] or Cu(0) generated *in situ*.[15] Herein, we report the inversion of the order of addition of reagents as abovementioned to acrylate monomer; Cu(II)Br_2 in acetonitrile mediates an extremely efficient Cu(II)Br_2-promoted bromination of the vinylic monomer at room temperature. Scheme 1a and b depict the reaction taking place with methyl acrylate and butyl acrylate (MA and BA, respectively).

The Cu(II)Br_2-mediated bromination process of MA and BA can be monitored by ^{1}H NMR directly in acetonitrile (Fig. 1a). The rate of bromination at 25 °C is similar for both monomers during the first hour of reaction. Approximately 50% of the initial monomer is converted to the corresponding dibromo-derivative in 2 h. Later, the rate of bromination is higher for MA than for BA. Note that no chlorination was observed under the same reaction conditions with Cu(II)Cl_2 at 25 °C or higher temperatures (Scheme 1e). Fig. 1b shows the ^{1}H NMR spectra for the Cu(II)Br_2-promoted bromination of MA obtained at different reaction times. The most obvious ^{1}H NMR marker that confirms the Cu(II)Br_2-promoted bromination is the disappearance of the characteristic vinylic signals of MA (H_{1-3}) and the emergence of new signals corresponding to the dibro-

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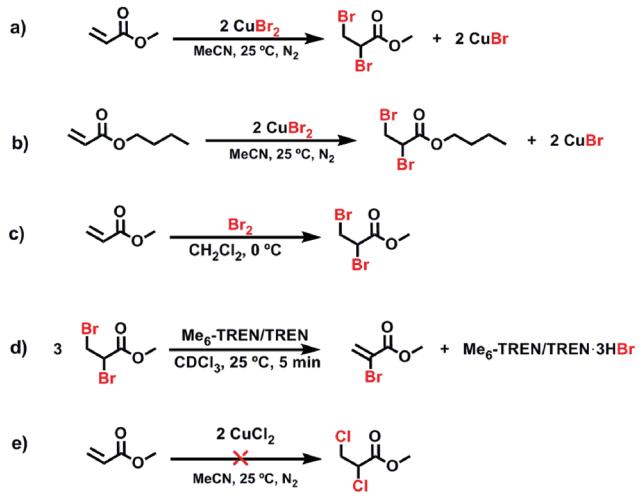

Scheme 1 Cu(II)Br_2-dibromination of MA and BA in acetonitrile at 25 °C (a and b), dibromination of MA with Br_2 (c), dehydrobromination of methyl 2,3-dibromopropionate mediated by Me_6-TREN or TREN (d), and non-observed Cu(II)Cl_2-promoted dichlorination of MA in acetonitrile at 25 °C (e).

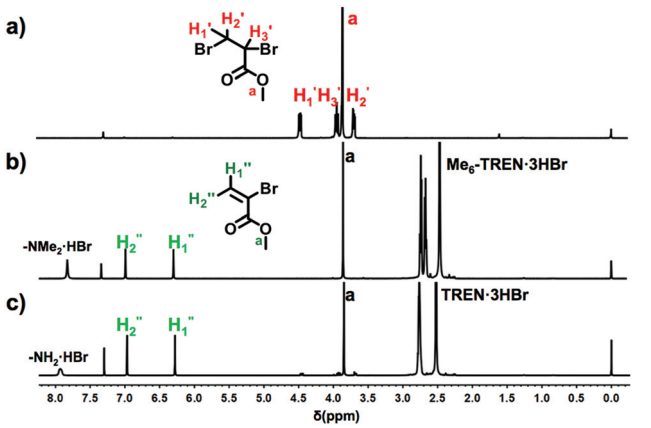

Fig. 2 E2 elimination of methyl 2,3-dibromopropionate promoted by ligand. 500 MHz ^{1}H-NMR spectra recorded in $CDCl_3$ of (a) methyl 2,3-dibromopropionate produced by dibromination of MA with Cu(II)Br_2, (b) methyl α-bromoacrylate produced from methyl 2,3-dibromopropionate in the presence of a stoichiometric amount of Me_6-TREN, and (c) methyl α-bromoacrylate produced from methyl 2,3-dibromopropionate in the presence of stoichiometric amount of TREN.

minated derivative ($H_{1'-3'}$ and a′). Fig. 2a shows the ^{1}H NMR spectrum of methyl 2,3-dibromopropionate isolated after the Cu(II)Br_2-dibromination of MA.

Note that the bromination of acrylates with Cu(II)Br_2 provides the same product as that generated by bromination with Br_2 (Scheme 1c).[16] It is also important to point out that no bromination occurs when DMSO is used as a solvent under strictly similar conditions. However, the fact that the Cu(II)Br_2-promoted halogenations of various unsaturated compounds have been reported to occur in other polar solvents, such as alcohols and DMF,[17] suggests that it may also take place in DMSO under other conditions.

Control experiments carried out in the presence of classic SET-LRP ligands, such as tris(2-dimethylamino ethyl)amine (Me_6-TREN) and tris(2-aminoethyl)amine (TREN), pointed towards the importance of the mixing order of reagents to avoid this undesired reaction during LRP protocols.

In fact, when the reaction mixture was prepared by dissolving a monomer, a ligand, and Cu(II)Br_2 in acetonitrile, no

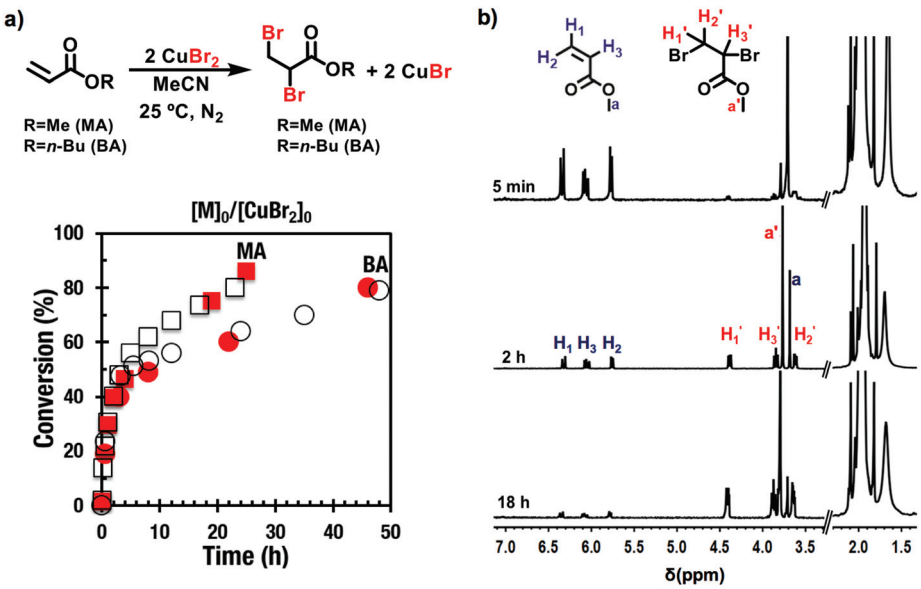

Fig. 1 Cu(II)Br_2-mediated dibromination of acrylates in acetonitrile at 25 °C. (a) Conversion *vs.* time plots in the bromination of MA and BA. Data in different colors are obtained from duplicated experiments performed by different researchers. (b) 500 MHz ^{1}H-NMR spectra obtained over time for the bromination of MA.

dibromination product was detected by ^{1}H NMR after 24 h when the reaction was carried out at room temperature. However, note that the addition of stoichiometric amounts of Me_6-TREN or TREN to methyl 2,3-dibomopropionate in $CDCl_3$ resulted in complete disappearance of the signals associated with this product in a few minutes at 25 °C (Fig. 2b and c, respectively). Inspection of the ^{1}H NMR spectra clearly indicates the base-mediated spontaneous E_2 dehydrobromination process that generates the corresponding α-bromoacrylate derivative. The two characteristic germinal protons of methyl α-bromoacrylate appear at 6.3 and 7.0 ppm ($H_{1''}$ and $H_{2''}$, respectively). The same reaction was observed using Me_6-TREN and TREN although the methylated ligand mediated a faster E2 elimination reaction. In this case, the complete disappearance of the characteristic signals of the dibrominated acrylate was observed after 5 min α-Haloacrylates are very reactive monomers[18] and Michael acceptors[19] that undergo radical polymerization and Michael addition with a variety of Michael donors. The halogenation of olefins with both Cu(II)Br_2 and Cu(II)Cl_2 is known to organic chemists, but has not been extensively investigated from the mechanistic and preparative points of view.[17] However, these side reactions seem to have been unknown to the polymer chemistry community. Hence, when the order of addition of the acrylate monomer, solvent, Cu(II)Br_2, and ligand is not maintained in a proper sequence, α-bromoacrylate derivatives can be generated in the reaction mixture, and their copolymerization with the parent acrylate can generate hyperbranched/crosslinked rather than linear polymers.[20] In addition, α-bromoacrylates can provide Michael adducts with the ligand and generate new initiators that can affect the functionality of the polymer chain-end(s).[21] A series of control experiments was performed to demonstrate that the presence of α-bromoacrylate derivatives is undesirable. The Cu(0) wire/Me_6-TREN-catalyzed SET-LRP of MA was investigated in the presence of 3% of methyl α-bromoacrylate at 25 °C in a biphasic acetonitrile/water 8/2 v/v mixture.[6b] Under these conditions, the progressive formation of an insoluble gel on the Cu(0) wire surface was observed. ^{1}H NMR analysis showed that no soluble polymer was present in the reaction mixture. This gel, generated by crosslinking of poly(methyl acrylate) (PMA) chains containing methyl α-bromoacrylate repeating units, was insoluble in common organic solvents. Gel formation was also observed in our laboratory and by others in aqueous SET-LRP.[2b,22,23] Upon repeating the polymerization in a homogeneous reaction mixture using DMSO as a solvent, nearly identical results were obtained. Attempts to avoid the formation of the crosslinked material by reducing the amount of Cu(0) wire or preforming polymerization in the presence of externally added Cu(II)Br_2 deactivator (5 mol% relative to initiator) were unsuccessful (Fig. 3). These results support the importance of avoiding traces of α-bromoacrylate derivatives in the polymerization mixture to practice clean and efficient polymerization processes.

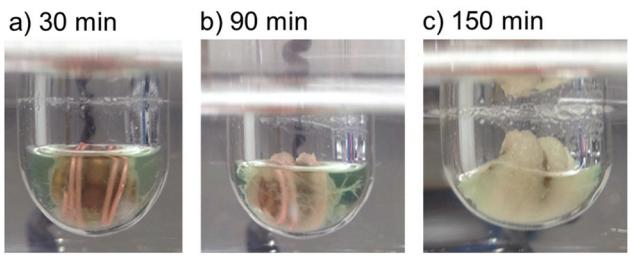

Fig. 3 Gel formation during the Cu(0) wire-catalyzed SET-LRP of MA in the presence of 3 mol% methyl α-bromoacrylate in DMSO. Reaction conditions: MA = 0.97 mL, methyl α-bromoacrylate = 54 mg, DMSO = 0.5 mL, [monomers]/[MBP]/[Me_6-TREN]/[Cu(II)Br_2] = 222/1/0.1/0.05, 12.5 cm Cu(0) wire 20 gauge, 25 °C.

Conclusions

Cu(II)Br_2, but not Cu(II)Cl_2, dibrominates acrylate monomers, such as MA and BA, in acetonitrile at 25 °C to generate the corresponding dibrominated derivative. Subsequent addition of a stoichiometric amount of Me_6-TREN or TREN to this product spontaneously produces α-bromoacrylate. This bromination reaction does not occur in the presence of a ligand. α-Bromoacrylates are reactive monomers that are known to undergo radical polymerization. However, under SET-LRP and ATRP conditions, α-bromoacrylates would produce hyperbranched polymers. The products are also very reactive Michael acceptors that undergo additional side reactions with excess ligand and other Michael donors including Me_6-TREN and TREN. These side reactions together with the electrophilic halogenation of acetone with Cu(II)Br_2 reported recently by our group[6d] must be considered during the practice of current SET-LRP and ATRP methodologies as well as during the invention of new processes.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

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