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IBX-mediated oxidation of unactivated cyclic amines: application in highly diastereoselective oxidative Ugi-type and aza-Friedel–Crafts reactions†

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The first *o*-iodoxybenzoic acid (IBX) mediated oxidation of unactivated amines to imines is described. A range of *meso*-pyrrolidines were shown to be suitable substrates. The chemical space was further explored with one-pot oxidative Ugi-type and aza-Friedel–Crafts reactions, which proved to be highly diastereoselective.

The chemistry of hypervalent iodine reagents (Fig. 1) has received major interest in recent years as a result of the increasing number of new reagents and their application in diverse chemical transformations.¹ In particular, *o*-iodoxybenzoic acid $(IBX)^2$ has experienced increasing attention owing to its broad applicability and high chemoselectivity. Santagostino *et al.* developed a convenient and cost-efficient synthesis of high purity IBX by the treatment of 2-iodobenzoic acid with oxone in aqueous medium,³ which renders IBX an easily accessible reagent. Chemical transformations mediated by IBX



Fig. 1 A selection of commonly used and commercially available hypervalent iodine reagents and their acronyms.

Department of Chemistry & Pharmaceutical Sciences and Amsterdam Institute for Molecules Medicines and Systems (AIMMS), VU University Amsterdam, De Boelelaan 1083, 1081 HVAmsterdam, The Netherlands. E-mail: r.v.a.orru@vu.nl include the selective oxidation of primary and secondary alcohols to the corresponding aldehydes and ketones as well as dehydrogenation of aldehydes and ketones to α , β -unsaturated carbonyl compounds. Nicolaou *et al.* described the oxidation of benzylic amines as well as amines that aromatize upon oxidation,^{4,5} however, the oxidation of unactivated aliphatic amines with IBX was not investigated.⁶

The direct α -functionalization of amines is a highly interesting transformation that attracted great attention in recent years.⁷ Consequently, transition metal-catalyzed oxidative versions of important C–C bond-forming reactions such as Mannich, Strecker, aza-Henry and aza-Friedel–Crafts reactions have been developed.⁸ A limited number of examples of the application of IBX in oxidative multicomponent reactions has been described, *i.e.* oxidative Strecker,⁹ Passerini,¹⁰ Ugi and Ugi-type¹¹ reactions. Although unactivated alcohols were suitable substrates, the scope of the amine component is basically unexplored with the exception of a small selection of α -activated amines, such as benzylic amines, α -amino nitriles and α -amino esters.

Herein, we report a mild and selective oxidation of unactivated cyclic amines with IBX to access the corresponding imines. The oxidation can be combined in one pot with the addition of *C*-nucleophiles, providing oxidative Ugi-type and aza-Friedel–Crafts reactions.

In light of our continued interest in the functionalization of imines, in particular 1-pyrrolines,¹² we envisioned a clean and fast oxidation of unactivated *meso*-pyrrolidines. Examination of the currently available methods revealed that the oxidation of unactivated secondary amines is rather challenging.¹³ Given the recent regained interest in hypervalent iodine reagents, we decided to explore their ability to oxidize aliphatic amines. We started our investigation with the oxidation of *meso*-pyrrolidine **1a** with different commercially available hypervalent iodine reagents at room temperature in the typically used solvent DMSO (Table 1, entries 1–4).⁴ The desired 1-pyrroline (**2a**) was obtained in high yield (Table 1, entry 4) with only one equivalent of IBX, while oxidants such as (diacetoxy)iodobenzene (PIDA), [bis(trifluoroacetoxy)]iodobenzene (PIFA) and Dess-Martin



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[†]Electronic supplementary information (ESI) available: Optimization data, experimental procedures, compound characterization data, copies of ¹H and ¹³C spectra, and X-ray crystallographic data of compound **3i**. CCDC 1400648. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/ c5ob01519g

 Table 1
 Optimization of reaction conditions for the oxidation of mesopyrrolidine 1a^a



 a Conditions: amine (0.25 mmol), oxidant (1 eq.), solvent (0.2 M). b Yield determined by adding 2,5-dimethylfuran (0.5 eq.) after the reaction workup as standard for NMR spectroscopy. c Closed vessel.

periodinane (DMP) gave poor to moderate yields (Table 1, entries 1–3). A solvent screen revealed that the oxidation proceeds well in a range of protic as well as aprotic solvents in which IBX is virtually insoluble (see ESI†), although an increased temperature and reaction time were required (60 °C, 1 h). Superior results were obtained using CH_2Cl_2 (Table 1, entry 5),¹⁴ which prompted us to select this solvent for a screening of the substrate scope.

To our delight, a range of aliphatic *meso*-pyrrolidines was selectively oxidized by IBX towards the corresponding 1-pyrrolines in good to excellent yield (Table 2, 70–97%). Hemiaminal **2f** is a highly interesting building block for the synthesis of aza-sugars, but was obtained in moderate yield presumably as a result of instability due to its increased electrophilicity.¹⁵ Under the same conditions, reactions of monocyclic pyrrolidines gave mixtures of the corresponding pyrrolines and pyrroles.¹⁶ We hypothesize that this overoxidation is caused by tautomerization of the initially formed imines to the corresponding enamines, which subsequently undergo a second oxidation leading to pyrroles. In case of bi- and tricyclic 1-pyrrolines **2a–f**, tautomerization is prevented and over-oxidation does not occur.

Imines are interesting inputs for a wide variety of complexity-generating reactions as a result of their electrophilic as well as nucleophilic properties. For example, imines serve as templates for many multicomponent reactions (MCRs), a category of reactions that create a high degree of diversity and complexity in a single step.¹⁷ One of the most studied and widely applied MCRs is the Ugi reaction, which has proven to be a powerful tool for rapid synthesis of lead compounds in drug discovery.¹⁸ Consequently, we envisioned a diastereoselective oxidative Ugi-type three-component reaction for the synthesis of *N*-acylprolyl amide derivatives.¹⁹

For a screening of the reaction conditions, the reaction between *meso*-pyrrolidine **1a**, benzoic acid and *tert*-butyl isocyanide was investigated (Table 3). In agreement with earlier



Table 2 Scope study for oxidation of meso-pyrrolidines 1 with IBX^a



^{*a*} Conditions: amine (0.25 mmol), IBX (1 eq.), DCM (0.2 M), 60 °C, 1 h, closed vessel. Isolated yield, unless stated otherwise. ^{*b*} Yield determined by adding 2,5-dimethylfuran (0.5 eq.) after the reaction workup as standard for NMR spectroscopy and proposed structure (2f) was not fully characterized (see ESI). MeCN as solvent.

 Table 3
 Optimization of reaction conditions for the oxidative Ugi-type three-component reaction^a



^{*a*} Conditions: amine (0.25 mmol), benzoic acid (1.5 eq.), *tert*-butyl isocyanide (1.5 eq.), IBX (1 eq.), solvent (0.5 M), 60 °C, 24 h, closed vessel. ^{*b*} Yield determined by adding 2,5-dimethylfuran (0.5 eq.) after the reaction workup as standard for NMR spectroscopy.

reports,^{10,11} a high concentration of reagents proved to be beneficial for the reaction outcome (see ESI†). The solvent of choice for most Ugi reactions, MeOH, was used as reaction medium with modest efficiency (Table 3, entry 1). Competing oxidation of the solvent could pose a problem, although previous reports suggest that the oxidation of amines is generally much faster than alcohols.^{4a,b,11b} Considering the complexity of the reaction, satisfactory results were obtained using either MeCN or CH_2Cl_2 as the solvent (Table 3, entries 2 and 3). As a consequence of the superior results obtained for the oxidation of a variety of *meso*-pyrrolidines in CH_2Cl_2 , this solvent was selected for investigation of the reaction scope. The one-pot reaction could be performed with a range of *meso*-pyrrolidines, affording the corresponding dipeptides in modest to good yields (Table 4, 41–61%). A range of electronically diverse carboxylic acids were suitable reaction partners, although it should be noted that lower yields were observed for aliphatic acids such as acetic acid (**3e**, 43%). Various aliphatic and aromatic isocyanides were compatible with the oxidative Ugi-type reaction as well. Although hemiaminal **2f** was found to be unstable upon isolation, Ugi adduct **3h** could be obtained in 45% yield as a single diastereoisomer. Notably, 3,3-dimethyl-indoline – with blocked benzylic positions to prevent benzylic oxidation²⁰ – could also be applied with modest efficiency (**3j**, 35%).²¹



For the majority of examples, a single diastereoisomer of the dipeptide was isolated (**3a-h**). However, *exo*-configured dipeptide **3i** was obtained as a mixture of diastereoisomers (Fig. 2).²² The increased diastereoselectivity with *endo*-configured



Fig. 2 (a) Steric rationalization for superior diastereoselectivity for the Ugi-type reaction of *endo*-configured **2a** compared to *exo-***2c**. (b) Plot of the molecular structure of major diastereoisomer **3i** with displacement ellipsoids drawn at 50% probability.[†]

 Table 5
 Oxidative aza-Friedel-Crafts reaction^a



^{*a*} Conditions: amine (0.50 mmol), carboxylic acid (1.5 eq.), isocyanide (1.5 eq.), IBX (1 eq.), DCM (0.5 M), 60 °C, 48 h, closed vessel. Isolated yield. Only one diastereoisomer observed, unless stated otherwise. ^{*b*} Ratio determined by NMR analysis of the crude mixture.²²

^{*a*} Conditions: 1. amine (0.25 mmol), IBX (1 eq.), DCM (0.2 M), 60 °C, 1 h; 2. nucleophile (2.0 eq.), TFA (2.0 eq.), 60 °C, 1 h, closed vessel. Isolated yield. Only a single diastereoisomer was observed, unless stated otherwise. ^{*b*} Diastereoisomers were inseparable; ratio determined by NMR analysis of the crude mixture.

imines^{11*a*} such as 2**a** is explained by steric congestion on the concave face of the molecule, facilitating selective attack of the nucleophile from the other side (Fig. 2a). For *exo*-configured 2**c**, the steric effect is expected to be less pronounced.

In order to expand the molecular diversity available by reactions of *in situ*-generated bicyclic pyrrolines, we decided to explore the aza-Friedel–Crafts reaction.²³ Our one-pot methodology showed to be effective in an oxidative aza-Friedel–Crafts reaction with pyrrole and indoles as a two-step procedure, giving 2-substituted pyrrolidines in modest to good yield (Table 5, 48–75%) and high to excellent diastereoselectivity. The yield of pyrrolidine **4c** even exceeded the yield of its hemiaminal intermediate **2f**, supporting our hypothesized instability of the latter species. Unfortunately, 6-nitro- and 3-methylsubstituted indoles were not suitable reaction partners, presumably as a result of their reduced nucleophilicity.

In conclusion, we have developed the first IBX-mediated oxidation of unactivated aliphatic amines to give 1-pyrrolines. Moreover, an efficient one-pot protocol for diastereoselective α -functionalization of *meso*-pyrrolidines in oxidative Ugi-type and aza-Friedel–Crafts reactions is presented.

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