Unique one step, multicomponent α,β,β-oxidations of carbamates with Willgerodt-like hypervalent iodine reagents—an example of triple C–H bond activation

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Dedicated to the memory of Professor Ivar Ugi, 1930–2005

Abstract—This communication reveals a novel multicomponent oxidation of saturated, urethane protected nitrogen heterocyclic systems. The oxidation is facile, general, high yielding and involves the application of readily-made hypervalent iodine reagents, giving an α,β,β-oxidation pattern relative to the nitrogen of the heterocycle. The oxidation is multicomponent type III, in that the substrate, reagent and solvent provide the three inputs during the reaction. The transformation also represents an example of triple C–H bond activation. A mechanistic rationale for this is proposed.
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In 1886 dichloro-iodobenzene, **1**, often referred to as Willgerodt's reagent was discovered.[1] Since that time, particularly in the last 20 years, the field of hypervalent iodine chemistry has experienced a surge of interest and many new polyvalent iodine reagents have been developed with a broad spectrum of functional applications in synthetic methodology.[2] Key review articles by Moriarty et al. cover critical developments in the area.[3] Our work was based upon the work of Magnus, who developed the versatile iodosobenzene/TMSN$_3$ reagent combination.[4] One of its many applications in enabling synthetic methodology was in the direct azidonation (i.e., oxidation) of amides, carbamates and ureas giving the α-azido product, an ionizable precursor to *N*-acyliminium ions.[5] The importance of the latter reactive intermediates in total synthesis is well documented[6] and several alternative non-oxidative procedures have been widely employed for their generation.[7] The Magnus transformation, however, represented one of the first non-electrochemical[8] direct chemical oxidations of saturated nitrogen heterocycles protected as amides. Several more have been developed in the last decade.[9] The main drawback preventing widespread use of the Magnus procedure, was that the suspected reactive intermediate PhI(N$_3$)$_2$ is very sensitive to decomposition of iodobenzene and 3N$_2$ with an occasional violent explosion. It thus seemed prudent to explore alternatives to azide of the class PhIX$_2$ to probe the feasibility of equivalent, safer transformations. Willgerodt's reagent, PhICl$_2$, was thus seen as the ideal starting point, Scheme 1.
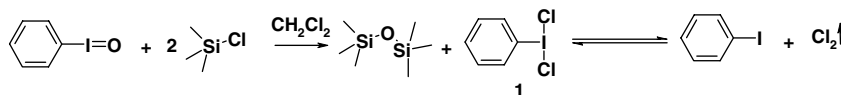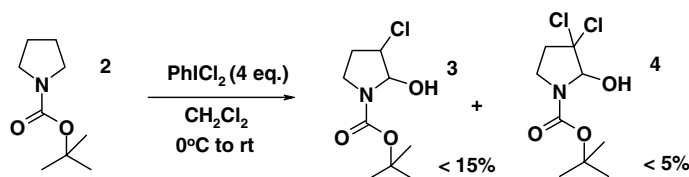

Scheme 1.

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PhICl$_2$ is prepared in situ via treatment of iodosobenzene[10] with TMSCl. Considerable attention has been paid to its stability, which can be attenuated with differing substituents on the aryl ring.[11] As seen from Scheme 1, it can be viewed as a chlorine surrogate and hence from the onset attempts were made to avoid substrates containing activated aryl rings to help avoid competing electrophilic substitution reactions of chlorine. Studies started with urethane protected substrates based on their excellent oxidative potential with PhI(N$_3$)$_2$.[4] Surprisingly two new products were observed upon treatment of BOC-pyrrolidine, 2, with PhICl$_2$, albeit only in low isolated yield, Scheme 2.

The products of the reaction were tentatively assigned as the α-hydroxy β-chloro oxidized product, 3, and the α-hydroxy β-dichloro product, 4. Intrigued by these complex oxidations, optimization efforts commenced. It was suspected that BOC instability under acidic conditions was the reason behind the low yield and mass recovery. Following the proposed mechanism of Magnus for the PhI(N$_3$)$_2$ oxidation of BOC protected pyrrolidines to α-azido pyrrolidines, the following ionic mechanism is proposed to explain their formation,

Scheme 3. However, a radical mechanism has not been definitively ruled out at this time.[4]

Noteworthy are oxidations with similar hypervalent reagents that occur with reduction of the I^{III} species to the more stable monovalent oxidation state.[12] The same change in oxidation state occurs in Scheme 3, where it is envisioned that a theoretical requirement of 3 equiv of PhICl$_2$ is needed for complete conversion to 4. Thus, interaction of the BOC carbonyl with I^{III} affords the intermediate, 5, which undergoes proton loss to generate the corresponding N-acyliminium ion, 6, and 1 equiv of HCl. This species could then be trapped with chlorine to give 7, although no α-chloro substitution was detected.[13] Proton loss or elimination of HCl, gives the enamide 8, which is susceptible to chlorination facilitated by the Cl surrogate nature of PhICl$_2$. This regenerates the α,β-chloro substituted N-acyliminium ion, 9 that can be trapped by adventitious water, giving stable 3, or reform α,β-chloroenamide, 10. This enamide is again exposed to chlorination, reforming the dichloro substituted N-acyliminium ion, 11, which is finally trapped with water to give the α,β,β-oxidized product, 4. Interestingly, during the reaction for full conversion to 4, 4 equiv of HCl are
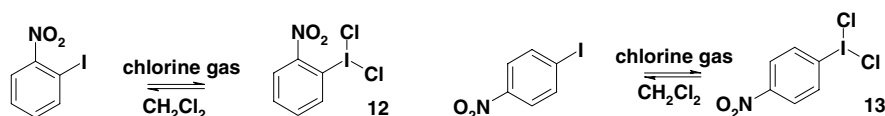

Scheme 2.
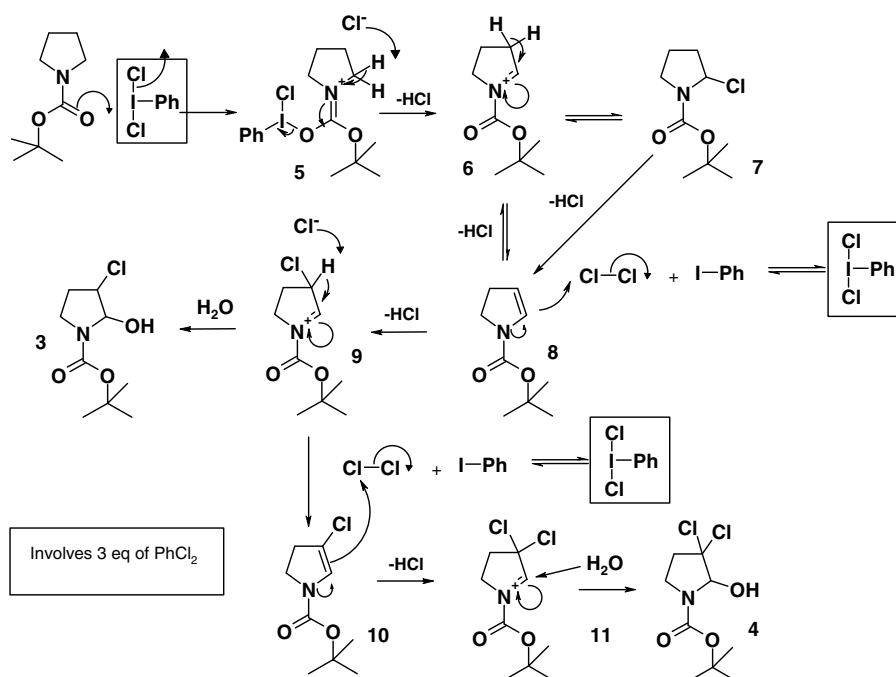
Scheme 3.

generated. The immediate conclusion one draws for low product recovery is acid mediated loss of the butyloxy group and further degradation of deprotected products. Additionally, the well studied stability[1] of PhICl$_2$ was poor, which initiated a search for a more shelf-stable yet reactive analog. Simply adding electron withdrawing groups helped shift the equilibrium of the decomposition pathway towards the I^{III} species. Both the *ortho*-nitro, **12**, and *para*-nitro, **13**, ArICl$_2$ reagents were prepared, as shown in Scheme 4.[14]

Decomposition was monitored in CDCl$_3$ by ^{1}H NMR, determining that the *para*-nitro species, **13**, was the most stable, exhibiting only 12% decomposition after 24 h at room temperature. Compound **12** completely disappeared after 45 h at −20 °C. Thus, the following study was performed with an acid stable isopropyloxy protecting group, **14**, and *p*-NO$_2$–PhICl$_2$, **13**, Table 1 (Scheme 5).

Encouragingly, switching to the acid stable urethane and I^{III} reagent with a longer half-life, excellent isolated

yields were obtained for **16** (R = OH, 85%, entries 5 and 9) and also **16** (R = OCH$_3$, 80%, entry 13). The latter result demonstrates classical *N*-acyliminium ion chemistry in its ability to ionize and exchange nucleophiles. With the conditions of entry 9, Table 1, in hand, further cyclic and acyclic systems were evaluated, Figure 1.

The methodology proved general for six, **17**, and seven membered rings, **18**. The α,β,β-oxidized product was also obtained in moderate yield for the acyclic system, **19**. Despite this, broad utility of the transformation would require an acid, stable yet easily removable protecting group to allow functionalization of the ring nitrogen. To this end, benzyloxycarbonyl (Cbz) was investigated, entry 9 conditions successfully gave **20** (75% isolated yield) and oxidized the benzoyl protected pyrrolidine to **22** in 52% yield, with the remaining mass balance starting material. Excitingly, pyrrolidine **21** was produced with 5 equiv of **13** in CH$_3$CN/5%CH$_3$OH at 150 °C in only 5 minutes by microwave irradiation.

Scheme 4.
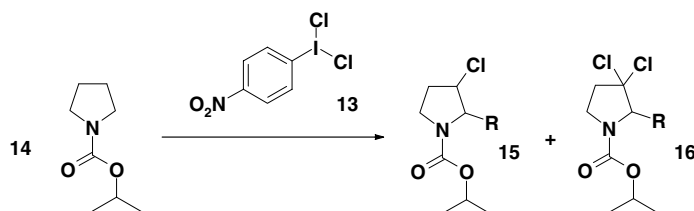
Scheme 5.

Table 1.

Entry	Solvent	Temperature	Time	Equivalents	R	Isolated yield[b] (%) **15**	Isolated yield[b] (%) **16**
1	CH$_2$Cl$_2$	rt	48 h	4	OH	0[e]	36
2	CH$_3$CN	0 °C to rt	4 h	5	OH	33	37
3	CH$_3$CN	rt	8 h	4	OH	0	64
4	CH$_3$CN	45 °C	4 h	3.5	OH	0	54
5	CH$_3$CN	45 °C	1 h	4	OH	0	85
6	CH$_3$CN	45 °C	1 h	5	OH	0	78
7	CH$_3$CN	150 °C	5 min	5	OH	0	71
8[a]	CH$_3$CN/5% H$_2$O	0 °C	5 h	4	OH	31	
9	CH$_3$CN/15% H$_2$O	45 °C	2 h	4	OH	0	88
10	CH$_3$CN/5 equiv MeOH	0 °C to rt	1 h	2.5	OH	37	0
11	CH$_3$CN/5%MeOH	0 °C	3 h	4	OCH$_3$	59[c]	0
12	CH$_3$CN/5%MeOH	45 °C	2 h	4	OCH$_3$	35	37
13[d]	CH$_3$CN/5%MeOH	45 °C	1 h	4	OCH$_3$	0	80

[a] Quench with 10% Na$_2$S$_2$O$_3$ and NaHCO$_3$.
[b] Isolated yields after purification via flash column chromatography.
[c] Isolated 20% of R = OH product. Reaction quenched with 10% Na$_2$S$_2$O$_3$.
[d] Methanol was added after 1 h and reaction mixture evaporated in vacuo.
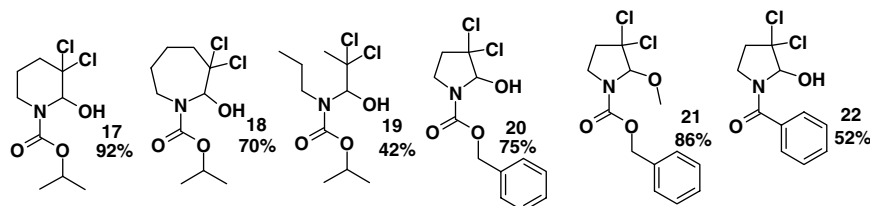[e] Not detected.
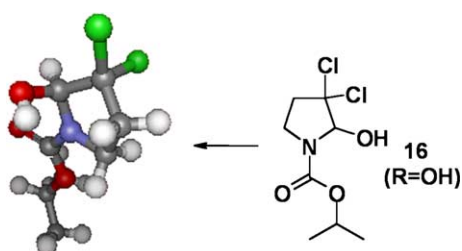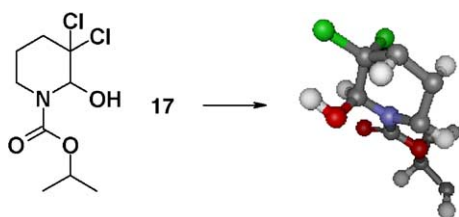
Figure 1.

Figure 2.

Figure 3.

With many products containing two chlorine atoms, recrystallization for X-ray crystallographic studies and structural confirmation proved straightforward (Figs. 2 and 3). Structures were obtained for **16** (R = OH) and **17**, clearly showing the α-hydroxy (red-white = O–H), β-dichloro (green) substitution patterns.[15]

In summary, a highly complex mechanistic, yet facile to perform transformation has been revealed. The oxidative reaction is multicomponent in that the substrate, reagent and solvent provide the three inputs during the reaction. The α,β,β-substitution pattern represents the equivalent of a unique triple C–H bond activation process, with a logical ionic mechanism to explain this. The oxidation proved general for several substrates and protecting groups and further studies are on-going in this area. Experiments to study the effect of attenuating the reactivity of the I^III reagent and alternative ligands to chlorine will be reported in due course. Additional studies of mechanism and the chemical transformations of products are also under investigation.

Acknowledgements

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15. Further structural confirmation for **16** (R = OMe) was also provided by a 2D NOESY, shown overleaf (Note: the isopropyl methyl signals are omitted from the ¹H NMR).