One-pot tandem living radical polymerisation–Huisgens cycloaddition process (“click”) catalysed by *N*-alkyl-2-pyridylmethanimine/Cu(I)Br complexes†

Giuseppe Mantovani, Vincent Ladmiral, Lei Tao and David M. Haddleton*

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Azide terminally functional poly(methyl methacrylate)s (M_n = 4000–6000, PDI = 1.21–1.28) have been prepared by living radical polymerization and successfully reacted with alkynes in a Huisgen cycloaddition (click) reaction in one pot using the same catalyst for both processes.

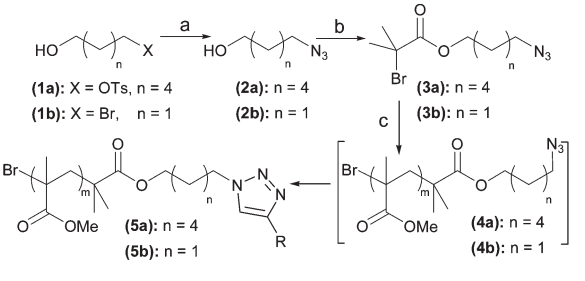
“Click chemistry” is a general term that identifies a class of chemical transformations with a number of attractive features including excellent functional-group tolerance, high yields and good selectivity under mild experimental conditions. This is coupled with the use of readily available reagents and usual avoidance of chromatographic purification of products.[1,2] Among these reactions, the Huisgen 1,3-dipolar cycloaddition has been receiving increasing interest following the emergence of enormous improvement in regioselectivity and yields in the presence of copper(I)-based catalysts. An acceleration of the reaction rate of approximately seven orders of magnitude has been observed using Cu(I).[3,4] This discovery has led to its application in a many processes including the synthesis of therapeutics,[5,6] protein-based biohybrids,[7–11] sugar arrays,[12] dendrimers[13,14] and functional polymers.[15–18] The overall reaction is a cycloaddition of an alkyne and an organic azide to give a five-membered 1,2,3-triazole. The resulting “clicked” products can even be obtained *via in situ* generation of the required organic azides from organic halides–NaN_3 in the presence of an alkyne and a copper catalyst, avoiding the need to handle organic azides.[19] The proposed mechanism for a copper(I)-catalysed reaction involves the addition of a Cu(I)-acetylide to an azide in a stepwise sequence, giving a five-membered vinyl cuprate which yields the triazole product.[3,20] The required Cu(I) catalysts are usually prepared by either *in situ* reduction of Cu(II) salts or by use of an appropriate Cu(I) complex with triphenylphosphine,[13,16] mono[3,4] or polydentate[8,10,21] nitrogen ligands.

Transition-metal mediated living radical polymerisation (TMM-LRP, often termed ATRP) has rapidly developed as a way to new functional materials. This process shares a number of important features with click chemistry including robustness, versatility and excellent tolerance towards many functional-groups, including water.[22,23] We envisaged the possibility that these two reactions could share the same catalyst and in particular we focused our attention towards Cu(I)Br–iminopyridine catalytic systems.[24]

We reasoned that a process that combines Cu(I)-catalysed Huisgen cycloaddition and LRP could allow for a one-pot synthesis of a wide variety of products spanning from new α-functional and grafted/star shaped polymers to biohybrid materials. Our synthetic strategy involved the synthesis of appropriate azido-initiators, polymerisation of methacrylic monomers in the presence of a Cu(I)-based catalyst followed by a subsequent *in situ* “clicking” to functional terminal alkynes. It is noted that azide terminally functional polymers have been prepared previously by transformation of terminal halides with sodium azide.[25] However, in this case quantification proved difficult and as termination events always occur in living radical polymerization, of any type, the functional initiator approach is preferred.

The Cu(I)/Cu(II)–iminopyridine complexes employed in LRP are reported to be distorted tetrahedral N_4–Cu(I) and trigonal bipyramid N_4–Cu(II)X derivatives, although many coordinating products, monomer, solvent and additives can also coordinate to the metal centre affecting the reactivity of the catalytic system.[26,27] We first verified that these copper complexes were active catalysts for Huisgen-type cycloadditions. Reaction of 1-octyl azide and propargyl alcohol in toluene at 70 °C, using 10% copper catalyst (Cu(I)Br–Cu(II)Br_2–*N*-ethyl-2-pyridylmethanimine 0.95 : 0.05 : 2)[28] gave complete conversion of the reactants in less than one hour, with exclusive formation of the 1,4-disubstituted adduct. In the absence of the catalyst a conversion of 35% was reached after 2 days, with a 1.5 : 1.0 ratio between the two possible regioisomers, in favour of the 1,4, in agreement with previous reports.[3]

Initiators (**3a** and **3b**) were prepared as shown in Scheme 1. The azido-alcohol intermediates (**2**) were obtained by treatment of bromo and tosyl alcohols with NaN_3 in refluxing acetone–water solution. Subsequent acylation of (**2**) with 2-bromoisobutyryl



Scheme 1 *Reagents and conditions*: a) NaN_3, acetone–water, reflux, b) 2-bromoisobutyryl bromide, Et_3N, Et_2O, 0 °C to ambient temperature, c) *i.* methyl methacrylate, *N*-alkyl-2-pyridylmethanimine–Cu(I)Br; *ii.* RC≡CH.

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† Electronic Supplementary Information (ESI) available: experimental procedure and characterisation of prepared compounds. See http://www.rsc.org/suppdata/cc/b5/b500558b/

*D.M.Haddleton@warwick.ac.uk

bromide and triethylamine gave the desired azido-ester initiators (**3a** and **3b**). Polymerisation of methyl methacrylate using (**3a** and **3b**) as the initiators gave good first order kinetic plots, regardless of the length of the linker connecting the azide moiety and the polymer backbone (Fig. 1).

The initiating efficiency of (**3b**) was found to be higher (close to 100%) than that observed for (**3a**), a result that may be ascribed to the different steric effects on the initiating centre. The α-functional polymers obtained from (**3a**) also showed a lower content of azide chain-ends (75–86% depending on the conditions employed) in contrast to the apparent 100% content for the polymers obtained from (**3b**) in toluene at 90 °C. ^{1}H NMR analysis revealed that this decrease in the azide content occurs mainly at the early stages of the polymerisation and that was observed even at reduced polymerisation rates achieved by both reducing the amount of Cu(I) catalyst and by addition of Cu(II)Br_2 to the reaction mixture. This behaviour may be related to an intramolecular cyclisation involving the azide moiety and the propagating centre and will be the subject of further investigation.

The reactivity of the α-functional azide polymers was demonstrated by the addition of propargyl alcohol to the polymerisation mixture at high monomer conversion (87–95%) and monitoring the disappearance of the -CH_2N_3 signal (triplet at 3.2 and 3.4 ppm for (**4a**) and (**4b**) respectively) in the ^{1}H NMR. The final "clicked" polymers showed a pattern of signals analogous to that observed for the octyl azide–propargyl alcohol adduct. All of the click reactions were complete after stirring the reaction mixture at 70 °C overnight. Some free iminopyridine ligand was detected during the cycloaddition step, ascribed to a certain degree of coordination of the triazole product to the metal. The sequential LRP–Huisgens cycloaddition process proved to be efficient in a range of solvents including toluene, anisole, and poly(ethylene glycol) (M_n ~400, PEG_{400}).[29] The efficiency of the click reaction was further investigated in the presence of a range of model functional alkynes including the diaza (**6**) and coumarin (**7**) dyes (Fig. 2). The observed reactivity did not differ significantly from that observed where propargyl alcohol was employed as the "alkyne" substrate, giving the α-functional polymers in close to 100% yields.

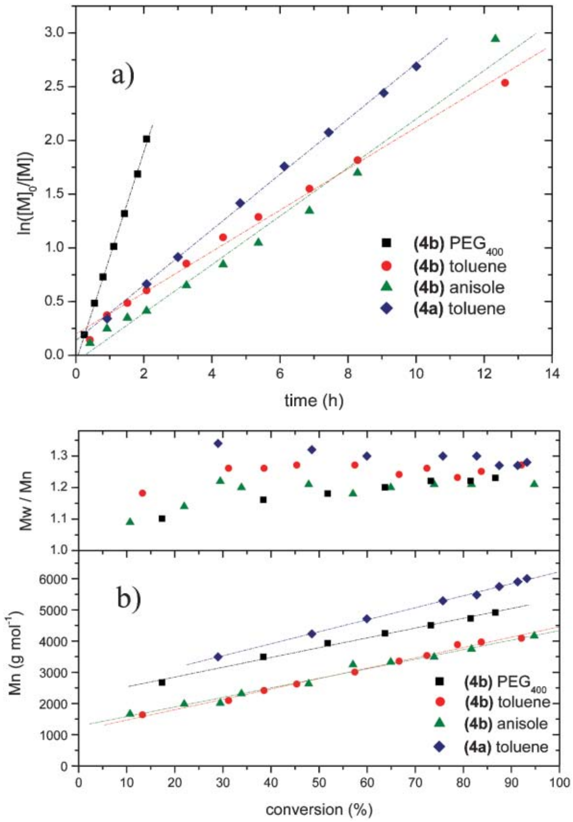

Fig. 1 Polymerisation of MMA with initiators (**3a**) and (**3b**) in a range of solvents. Reaction conditions: [MMA] : [(**3**)] : [Cu(I)Br] : [*N*-alkyl-2-pyridylmethanimine] = 40 : 1 : 1 : 2, 70 °C (when PEG was employed as the solvent 5% of Cu(II)Br_2 was also added). (a) Pseudo-first order kinetic plots. (b) Dependence of M_n and M_w/M_n with conversion.

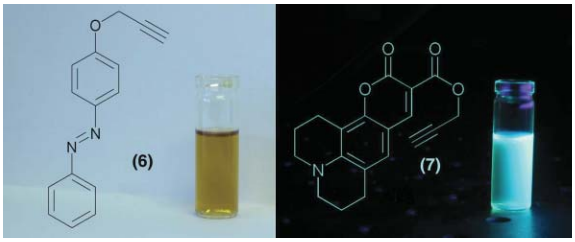

Fig. 2 Dilute solutions of purified "clicked" polymers (**5b**) with dyes (**6**) and (**7**), taken under visible and UV light (λ = 350 nm) respectively.

In summary, we report the first example of a one-pot tandem copper(I)-catalysed sequential LRP–Huisgens cycloaddition process. The synthetic protocol developed for the required azido-initiators is very general and can allow for easy modification both the nature and the size of the spacer between the azido moiety and the initiating centre. The Cu(I)Br–iminopyridine complexes employed have shown great versatility, catalysing efficiently both of the processes, under a number of different experimental conditions. This approach constitutes a very powerful tool for the one-pot synthesis of a number of new materials such as new grafted polymers, functional surfaces and bioconjugates.

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Giuseppe Mantovani, Vincent Ladmiral, Lei Tao and
David M. Haddleton*
Department of Chemistry, University of Warwick, Coventry, UK
CV4 7AL. E-mail: D.M.Haddleton@warwick.ac.uk;
Fax: +44 24 7652 8267; Tel: +44 24 7652 3256

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