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The α-halogenation of α,β-unsaturated carbonyls and dihalogenation of alkenes using bisacetoxyiodobenzene/pyridine hydrohalides

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ABSTRACT

A procedure for the α-chlorination or bromination of a number of α,β-unsaturated carbonyls, and the dichlorination or bromination of alkenes, is developed using bisacetoxyiodobenzene (BAIB) and the HCl or HBr salt of pyridine. The reaction proceeds in an acceptable to a good yield and has a broad substrate scope. The dibromination is also achieved using a chiral I[V] reagent, although little enantioselectivity could be achieved.

Recently, gymnastatin F (**1**), isolated from the cellular extracts of the *Halichondria* sponge-derived fungus *Gymnascella dankaliensis*, was shown to inhibit dramatically the growth of P388 lymphocytic leukemia cells.[1] While the total synthesis of gymnastatin F (**1**) is yet to be achieved the formation of the deschloro analog of its biological precursor, gymnastatin A (**4**), has been reported by Wipf, via dearomatization of a tyrosine derivative as the key step (Fig. 1).[2]

As part of our studies towards the synthesis of gymnasatin F (**1**), the tandem TBS deprotection and oxidation of enone **5a**[3] were required (Scheme 1). It has been observed that modified Cr[VI] reagents are able to remove silyl protection from primary alcohols and effect their oxidation,[4] thus a similar transformation using pyridinium chlorochromate (PCC) was attempted. Unfortunately, oxidative deprotection could not be achieved when enone **5a** was exposed to PCC. This outcome was attributed to the rapid decomposition of the desilylated enone.[5] To enhance the rate of oxidation, the reaction was repeated using PCC and bisacetoxyiodobenzene (BAIB)/TEMPO.[6] While these conditions provided some aldehyde, α-chlorinated enone **6a** was the major product (Table 2, entry 10).[7]

Since this transformation introduces chlorine as ultimately required to access gymnastatin F (**1**), it was decided to investigate its utility. Furthermore, while there are various methods for the α-bromination[8] or α-iodination[9] of enones, there are far fewer procedures for α-chlorination.[10,11] Most procedures for the α-chlorination of enones utilize strong oxidants such as Oxone®,[10a–c] MCPBA,[10d] or dimethyldioxirane[10e] to generate electrophilic chlorinating agents; or potentially toxic and expensive selenium-based reagents.[10f,10g] There is a single report on the use of BAIB in the presence of TMSCl to achieve α-chlorination; however, this example is limited to flavanone substrates.[11] The opportunity to develop operationally simple and broadly applicable conditions for the α-chlorination of enones, and our own synthetic needs, prompted an exploration of the utility of this reaction.

In order to simplify the optimization studies, enone **5a** was replaced with cyclohexen-2-one (**5b**), which reacted to provide α-chloro enone **6b** in a similar yield (Table 1, entries 1 and 2).

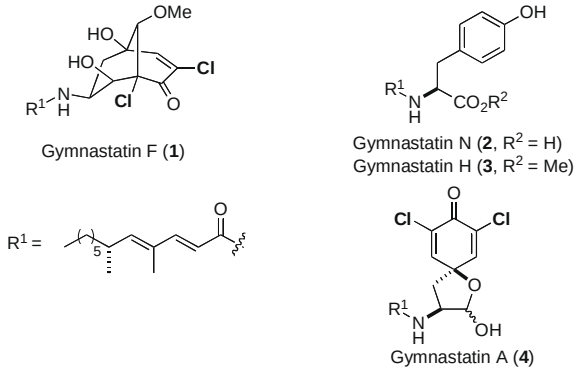
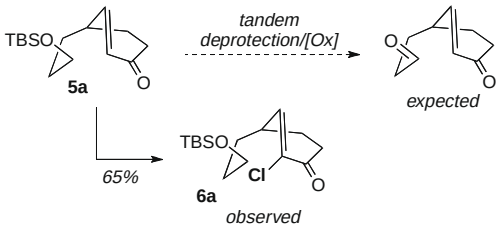


Figure 1.



Scheme 1.

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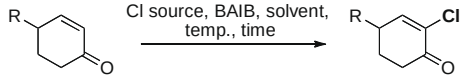
Table 1
Optimization of the α-chlorination of cyclohexenones **5a** and **5b**



5a, R = $(CH_2)_3OTBS$
5b, R = H

6

Entry	Enone	Cl source	BAIB (equiv)	Solvent	Temp[a]/time	Yield[b] (%)
1[c]	**5a**	PCC (1 equiv)	1	CH_2Cl_2/DMF[d]	−40 °C 14 h	65 (80)
2[c]	**5b**	PCC (1 equiv)	1	CH_2Cl_2/DMF[d]	−40 °C 14 h	68 (80)
3	**5b**	PCC (1 equiv)	1	CH_2Cl_2/DMF[d]	−40 °C 14 h	67 (80)
4	**5b**	PCC (1 equiv)	1	CH_2Cl_2/DMF[d]	rt 14 h	69 (80)
5	**5b**	PCC (2.4 equiv)	1.2	CH_2Cl_2	rt 14 h	88 (100)
6	**5b**	C_5H_5N·HCl (2.4 equiv)	1.2	CH_2Cl_2	rt 6 h	91 (100)

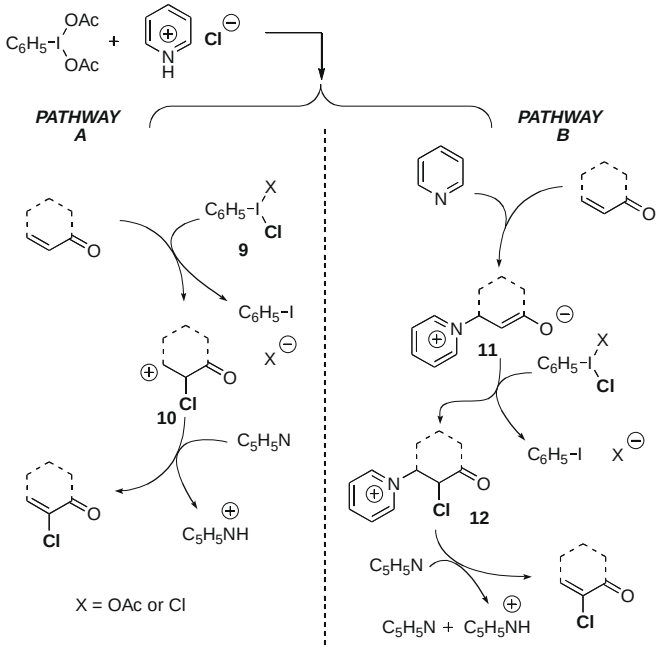
[a] Reactions were set up at the indicated temperature and allowed to warm to room temperature in the cooling bath.
[b] Isolated yield after column chromatography, conversion in parentheses determined by ^1H NMR analysis.
[c] TEMPO (0.1 equiv).
[d] 5% DMF in CH_2Cl_2.

Removal of TEMPO and DMF, relevant for the attempted tandem deprotection and oxidation, was found to have no bearing on the reaction outcome (Table 1, entries 3 and 5). Similarly it was found that the reaction could be conducted at ambient temperature rather than at −40 °C (Table 1, entry 4). At this juncture, the molar equivalents of PCC were increased allowing the reaction to reach completion, providing chloride **6b** in 88% yield (Table 1, entry 5). Finally, it was reasoned that PCC was simply serving as a source of pyridine hydrochloride. This proved to be the case, and when PCC was replaced with Py·HCl, the transformation was achieved in 91% yield over 6 h (Table 1, entry 6).[12]

Having developed conditions for the α-chlorination of cyclohexenone **5b** the scope of the reaction was investigated. When Py·HCl was replaced with Py·HBr, α-brominated cyclohexenone **7b** was formed in a good yield (Table 2, entry 2).[6] While this transformation can be achieved with a number of reagents,[8] it was satisfying that conditions for chlorination translated to the bromination. Introduction of a methyl group at the β-position of the enone had no bearing on the reaction outcome with 2-chloro-3-methylcyclohex-2-enone (**6c**) forming in 75% yield (Table 2, entry 3). The chlorination of 4,4-dimethylcyclohexenone was investigated and found to give the expected chloride **6d** in 94% yield, although a longer reaction time, and increased stoichiometry of both BAIB and Py·HCl were required (Table 2, entry 4). The success of this reaction bodes well for the synthesis of gymnastatin F (**1**), which bears γ-disubstitution. The α-chlorination of cyclopentenone (**5e**) (Table 2, entry 5) proceeded using the same modifications necessary for enone **5d**.

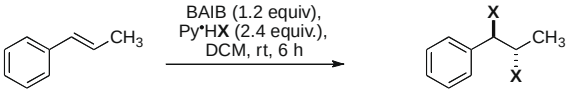
The chlorination of both acrolein (**5f**) and methyl vinyl ketone (**5g**) proceeded to give an excellent yield of the expected products without appreciable decomposition (Table 2, entries 6 and 7). The suitability of this reagent system to these sensitive substrates attests to the mildness of the reaction conditions. Cinnamaldehyde (**5h**) also reacted smoothly to provide **6h** in good yield (Table 2, entry 8). Finally, the chlorination of (*E*)-4-phenylbut-3-en-2-one (**5i**) was achieved in an acceptable 54% yield (Table 2, entry 9), proving the suitability of these conditions for acyclic α,β-unsaturated ketones.

Mechanistically, the α-chlorination may proceed by one of two pathways. In both pathways oxidation of Py·HCl by BAIB generates an electrophilic chlorine source, such as **9**, or an ionized form. In pathway A, reaction of this species with the α,β-unsaturated carbonyl affords carbocation **10** which, following deprotonation, provides the α-chlorinated product. Alternatively, pathway B involves activation of the α,β-unsaturated carbonyl-containing compound by pyridine, providing β-pyridinium enolate **11**, which upon reaction with electrophilic chlorine gives intermediate **12**. Elimination would then provide the expected product (Scheme 2).



Scheme 2.

In order to gain insight into the reaction mechanism, the bromination of (*E*)-prop-1-enylbenzene (**13a**) was attempted. If activation of the alkene by conjugate addition is required, then this substrate should prove unreactive. The reaction gave dibromide **14a** in a high yield and with *anti*-addition of the halogens. The analogous dichlorination was successful; however, stereocontrol was diminished and dichloride **15a** formed as a 2:1 mixture of diastereoisomers (Eq. 1).

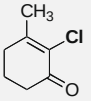
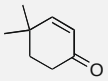
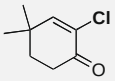
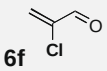
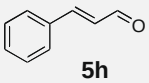
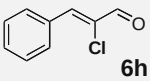
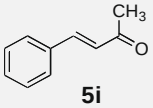
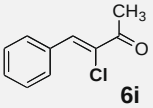
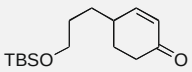
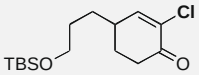
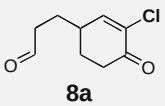


13a

14a (X = Br): 80%
15a (X = Cl): 79% (dr 2:1)

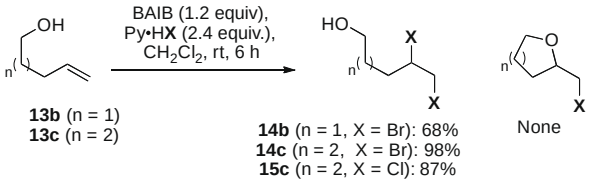
(1)

Table 2
Scope of the halogenation of enones and enals

Entry	Enone	Product[a]	Yield[b] (%)
1	 **5b**	 **6b**	91
2[c]	 **5b**	 **7b**	89
3	 **5c**	 **6c**	75
4[d]	 **5d**	 **6d**	94
5[d]	 **5e**	 **6e**	69
6[d]	 **5f**	 **6f**	84[e]
7	 **5g**	 **6g**	88[e]
8	 **5h**	 **6h**	76
9	 **5i**	 **6i**	54
10a[f]	 **5a**	 **6a**	65
b[f]		 **8a**	24

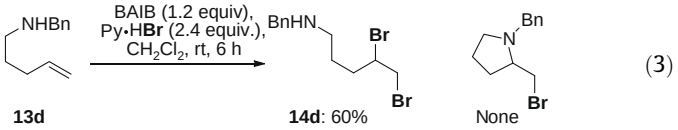
[a] Reactions conducted using the conditions from Table 1, entry 6.
[b] Isolated yield after column chromatography, except as noted.
[c] Performed using Py·HBr.
[d] After 6 h, an additional 1.2 equiv of BAIB and 2.4 equiv of Py·HCl were added.
[e] Isolated by distillation and contaminated with some iodobenzene.
[f] Performed using the conditions from Table 1, entry 1 and products **6a** and **8a** were isolated.

Since direct halogenation of the alkene implicates a cationic intermediate, it was reasoned that compounds bearing a nucleophilic heteroatom should provide heterocycles. When pent-4-en-1-ol (**13b**) was exposed to BAIB and Py·HBr, none of the tetrahydrofuryl product formed, and only dibromide **14b** (X = Br) was isolated. Similar results were obtained when carbon-elongated analog **13c** was reacted in the presence of either Py·HCl or Py·HBr (Eq. 2).



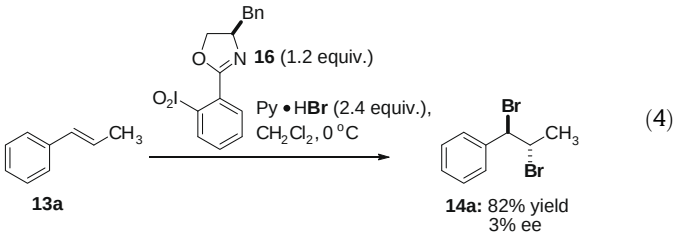
(2)

Trapping with amine **13d**[13] was equally unsuccessful with only dibromide **14d** isolated (Eq. 3). Thus it appears that the halogenation proceeds via pathway A but that trapping of the intermediate by the halide is faster than cyclization.



(3)

The dihalogenation, and specifically dichlorinations, described above, further demonstrate the utility of our reagent system, which tolerates protected amine and unprotected alcohol functionalities. Surprisingly, an array of reagents for the dichlorination of alkenes has not been reported.[14] More uncommon still are examples of the enantioselective dihalogenation of alkenes.[15] Our interest in the development of chiral I[V] reagents for enantioselective reactions,[16] along with success in the dihalogenations (Eqs. 1–3), led to an investigation into the asymmetric version of the dihalogenation reaction. Birman has recently reported enantiopure oxazole-containing iodoxyarenes (for example **16**) for an asymmetric oxidative dearomatization/Diels–Alder reaction.[17] Having previously prepared analogous iodides[18] it was possible, equipped with these conditions, to access the desired iodoxyarene. Unfortunately, while this enantiopure reagent mediated the dibromination of **13a**, little asymmetric induction was observed (Eq. 4).[19] Solvent and temperature modifications were unable to improve significantly the enantioselectivity.



(4)

A mild method for the α-halogenation of α,β-unsaturated carbonyls has been developed based on the use of BAIB and hydrohalide salts of pyridine. In the case of chlorination, this constitutes a useful reagent system that allows the conversion of a range of sensitive substrates into their chlorinated analogs. The reaction appears to involve initial halogenation of the alkene providing an intermediate cation, which is then deprotonated to regenerate the olefin. The conditions are also suitable for the dihalogenation of simple isolated alkenes. This transformation has been achieved with six alkenes, which all react smoothly and in good to high yield. Unfortunately, while this reaction can be achieved using a chiral BAIB surrogate, very little asymmetric induction was observed.

Acknowledgements

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5. In other studies directed towards the synthesis of the gymnastatins it has been observed that the deprotected form of compound **5a** is unstable. These studies will be reported in due course.
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7. 4-(3-(*tert*-Butyldimethylsilyloxy)propyl)-2-chlorocyclohex-2-enone **6a** ^{1}H NMR (500 MHz, CDCl3) δ 7.04 (dd, J = 3.0 and 1.5 Hz, 1H), 3.64 (t, J = 6.0 Hz, 2H), 2.70 (dt, J = 17.0 and 5.0 Hz, 1H), 2.64–2.55 (m, 1H), 2.54–2.44 (m, 1H), 2.19–2.10 (m, 1H), 1.80–1.70 (m, 1H), 1.66–1.48 (m, 4H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (125 MHz) 151.2, 131.9, 62.9, 38.1, 37.5, 31.2, 30.2, 28.7, 26.2, 18.6, -5.1; ν_{max} 2953, 2930, 2858, 1702, 1605, 1472, 1463, 1256, 836, 777 cm^{-1}; HRMS (ESI) Found (M+Na$^+$), 325.1366 $C_{15}H_{27}ClO_2Si$ requires (M+Na)$^+$ 325.1367.
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11. Rho, H. S.; Ko, B.-S.; Ju, Y.-S. *Synth. Commun.* **2001**, *31*, 2101.
12. A magnetically stirred solution of cyclohexen-2-one (51.2 mg, 0.518 mmol) in CH_2Cl_2 (4 mL) was treated with BAIB (193.8 mg, 0.60 mmol) and pyridine·HCl (145 mg, 1.25 mmol). The solution was stirred for 6 h at which point the starting enone had been consumed as judged by TLC analysis. The reaction mixture was diluted with CH_2Cl_2 (5 mL), then, washed with HCl (10 mL of a 1 M solution). The aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL) and the combined organic extracts washed with brine (5 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to afford a yellow oil that was subjected to flash column chromatography (silica gel, 1:4 v/v ethyl acetate/hexanes) and, upon collection and evaporation of the appropriate fractions (R_f 0.2) gave **6b** (61.2 mg, 91%) the ^{1}H NMR and ^{13}C NMR data of which matched those reported in the literature.[10a]
13. Prepared by alkylation of the corresponding amine: Gribov, D. V.; Hultzsch, K. C. *Angew. Chem., Int. Ed.* **2004**, *43*, 5542.
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