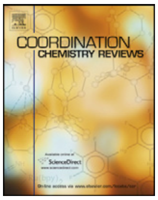
Coordination Chemistry Reviews 256 (2012) 2893–2920

Contents lists available at SciVerse ScienceDirect

Coordination Chemistry Reviews

journal homepage: www.elsevier.com/locate/ccr



Review

PEG as an alternative reaction medium in metal-mediated transformations

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ARTICLE INFO

Article history:
Received 13 February 2012
Received in revised form 22 May 2012
Accepted 23 May 2012
Available online 19 June 2012

ABSTRACT

Poly(ethylene glycol)s (PEGs) are an interesting environment-friendly alternative to classical solvents. Their combination with metals and metallic salts provides powerful reaction systems for a wide variety of transformations. This study presents an overview of the various reactions developed in PEG together with a metallic species. The influence of PEG on the reaction course, the stabilizing effects of the polymer

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http://dx.doi.org/10.1016/j.ccr.2012.05.027

Keywords:
Poly(ethylene glycol)
PEG
Catalysis
Organometallic chemistry
Transition metals
Post-transition metals
Palladium
Copper
Lewis acids
Nanoparticles
Microwaves
Cross-coupling
Heterocycles
Recycling

on the metals and the recycling possibility are reported for the various metallic elements of the periodic table.

1. Introduction

Poly(ethylene glycol)s (PEGs) are omnipresent polymers in everyday lives: because they present low toxicity [1], they are market approved for food [1] and for biomedical applications [2,3], especially in the field of drug discovery [4], due to their hydrophilicity, decreased interaction with the blood and high biocompatibility. They are also used as soluble polymeric supports in organic synthesis [5], and as eco-friendly solvents, are able to substitute volatile or halogenated organic solvents. PEGs are not flammable or corrosive. They are benign and readily commercially available at low cost, being formed from ethylene oxide by simple ring epoxide opening. PEGs are amphiphatic polymers, with a high solubility in water and in many organic solvents including toluene, dichloromethane, alcohol, and acetone. They are insoluble in less polar solvents such as hexane, cyclohexane or diethyl ether [6], and in $scCO_2$ [7].They are able to dissolve common organic solids, metal phosphine complexes [7] and they present some interesting characteristics, including high polarity, high boiling point and expandability with CO_2 [7]. Moreover, PEGs are stable to acidic or basic, oxidative or reductive conditions and at high temperatures (up to 150–250 °C). However, the polyether structure is an easy target for thermal oxidative degradation in the presence of oxygen atmosphere at elevated temperature (over 70 °C), to form PEG peroxides leading to a random chain scission process with the formation of complex mixtures of many oxygenated low-molecular weight PEGs [8].

Special properties arise also from their cation complexation ability being acyclic analogs of crown ethers [9]: the same PEG can coordinate metal cations of different sizes, due to a flexible helical conformation, generating cavities with variable sizes. However, the complexation ability of solid metal alkali salts, for example, depends both on the nature of the cation and of the anion as well as on the PEG molecular weight. From this point of view, PEGs behave as 'crown-like' agents, which the application is of a considerable interest due to their low cost compared to the crown ethers.

They find application in substitution, oxidation, reduction and organometallic reactions [10]. PEGs with low molecular weight (less than 800 Da) are viscous liquid at room temperature. Those having a molecular weight above 900 Da are waxy solids, but they melt at a moderate temperature (45–55 °C) and can therefore be used as a suitable liquid medium. The focused heating generated by the microwave enables to reach a high temperature in a short time, accelerating the preparation of molecules with cleaner and sometimes increased selectivity. Under microwave irradiation the heating characteristics of a solvent or chemical depend on their dielectric properties [11]. Able to absorb electromagnetic energy and to convert it into heat, ethylene glycol is an excellent susceptor for the microwave irradiation because of its permanent dipole and high boiling point [12]. In fact, the ability of a specific material to convert microwave energy into heat at a given frequency and temperature is determined by the so-called loss tangent ($\tan\delta$) [13–15]. Unfortunately, no data are available for the $\tan\delta$ value of PEGs (for ethylene glycol, $\tan\delta = 1.350$) [16], but it can be supposed that a high $\tan\delta$ characterizes PEG-based reaction media, favoring good adsorption of microwave energy, and consequently efficient heating. So far, despite the lack of volatility, PEGs have not been used extensively in organic transformations involving microwave activation [17]. The intrinsic characteristics displayed by PEGs allowed the development of synthetic methods for the generation of metal nanoparticles (NPs) as catalysts in organic synthesis, according to the principles of the polyol method [18–21]. The process was first [18–20] introduced to produce submicron-sized metal powders of uniform shape and narrow size distribution at low temperature under closed-system conditions. The metal species is reduced in solution at a temperature usually below that used either by solid-state methods or under reducing conditions in the presence of hydrogen. The redox [22,23] process involves the simultaneous reduction of the metal precursor, suspended in a liquid polyol (usually ethylene glycol), and oxidation of the polyol solvent. The polyol acts not only as the reaction solvent but also as a reducing agent and stabilizer, limiting particles growth and preventing their agglomeration and sintering, as demonstrated by transmission electron microscopy (TEM) micrographs. However, optimization of the experimental parameters is necessary depending on the metal compound that is used. The main parameters driving the size, the morphology and size distribution of the NPs are mainly the reaction temperature and time, together with the PEGs length chain [24,25]. For this reason, the association of the advantages of microwave irradiation together with the intrinsic characteristic of PEGs (high permanent dipole) is a powerful tool to generate NPs. Moreover, also the mode and order of reagent additions, the use of additives (nucleating and protective agents) and the substrate concentration are important factors to take into accounts in the optimization of reaction conditions.

Last, but not the least, in using PEGs as the reaction solvent for metal-catalyzed organic reactions is the easy recovery of the products and the possibility to recycle the PEG-metal catalytic system. Mainly, two protocols can be used, depending on the physical state of PEGs used in the experiment. In liquid PEGs (with a molecular weight less than 800 Da) hexane, cyclohexane or diethyl ether are added to the crude: the reaction product is usually recovered in the organic phase, while the metal catalyst remains in the PEGs phase and can be reused for further cycles by adding new substrates (Method A) (Fig. 1).

In some cases it could be necessary to add some water during the extraction, in order to reduce the viscosity of the PEGs medium and to allow an easier recovery of the product. In order to avoid the leaching of the metal catalyst in the organic phase, it is also possible to freeze the biphasic system organic solvent/PEGs before proceeding with the separation. In the case of solid PEGs (with a molecular weight above 1000 Da), the reaction product and