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Hofmann Rearrangement of Carboxamides Mediated by Hypervalent Iodine Species Generated in Situ from Iodobenzene and Oxone: Reaction Scope and Limitations

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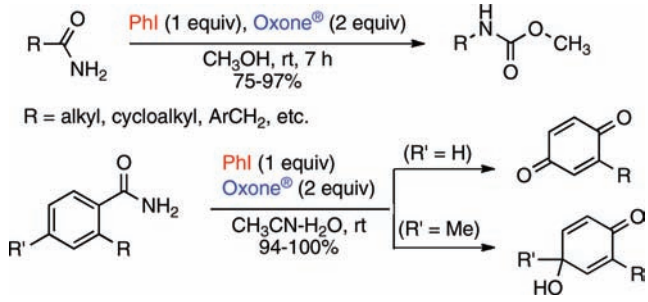
ABSTRACT



Alkylcarboxamides can be converted to the respective amines by Hofmann rearrangement using hypervalent iodine species generated in situ from PhI and Oxone in aqueous acetonitrile. On the basis of this reaction, a convenient experimental procedure for the preparation of alkylcarbamates using Oxone as the oxidant in the presence of iodobenzene in methanol has been developed. An efficient method for direct conversion of substituted benzamides to the respective quinone derivatives by treatment with Oxone and iodobenzene in aqueous acetonitrile has also been found.

In recent years, hypervalent iodine reagents have emerged as reagents of choice for various synthetically useful oxidative transformations.[1] The application of organoiodine(III) compounds as oxidants in Hofmann-type rearrangements[2−5] is especially important, and the Hofmann rearrangement using (diacetoxyido)benzene has even been realized in an industrial setting for the preparation of optically pure N_α-*n*-Boc-L-α,β-diaminopropionic acid[2a] in 100 kg quantities. Most common reagents for Hofmann-type rearrangements include (diacetoxyido)benzene,[2] [bis(trifluoroacetoxy)iodo]benzene,[3] and [hydroxy(tosyloxy)]iodobenzene[4] and their recyclable analogues.[5] Despite the recent surge of research activity toward hypervalent iodine-catalyzed reactions,[1k,l,o−r] the catalytic version of Hofmann rearrangement remains unknown. The goal of our present study is to explore the possibility of Hofmann rearrangement induced by hypervalent iodine species generated in situ from iodobenzene and an inexpensive commercial oxidant Oxone ($2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$).

We have recently found that active iodine(III) species [i.e., (hydroxy(phenyl)iodonium ion, **1**] can be efficiently generated in solution by simple treatment of iodobenzene with Oxone in aqueous acetonitrile at room temperature (Scheme

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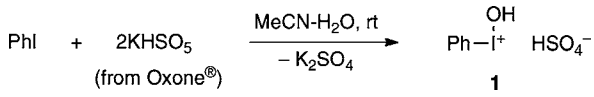
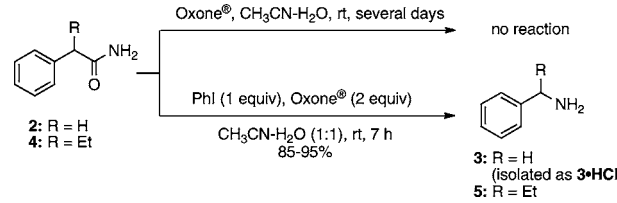
Scheme 1. Generation of Active Iodine(III) Species **1** from Iodobenzene and Oxone



1).[1s,6a] Further study of this reaction (Scheme 1) has led us to the development of a convenient experimental procedure for the preparation of [bis(trifluoroacetoxy)iodo]perfluoroalkanes and [bis(trifluoroacetoxy)iodo]arenes by oxidation of organic iodides using Oxone and trifluoroacetic acid.[6b] Moreover, based on this process (Scheme 1), we were able to develop a metalloporphyrin/iodine(III)-cocatalyzed oxygenation of aromatic hydrocarbons by Oxone in the presence of 5−20 mol % of iodobenzene and 5 mol % of a water-soluble iron(III)−porphyrin complex.[6c]

We have investigated the possibility of Hofmann rearrangement under different reaction conditions using 2-phenylacetamide **2** as a model substrate and Oxone as the oxidant. First, we found that no reaction occurred between amide **2** and Oxone in the absence of iodobenzene even after several days. Addition of iodobenzene to the reaction mixture resulted in the formation of benzylamine **3**, which was isolated as hydrochloride salt **3•HCl** after treatment with HCl using the purification procedure previously described by Loudon.[3a] The mixture of CH_3CN-H_2O (1:1, v/v) was found to be the best solvent system for this reaction. The optimized reaction affording benzylamine hydrochloride **3•HCl** in 95% yield required at least 1 equiv of iodobenzene and 2 equiv of Oxone (Scheme 2). The use of smaller amounts of

Scheme 2. Formation of Benzylamines by Hofmann Rearrangement of Carboxamides using Oxone



iodobenzene led to an incomplete conversion, and unfortunately, we were not able to realize the catalytic variant of this reaction. Under similar conditions, the reaction of 2-phenylbutyramide **4** afforded 1-phenylpropylamine **5** in 85% isolated yield (Scheme 2).

GC−MS studies have shown that various alkyl- and benzylamines can be obtained from the corresponding carboxamides (e.g., amides **6a**−**k** shown in Table 1**)** using this procedure. This procedure (Scheme 2), however, has only limited practical value because of the laborious protocol for isolation of amines or their hydrochloride salts from the reaction mixture. Therefore, we decided to apply our protocol to the preparation of carbamates, which are stable solids or nonvolatile liquids that can be easily isolated from the reaction mixture by extraction with ethyl acetate. In order to obtain methyl carbamates **7** as isolable products under our optimized reaction conditions, we investigated Hofmann rearrangement of carboxamides **6** in methanol; the results are summarized in Table 1.

In general, this procedure (Table 1) is a convenient method for the preparation of methyl carbamates in good yields. The

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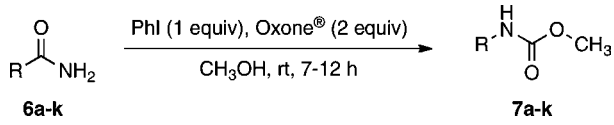
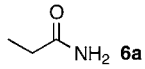
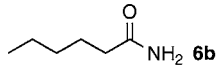
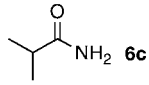
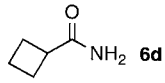
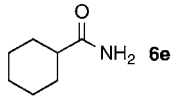
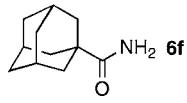
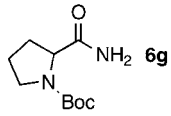
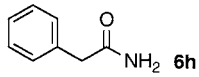
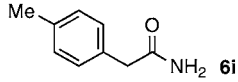
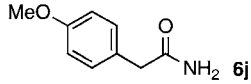
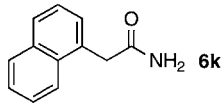
Table 1. Preparation of Carbamates **7** by Hofmann Rearrangement of Carboxamides **6** Using Oxone and Iodobenzene in Methanol[a]



6a-k **7a-k**

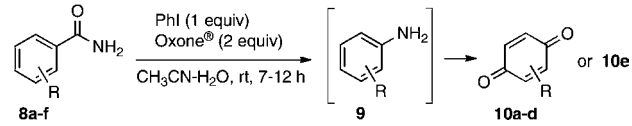
entry	amide **6**	product **7**[b,c]	yield [%][d]
1		**7a**	100[e]
2		**7b**	100[e]
3		**7c**	95
4		**7d**	92
5		**7e**	89
6		**7f**	90
7		**7g**	75
8		**7h**	97
9		**7i**	93
10		**7j**	95
11		**7k**	93

[a] All reactions of amides **6a**−**k** (1 mmol) were performed at room temperature in the presence of PhI (1 equiv) and Oxone (2 equiv) in CH_3OH (5 mL). [b] All previously reported products **6** were identified by comparison of their NMR spectra, GC−MS, and melting points with literature data. [c] Solid products were recrystallized from $CHCl_3$−hexane. [d] Isolated yields of analytically pure products, unless noted otherwise. [e] Yield was determined by GC analysis.

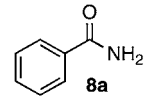
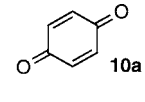
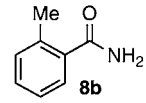
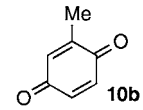
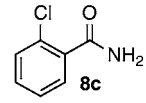
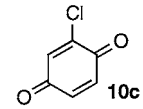
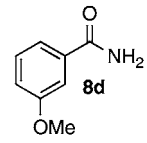
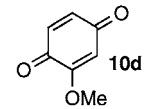
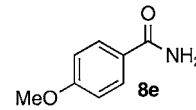
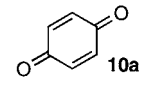
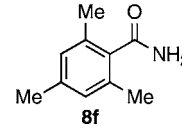
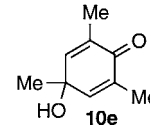
reaction is compatible with Boc protective groups (entry 7) and with methoxy-substituted aromatic rings (entry 10). Our procedure involves the use of commercially available and inexpensive reagents, PhI and Oxone, and the separation of products **7** can be performed by simple extraction of the reaction mixture with ethyl acetate after initial removal of methanol. The yields of products **7** are comparable to the previously reported preparation of methyl carbamates under basic conditions using the $PhI(OAc)_2$/KOH/MeOH system.[2f] Our procedure, however, is limited to the preparation of carbamates from alkylcarboxamides **6**; the reaction of arylcarboxamides with PhI and Oxone in methanol gives a complex mixture of products due to further oxidation of the initially formed arylamine derivatives. As it was well-documented in the literature, the formation of complex reaction mixtures (containing, in particular, azo compounds, ArN=NAr)[7a,b] is characteristic of the reactions of arylcarboxamides with hypervalent iodine reagents.[3b,4f,7]

Finally, we have investigated the reaction of arylcarboxamides **8** with PhI and Oxone in aqueous acetonitrile and were pleased to see that, in contrast to the reaction in methanol, these oxidations are highly selective and lead to the respective benzoquinone products **10** in almost quantitative yields (Table 2). No reaction occurred in the absence of iodoben-

Table 2. Preparation of Quinone Derivatives **10** by Oxidation of Arylcarboxamides **8** Using Oxone and Iodobenzene in Aqueous Acetonitrile[a]



8a-f **9** **10a-d**

entry	arylcarboxamide **8**	product **10**[b]	yield [%][c]
1			98
2			100
3			95
4			97
5			94
6			95

[a] All reactions of amides **8a**−**f** (1 mmol) were performed at room temperature in the presence of PhI (1 equiv) and Oxone (2 equiv) in CH_3CN-H_2O (1:1, v/v) (6 mL). [b] All previously reported products **10** were identified by comparison of their NMR spectra, GC−MS, and melting points with literature data. [c] Isolated yields of analytically pure products.

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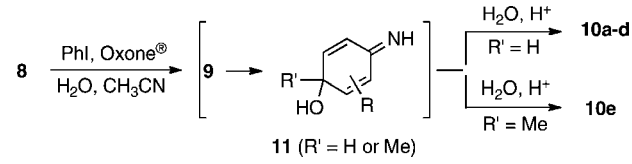
zene, while in the presence of 1 equiv of PhI and 2 equiv of Oxone (containing 4 equiv of active oxygen) the nonsubstituted benzamide **8a** or 4-methoxybenzamide **8e** afforded 1,4-benzoquinone **10a**, the *ortho*- and *meta*-substituted benzamides **8b**−**d** gave the corresponding substituted benzoquinones **10b**−**d**, and the reaction of 2,4,6-trimethylbenzamide **8f** yielded the expected product of oxidative *ipso*-substitution **10e** (Table 2).

The highly selective oxidative conversion of arylcarboxamides to the respective substituted benzoquinones is an unexpected result which probably may have some practical application taking into account the importance of oxidative spirocyclization in complex syntheses.[1h,n] From a mechanistic point of view, this result can be explained on the basis of the literature data. The initially generated electrophilic hypervalent iodine species **1** initiates the Hofmann rearrangement leading to arylamine **9** according to a well-established mechanism.[3b,4f,7] The arylamine **9** is further oxidized to the respective cyclohexa-2,5-dienimine **11**, which is subsequently hydrolyzed to the final product **10** (Scheme 3). A similar oxidation of substituted anilines to 4-substituted cyclohexa-2,5-dienimines has recently been reported in the literature.[8]

In summary, alkylcarboxamides can be converted to the respective amines by Hofmann rearrangement using hypervalent iodine species generated in situ from PhI and Oxone in aqueous acetonitrile. Based on this reaction, we have developed a convenient experimental procedure for the preparation of alkylcarbamates using Oxone as the oxidant in the presence of iodobenzene in methanol. An efficient method for direct conversion of substituted benzamides to the respective quinone derivatives by treatment with Oxone and iodobenzene in aqueous acetonitrile has also been found.

Scheme 3. Formation of Quinone Derivatives **10** in the Oxidation of Arylcarboxamides **8** Using Iodobenzene and Oxone



11 (R' = H or Me)

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Supporting Information Available: Experimental procedures and spectral data for key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL101993Q

(8) Basset, L.; Martin-Mingot, A.; Jouannetaud, M.-P.; Jacquesy, J.-C. *Tetrahedron Lett.* **2008**, *49*, 1551–1554.