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Amino fluorination : transition-metal-free N–F bond insertion into Diazocarbonyl Compounds

Dr. Ramesh Thakur
M.Sc., Ph.D. (Chemistry), B.R.A. Bihar University, Muzaffarpur, Bihar, India

INTRODUCTION

Diazoacetate derivatives play an important role in the synthetic community. Over the past century, signi cant advances have been made towards the generation of carbenoid intermediates triggered by transition-metals. The resulting reactive species can undergo valuable transformations, such as threemembered ring (cyclopropane, cyclopropene) formation, X–H bond insertion (X ¼ C, N, O, S, etc.) and ylide generation (Scheme 1a–c).1 van Vranken, Barluenga, Wang, and others have developed palladium- or copper-catalysed multiple component reactions of diazo compounds, which allow the installation of two separated functional moieties on the carbenic carbon via a single operation (Scheme 1d).2 Despite these important advances, the direct introduction of two functional groups to the same carbon center, namely gem-difunctionalization of donor/acceptor (D/A) carbenes, is still far from well developed.3,4 It is of note that these processes at least involve one C–C bond formation.5 Thus the studies on the gem-difunctionalization of D/A carbenes, which involves two distinct carbon heteroatom bond formations, would greatly enhance the synthetic applications of diazo compounds. Single substitution of hydrogen with uorine may alter the chemical and physical properties of a potential drug candidate by blocking undesired metabolism at a speci c site.6 In contrast to the relatively large number of reports on the catalytic insertion of N–H bonds to a-diazocarbonyl compounds,7 a simple yet appealing concept for the transition-metal catalysed N–F bond insertion has not been realized thus far. N-Fluorobenzenesulfonimide (NFSI) is inexpensive and shelf stable, and is o en employed as a mild electrophilic uorinating or aminating reagent.8,9 Recently, Liu10 and Zhang11 demonstrated that NFSI could serve as both an amino and 'uorine source for the transition-metal-catalysed amino uorination of alkenes (Scheme 2a). Inspired by these seminal works, we envisioned that NFSI might be an ideal candidate for the transition-metal catalysed N–F bond insertion into D/A carbenes (Scheme 2b). Although procedures for the amination7,12 or uorination13,14 of diazo compounds are known, to our knowledge, direct amino- uorination of diazo compounds remains unexplored. Herein, we present our primary results on gem-amino uorination of diazocarbonyl compounds under mild conditions. Kinetic studies and DFT calculations shed light on the mechanism of the current N–F bond insertion. Results and discussion Optimization studies and substrate scope We initiated our studies using the reaction of ethyl diazophenyl acetate 1a (ref. 15) with NFSI using CuBr as a precatalyst and bathocuproine (2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline; BC) as a ligand.11 Gratifyingly, in the presence of 5 mol% CuBr and 6 mol% BC, ethyl diazophenyl acetate 1a was completely consumed a er stirring in a reaction medium of 1,2- dichloroethane (DCE) at 60 C for 21 h, and the desired product 2a was obtained in a 79% NMR yield (Table 1, entry 1). To our surprise, the reaction proceeded equally well in the absence of both CuBr and BC, giving 2a in 89% yield (Table 1, entry 2). The reaction could complete in a comparably short time when the reaction was carried out at an elevated temperature (Table 1, entries 2–4 vs.

entry 5). A brief examination of the solvent effects revealed that DCE was still the best choice (Table 1, entries 6– 14). Notably, the reaction can also be performed in water, giving 2a in a moderate yield, which indicates an environmentallycompound contained a chiral auxiliary, an ester derived from (+)-menthol, a pair of diastereoisomers 2e were obtained in a ratio of 1 : 1. Interestingly, diazo compounds derived from cyclic esters and amides were proven to be viable substrates. N–F bond insertion of 1f and 1g gave the corresponding products 2f and 2g in 97% and 83% yields, respectively. The structure of 2f was conﬁrmed by X-ray crystallographic analysis.16 The effects of substituents on the phenyl ring were also examined. Both electron-withdrawing and electron-donating groups on the aromatic ring of 1 were tolerated under the reaction conditions. The reaction of diazo acetates bearing mild electron-withdrawing or electron-donating groups (ﬂuoro, chloro, bromo and methyl) at the para position of the phenyl ring gave the corresponding products in excellent yields (Table 2, 2h, 2i, 2m and 2o). Incorporation of one chloro group to the meta position had no obvious impact on the yields of the products (Table 2, 2i and 2k). Interestingly, the yield of 2l bearing two meta chloro substituents was decreased to 52%. While the diazo acetate bearing an ortho substituted group was not compatible to the current conditions (Table 2 and 2p), probably due to the steric hindrance effect. Similarly, strong electron-donating or -withdrawing substituents on the aromatic ring were amenable for the current aminoﬂuorination, albeit giving moderate yields (Table 2, 2n, 2r–t). Of note, vinyl and alkyl moieties remained intact (Table 2, 2v and 2w), indicating that the involvement of a free carbene intermediate is less likely (vide infra). Notably, the reaction could be scaled up to gram scale without sacriﬁcing the yield of 2a (5 mmol scale, 2.39 g 2a was obtained with a 97% yield). It is worthwhile to mention that the current conditions are not applicable to alkyl or heteroaryl acetate derived diazo compounds.17 Mechanistic studies Having uncovered an efficient method for N–F bond insertion, we sought to gain more insight into the reaction mechanism. Thus a series of additional experiments were subsequently carried out. Performing the reaction under irradiation by UV light, 2a was obtained in a much lower yield (Scheme 3a). Furthermore, evolution of N2 was signiﬁcantly slow in the absence of NFSI under otherwise identical conditions (Fig. S1†). These experiments also suggest that a pathway via a free carbene intermediate is unfavourable. Addition of the radicalscavenger 2,6-di-tert-butyl-4-methylphenol (BHT) had no obvious inﬂuence on the reaction efficiency (Scheme 3b), which indicates that a mechanism that involves free radical species is also less likely. Additionally, considering the diazo carbon atom is mildly nucleophilic and might be trapped by the electrophilic ﬂuorine atom, a subsequent displacement of dinitrogen by the imide moiety of NFSI would give 2a. With this consideration in mind, the following control experiment was carried out immediately. The combination of selectﬂuor, a reactive electrophilic ﬂuorinating reagent, with tetrapropyl ammonium benzenesulfonimide did afford 2a in 8% yield (Scheme 3c). Kinetic studies for the reaction of 1a with NFSI were further performed to get a deeper understanding of the reaction mechanism The activation parameters DH‡ ¼ 17.1 kcal mol1 and DS‡ ¼ 13.0 cal mol1 K1 were obtained from Eyring plots by varying the temperature from 313 to 353 K (Fig. 1A, top). The negative DS‡ value may suggest the generation of a bimolecular transition state involving NFSI and 1a. Similar kinetic behaviours were observed for the reactions of various para-substituted diazo phenyl acetates 1 with NFSI. A fairly linear Hammett correlation between log(kX/kH) and s+ was obtained with a reaction constant of r ¼ 0.81 (Fig. 1B, bottom). The small negative r value suggests that the transition

CONCLUSION

In conclusion, we have developed an unprecedented N–F bond insertion into diazocarbonyl compounds. The current method represents a facile approach to construct C–N and C–F bonds on the same carbon without any transition-metal as a catalyst or promoter. Mechanistic studies, including kinetic experiments and DFT calculations, revealed that a reaction sequence of electrophilic activation of 1 by NFSI, followed by an SN1 like displacement of dinitrogen by benzenesulfonimide is preferred. Further study on the asymmetric variant as well as the difunctionalization of the metal carbene is ongoing in our laboratory.

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