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Ugi Four-Component Reaction of Alcohols: Stoichiometric and Catalytic Oxidation/MCR Sequences

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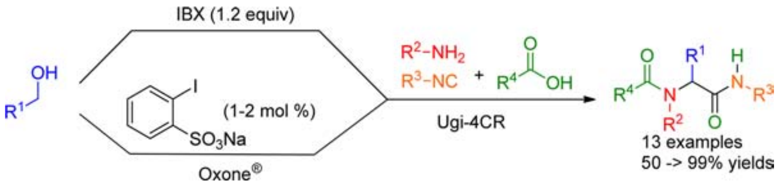
ABSTRACT



A new, simple, and efficient procedure for the one-pot Ugi four-component reaction of alcohols instead of aldehydes is described. Using a stoichiometric amount of IBX or only 1−2% of sodium 2-iodobenzenesulfonate in the presence of Oxone, a wide range of primary alcohols were oxidized to the aldehyde that were directly engaged in the Ugi four-component reaction to afford α-acetamidoamides in good to excellent yields.

The Ugi four-component reaction (Ugi-4CR)[1] is without a doubt one of the most investigated multicomponent reactions (MCR).[2] This reaction allows for a one-step synthesis of highly functionalized α-acetamidoamide **1**, a structure found in many biologically active compounds, from an aldehyde, an amine, a carboxylic acid, and an isocyanide.[3] Its application in pharmaceutical industry and in academic research underwent a dramatic increase over the past 20 years.[3,4] Furthermore, because of the increasing need for always more economic and environmentally friendly syntheses, the development of tandem oxidative processes[5] combining alcohol oxidation with multicomponent reactions is actually of great interest.[2,6,7] Indeed, most

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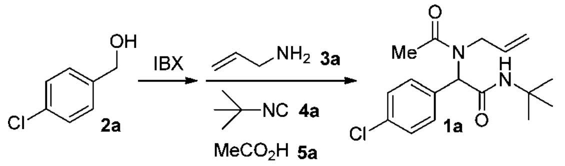
of the classic multicomponent reactions are based on the reactivity of aldehydes which are known to be unstable or difficult to handle. Moreover, when they are not commercially available, aldehydes are traditionally synthesized from the corresponding alcohols. Hence, the direct use of alcohols instead of aldehydes significantly increases the versatility and efficiency of these reactions.

Table 1. Optimization of the IBX-Mediated Alcohol Oxidation/Ugi-4CR Sequence[a]



entry	solvent	*C* (mol/L)	time (h)	yield[c] (%)
1	MeCN	0.3	64	50
2	MeCN	0.5	64	57
3[b]	MeCN	0.5	64	64
4[b]	MeCN/THF (1:1)	0.5	64	61
5[b]	MeCN/MeOH (1:1)	0.5	40	78

[a] General conditions: alcohol **2a** (1.0 equiv), IBX (1.2 equiv), MeCN at reflux for 3 h, then addition of **3a**, **4a**, and **5a** (molar ratio: **3a/4a/5a** = 1.2/1.5/1.5) at rt. [b] Imine preformed for 1 h. [c] Yields refer to chromatographically pure products.

However, to the best of our knowledge, the Ugi-4CR from alcohols under oxidative conditions has never been studied.[8] This reaction, which presents many potentially oxidizable intermediates and reactants, such as amine **3** or isocyanide **4**, presents a synthetic challenge and so we decided to investigate this reaction. We report herein the first IBX-mediated tandem oxidative Ugi four-component reaction of alcohols.[9] Furthermore, we also document that the same oxidative MCR proceeds efficiently using a catalytic amount of sodium 2-iodobenzenesulfonate and a stoichiometric amount of Oxone as a co-oxidant.

Knowing the compatibility of *o*-iodoxybenzoic acid (IBX)[10] with multicomponent reactions,[4b,7f,8a,11] the oxidation of *p*-chlorobenzyl alcohol **2a** in the presence of IBX followed by Ugi-4CR of the in situ generated 4-chlorobenzaldehyde with allylamine **3a**, *tert*-butyl isocyanide **4a**, and acetic acid **5a** (Table 1) was examined. On the basis of the work of More and Finney on the IBX-promoted oxidation of alcohols to their corresponding aldehydes, we initially chose acetonitrile as solvent.[12] Conducting the oxidation in refluxing MeCN, followed by the Ugi-4CR at room temperature over 64 h, the desired α-acetamidoamide **1a** was obtained in 50% yield (entry 1). Although modifications of the reaction conditions were limited by the necessity to be compatible with both the oxidation step and the Ugi multicomponent reaction, slight variations of the parameters were studied. First, the concentration proved to be a key factor to the success of the reaction. Although the Ugi reaction required high concentrations (0.5−2 M),[13] the oxidation step required more dilute conditions in order to keep the reaction mixture homogeneous. This is due to the poor solubility of the oxidant and its reduced form 2-iodosobenzoic acid (IBA). A concentration of 0.5 M furnished the best result (entry 2). Then, in accordance with previous observations on the Ugi reaction,[7] the preformation of the imine allowed us to significantly increase the yield (entry 3). Finally, the addition of methanol after the oxidation step permitted not only an increased yield of 80% but also a decrease of the reaction time from 64 to 40 h (entry 5).

With the optimum conditions in hand, the scope of the reaction was next examined using different alcohols, amines, carboxylic acids and isocyanides. The results are listed in Table 2. First, benzyl alcohols carrying either electron-donating or electron-withdrawing substituents have been successfully engaged in this sequence and afforded the Ugi-4CR adducts in good to excellent yields (**1a**−**e**). We then extended the procedure to various primary non activated alcohols. Although these substrates present a low reactivity under certain oxidative conditions[7a,d] or lead to side reactions such as overoxidation, aldol or Tishchenko reaction, a wide range of α-acetamidoamides was isolated in moderate to excellent yields from aliphatic alcohols (entries 5−11). It is noteworthy that unlike benzyl alcohols, the reaction is best to be performed in pure acetonitrile (entry 5). Another important feature of this procedure is the functional group compatibility. Indeed, in addition to the amine, isocyanide, and carboxylic acid functions implied in the reaction, other functional groups such as ethers (**2b**,**c**), halides (**2e**), ester (entry 9), alkene (**2f**), and hemiacetal (**2l**) functionalities were all tolerated. Finally, the enantiopure alcohol **2l** whose corresponding Garner aldehyde is known to be sensitive and difficult to handle was successfully engaged in this sequence (entry 11). Chiral HPLC analysis indicated that only a negligible amount of racemization occurred during the reaction, leading to two separable diastereomers in 82% yield (dr = 2:1) with 95% ee.

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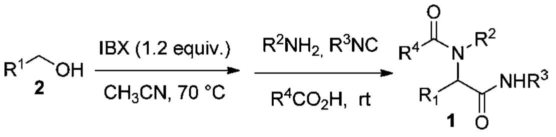
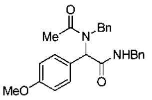
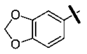
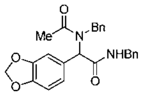
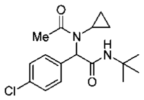
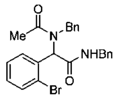
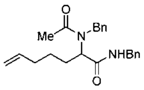
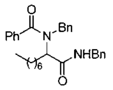
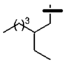
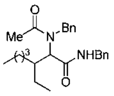
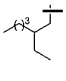
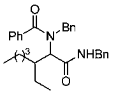
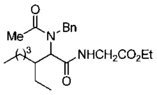
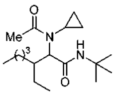
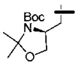
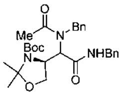
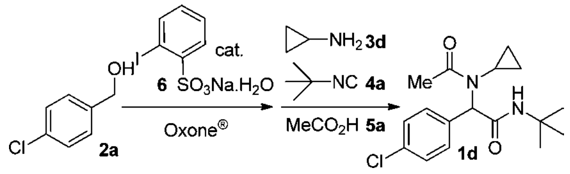
Table 2. Scope and Limitations of IBX-Mediated Ugi-4CR of Alcohols



entry	R^1	product	1	yield (%)/ dr^b
1^a	*p*MeOC$_6$H$_4$ (**2b**)		**1b**	97
2^a	 (**2c**)		**1c**	99
2^a	*p*ClC$_6$H$_4$ (**2d**)		**1d**	69
4^a	*o*BrC$_6$H$_4$ (**2e**)		**1e**	95
5	CH$_2$=CHC$_4$H$_{11}$ (**2f**)		**1f**	43^a/76^{c,d}
6^b	C$_8$H$_{17}$ (**2g**)		**1g**	50^c
7^b	 (**2h**)		**1h**	93^c (1:1)^e
8^b	 (**2h**)		**1i**	89^c (1:1)^e
9^b	 (**2h**)		**1j**	93^c (1:1)^e
10^b	 (**2h**)		**1k**	91^c (1:1)^e
11^b	 (**2l**)		**1l**	82^c (2:1)^{e,f}

^{a} Reaction conditions: alcohol **2** (1.0 equiv), IBX (1.2 quiv), MeCN at reflux for 2–4 h, then addition of molar ratio 3/**4**/5 = 1.2/1.5/1.5 and methanol at rt. ^{b} Yields referred to chromatographycally pure product. ^{c} Reaction in MeCN. ^{d} The imine was preformed for 2 h. ^{e} Determined based on the ^{1}H NMR spectrum of the crude material. ^{f} 5–6% of partial epimerization was measured by chiral HPLC analysis.

Table 3. Optimization of the Catalytic Alcohol Oxidation/ Ugi-4CR Sequence^a



entry	solvent	**3d** (equiv)	yield^b (%)
1	MeCN	1.2	17
2	MeCN/MeOH (1/1)	1.2.	12
3	MeCN/MeOH (4/1)	1.2	37
4^b	MeCN/MeOH (4/1)	2.5.	65

^{a} General conditions: alcohol **2a** (1.0 equiv), **6** (0.01 equiv), and Oxone (0.6 equiv) in MeCN at reflux for 3 h, then addition of **3d** and MeOH at rt. After 2 h, **4a** (1.5 equiv) and **5a** (1.5 equiv) were added. ^{b} Yields refer to chromatographically pure products.

Confident of the efficiency of this Ugi-4CR from alcohols using IBX as oxidant, we next explored the possibility of using a catalytic amount of hypervalent iodine. Vinod[14] and Giannis[15] have reported the oxidation of alcohols using a catalytic amount of IBX in combination with a stoichiometric amount of Oxone (2KHSO$_5$–KHSO$_4$–K$_2$SO$_4$). More recently, Ishihara established that the 2-iodoxybenzenesulfonic acid (IBS) is a stronger oxidant than IBX under nonaqueous conditions.[16] Although IBS is not stable enough to be isolated, it can be in situ generated from sodium 2-iodobenzenesulfonate (**6**) and Oxone allowing the selective oxidation of primary alcohols to aldehydes. Furthermore, we expected that the controlled addition of Oxone, a nontoxic, environmentally safe, inexpensive, stable and easy to handle co-oxidant,[17] will avoid side reactions such as an overoxidation of the aldehyde or oxidation of other reactants or intermediates of the Ugi-4CR. Hence, we investigated the Ugi-4CR from alcohols using 1–2% of sodium 2-iodobenzenesulfonate in the presence of Oxone. Using our previously optimized conditions, the Ugi-4CR product was obtained with 12% yield. A brief optimization study was performed and the results are summarized in table 3. The best conditions consisted of using an excess of amine (2.5 equiv) in a mixed solvent (acetonitrile/methanol = 4:1) in the presence of **6** (0.01 equiv) and Oxone (0.6 equiv). Under these conditions, the α-acetamido amide **1d** was isolated in a 65% yield.

With these conditions in hand, the protocol was applied to the synthesis of various α-acetamido amides **1**. Examples for this catalytic one-pot process are given in Scheme 1. First, the substituent effect on the aromatic ring of various benzyl alcohols was studied. We observed that benzyl alcohols bearing moderate electron-donating or electron-withdrawing substituents successfully afforded the corresponding Ugi-4CR products. However, with *p*-methoxybenzyl alcohol, the desired Ugi-adduct **1b** was isolated in

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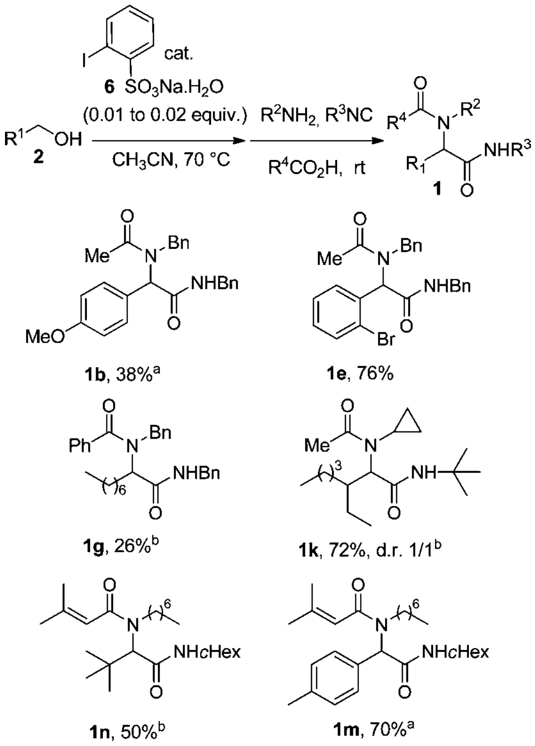
Scheme 1. Ugi-4CR of Alcohols under Catalytic Oxidative Conditions: Scope[a]



[a] Reaction conditions: alcohol **2** (1.0 equiv) and **6** (0.01 equiv) in MeCN at reflux for 2–4 h, then addition of molar ratio **3**/**4**/**5** = 2.5/1.5/1.5 and methanol at rt. [b] Reaction conditions: alcohol **2** (1.0 equiv), **6** (0.02 equiv), and anhydrous Na_2SO_4 in MeCN at reflux for 2–4 h, then addition of molar ratio **3**/**4**/**5** = 2.5/1.5/1.5 at rt.

only 38% yield. Nevertheless, we were pleased to observe that this method was also applicable to aliphatic alcohols. The catalytic oxidation of these nonactivated alcohols to aldehydes is known to be highly sensitive as it generally leads to the corresponding carboxylic acid or ester.[14] However, Ishihara showed that, using 2% of sodium 2-iodobenzenesulfonate **6** in nitromethane, a slow addition of the aliphatic alcohols to the oxidant could lead to the desired aldehyde.[16] In our case, we found that acetonitrile was the best solvent and α-acetamido-amides **1** were obtained in moderate to good yields when starting with β-substituted aliphatic alcohols (**1k**,**n**). Linear alcohols such as octanol also afforded the desired compound **1g** but with a low yield.

In summary, we have developed a highly efficient IBX-mediated Ugi-four component reaction of primary alcohols. The first example of an efficient MCR reaction of alcohols was documented in the presence of a catalytic amount of sodium 2-iodobenzenesulfonate using Oxone as the terminal oxidant. We believed that this eco-friendly tandem oxidative process could be extended to other MCRs.

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Supporting Information Available. Experimental details, characterization data, HPLC enantiomer analysis, and ^{1}H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.