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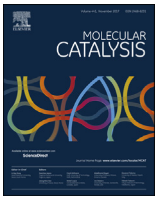

Research Paper

Cycloaddition of CO_2 to challenging *N*-tosyl aziridines using a halogen-free niobium complex: Catalytic activity and mechanistic insights

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ABSTRACT

An efficient and facile approach to the regioselective synthesis of *N*-tosyloxazolidinones from the corresponding *N*-tosylaziridines and CO_2 was developed using dual catalytic systems involving an early transition metal coordination compound as a Lewis acid and a nucleophilic cocatalyst. Among the screened Lewis acids, halogen-free niobium pentaethoxide ($Nb(OEt)_5$) displayed the best catalytic activity when used in the presence of tetrabutylammonium iodide (TBAI). Systematic DFT calculations, supported by catalytic experiments, demonstrate that CO_2 insertion is the rate determining step for this process and it is highly dependent on the steric hindrance at the niobium center.

1. Introduction

Carbon dioxide is an important greenhouse gas and a renewable and ubiquitous C1 source for the synthesis of chemicals [1,2]. The latter approach is regarded as a potential strategy to contribute managing the excess anthropogenic emissions by sequestration of CO_2 into useful chemicals and fuels [3–6]. With the volume of CO_2 currently converted to chemicals representing just a tiny fraction of global emissions [7,8], the development of a diversified and versatile portfolio of products able to provide a long-term storage of CO_2 is highly desirable [9–15]. In this context, the products of cycloaddition of CO_2 to three-membered heterocycles such as cyclic organic carbonates[16–19] and oxazolidinones[20] are being widely investigated. Focusing on the latter family of compounds, *N*-aryl and *N*-alkyl oxazolidinones can be mainly prepared by the cycloaddition of CO_2 to aziridines [21–24], by the cycloaddition of isocyanates to epoxides[25–27] or by the one pot reaction of epoxides, amines and CO_2 [28–31]. The synthesis of *N*-tosyloxazolidinones from CO_2, being a class of compounds that can serve as key intermediates for the preparation of synthons and biologically active compounds [32–36], requires the cycloaddition reaction of CO_2 to *N*-tosylaziridines. Because of the presence of the electron-withdrawing sulfonyl group at the nitrogen atom, this reaction generally requires harsher reaction conditions than the synthesis of the cognate *N*-aryl and *N*-alkyl compounds and very few systematic attempts to develop an efficient catalyst for this reaction have been undertaken.

Beside the application of $Pd_2(dba)_3/PPh_3/TBAT$ (dba: dibenzylideneacetone, TBAT: tetrabutylammonium difluorotriphenylsilicate) under mild conditions for the special case of *N*-tosyl-5-vinylaziridines [37], *in situ*-generated *N*-heterocyclic carbenes (NHCs) were reported to afford 5-aryl-3-tosyloxazolidin-2-ones in good yields at moderate temperatures and CO_2 pressure (80 °C, 20 bar) [38]. However, a high catalytic loading was required (20 mol% diisopropylphenylimidazolium chloride (NHC precursor) and 22 mol% KO*t*Bu). LiBr (20 mol%) is a readily available catalyst for the regioselective synthesis of the 4-aryl-3-tosyloxazolidin-2-ones

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regioisomers in moderate yields, but cannot afford the 5-aryl-3-tosyloxazolidin-2-ones analogues [39].

Coordination compounds of early transition metal halides such as yttrium, niobium and zirconium are readily available inexpensive Lewis acids that do not require the synthesis of sophisticated ligand systems to harness the metal center that could have an impact on the costs, molecular weight and sustainability of the catalyst [16]. These compounds have shown the ability to catalyze the cycloaddition of CO_2 to epoxides under ambient conditions [40,41] even in the case when diluted CO_2 from flue gas was employed as an impure feedstock [42,43]. The mechanistic aspects of the cycloaddition reactions promoted by such catalysts have been investigated revealing intriguing details; a bimetallic cooperative mechanism for the activation of CO_2 between two niobium centers being identified in solution and on silica support [44,45]. Nevertheless, their application to the cycloaddition reactions of CO_2 has been, so far, limited to the synthesis of cyclic carbonates.

Therefore, we explore here the catalytic activity of group III–V transition-metal complexes in combination with nucleophilic co-catalysts, for the cycloaddition of CO_2 to *N*-tosylaziridines. Beside readily available metal halides, early transition metals alkoxides were employed in this study in order to identify greener and less corrosive halogen-free Lewis acids [46]. We show here that $Nb(OEt)_5$ is a readily available and efficient, halogen-free catalyst for the synthesis of 5-aryl-3-tosyloxazolidin-2-ones under mild conditions when used in the presence of co-catalytic amounts of TBAI (Tetrabutylammonium iodide). Furthermore, the mechanism of this reaction is investigated by DFT calculations demonstrating that the process of CO_2 insertion is the rate determining step of the whole reaction and that this step is highly dependent on the steric hindrance at the niobium center.

2. Experimental

General information, details on the computational methods and on the preparation of the aziridine substrates according to published procedures are provided in Appendix A (see Supplementary material).

2.1. Catalysis experiments

For a typical cycloaddition reaction, **1a** (273 mg, 1 mmol), $Nb(OEt)_5$ (21 mL, 0.08 mmol, 8 mol%) and TBAI (24 mg, 0.08 mmol, 8 mol%) were dissolved under a protective atmosphere in diethylether (3 mL) in a 50 mL stainless steel autoclave. CO_2 (30 bar) was added and the reaction vessel was heated to 80 °C. After stirring for 48 h, the reactor was cooled by an ice bath and the residual pressure was carefully vented. After withdrawal of an aliquot of the reaction for ^{1}H NMR analysis of the crude reaction, the reaction solvent was evaporated under reduced pressure and the product was purified by flash column chromatography (hexane/dichloromethane 8:2) yielding **1b** (288 mg, 0.91 mmol, 91%).

3. Results and discussion

3.1. Catalytic investigation

The initial catalysis study was performed at 80 °C under 30 bar CO_2 using 2-phenyl-*N*-tosyl aziridine (**1a**) as a benchmark substrate (Table 1). Diethyl ether (DEE) resulted as the best solvent for this reaction after an initial screening. In general, at the end of the reaction the formed **1b** isomer could be nearly completely isolated by column chromatography. Therefore, the large discrepancy between **1a** conversion and **1b** isolated yield observed In some cases (*i.e.* Table 1, Entries 4, 6, 10–12) is to attribute to the formation of various by-products as observed in the crude ^{1}H NMR of the reaction mixture.

Among the selected early transition metal compounds, $Nb(OEt)_5$ (Table 1, Entry 8) showed complete **1a** conversion and the highest isolated yield of the target product **1b** with high regioselectivity. Niobium-based catalysts showed generally the best regioselectivity for **1b** *versus* its **1c** isomer. $NbCl_5$ (Table 1, Entry 7) afforded exclusively **1b**, albeit in moderate yields. $Nb(OEt)_5$ was selected for further investigation (Table 1, Entries 9–13) taking into account the use of different nucleophilic cocatalysts such as TBAC (tetrabutylammonium chloride), TBAB; (tetrabutylammonium bromide), pyridine bases of different nucleophilicity, DMAP (*N*,*N*-dimethylamino pyridine) and PPY (4-pyrrolidinopyridine) [47], and amidine base DBU (1,8-Diazabicyclo[5.4.0]undec-7-ene). In agreement with previously published mechanistic studies on the cycloaddition of CO_2 to aziridines, the cocatalyst plays a crucial role by serving as a nucleophile for the ring-opening of the niobium-coordinated aziridine substrate and as a leaving group in the final step of cyclization following CO_2 activation (*vide infra* in the DFT section for a more detailed mechanistic picture) [21,48]. Furthermore, the regiochemistry of the initial nucleophilic attack of the cocatalyst on the aziridine determines the regioselectivity of the reaction [21,39].

This screening confirmed quaternary ammonium salts, and in particular TBAI, as the most suitable nucleophilic co-catalysts. Strong nitrogen nucleophiles such as DBU and PPY failed to produce any appreciable amount of product (Table 1, Entries 11, 13). In the case of PPY, the starting material was recovered unreacted. A possible explanation for this observation could be a stable interaction between strong aminopyridine nucleophiles and niobium complexes as suggested by previous studies. [41]. In the case of DBU, we observed complete conversion of the starting material but the target product was not formed. In the ^{1}H NMR spectrum of the reaction mixture a main by-product was observed displaying a downfield shift with respect to the aziridine protons of **1a**, but lower than expected for the formation of the oxazolidinone product. These signals are likely to arise from the formation of the intermediate product of aziridine-ring opening without the insertion of CO_2. The pair $Nb(OEt)_5$/DMAP, being a completely halogen-free system, produced **1b** in moderate yields but with low regioselectivity (Table 1, Entry 12) reflecting the higher tendency of the strong pyridine nucleophile to attack the less sterically hindered carbon atom of the aziridine ring [21]. Consistently, when exploring the effect of the counterion of the quaternary ammonium salt (Table 1, Entries 8–10), only a limited effect on the yield of the reaction was observed, however, the regioselectivity decreased in the order TBAI ⋙ TBAB ⋙ TBAC thus following the inverse trend of nucleophilicity ($Cl^- \ggg Br^- \ggg I^-$) of the halogen anion in the aprotic reaction medium [49]. Whereas the regioselectivity of the nucleophilic ring-opening of phenyl substituted three-membered heterocycles is generally directed to the phenyl-bearing carbon by the electronic effects of the aromatic ring [50], it is likely that the tendency to attack the least sterically hindered carbon increases when more nucleophilic species (TBAB, TBAC and DMAP) are used as cocatalysts leading to the observed decrease of regioselectivity.

Further investigation was dedicated to the study of the influence of the reaction parameters (temperature and pressure) on the catalytic efficiency of $Nb(OEt)_5$/TBAI in the cycloaddition of CO_2 to **1a**. When the reaction temperature was varied under 30 bar CO_2 pressure (Fig. 1a) a low yield of **1b** was observed at 50 °C. Nevertheless, moderate yields of the target product were obtained already at 60 °C whereas for $T \geq 70$ °C high to quantitative yields of **1b** were afforded.

The reaction yield appears to be strongly dependent on CO_2 pressure (Fig. 1b). Indeed, despite the catalyst displaying some