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Synthesis of β-Substituted α-Iodocycloalkenones

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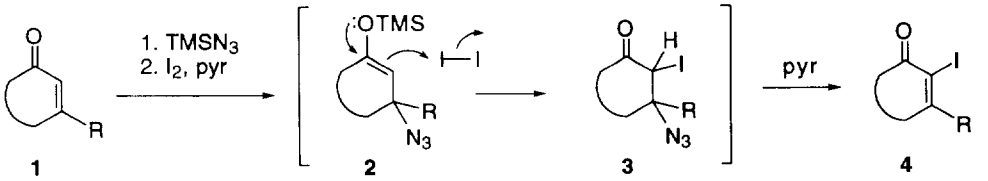
Abstract: Iodination of β-substituted cycloalkenones with $TMSN_3/I_2$/pyridine in dichloromethane is reported.

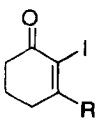
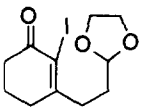
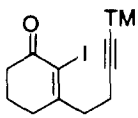
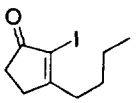
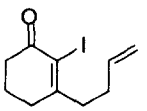
α-Iodocycloalkenones are versatile synthetic intermediates for the synthesis of many biologically active natural products.[1] McIntosh,[2] Johnson[3] and Mc Nelis[4] have reported three methods for the synthesis of α-iodocycloalkenones. However we found that these methods are not suitable for the preparation of some α-iodocycloalkenones with a β-substituent.[5] Herein we report an efficient method using trimethylsilyl azide and a mixture of iodine and pyridine for the iodination of β-substituted cycloalkenones.

Scheme 1



Treatment of a β-substituted cycloalkenone with trimethylsilyl azide and a mixture of iodine and pyridine sequentially in dichloromethane afforded the corresponding β-substituted α-iodocycloalkenone.[6] Conjugate addition of trimethylsilyl azide to cycloalkenone **1** gave an intermediate β-azido trimethylsilyl enol ether **2**, which on subsequent iodination gave α-iodo-β-azidoketone **3**. Elimination of HN_3 from compound **3** by pyridine afforded α-iodocycloalkenone **4**, Scheme 1.

Table 1 Iodination of Cycloalkenones

Product[a] and Yield[b]	Molar Ratio of $TMSN_3/I_2$	Reaction Time (h)	Product[a] and Yield[b]	Molar Ratio of $TMSN_3/I_2$	Reaction Time (h)
					
			11 86%	2.5/4	24
5 R = H 81%	1.5/2	12			
6 R = Me 75%	2/2	12			
7 R = Et 70%	2/2	12			
8 R = *n*-Bu 80%	2/2	12			
9 R = *i*-Pr 78%	2/3	36			
			12 85%	2/2	18
					
10 56%	2/2.5	24	**13** 35%	2.5/4	24

[a] All iodination products were characterized by IR, NMR, MS and HRMS. [b] Isolated yield.

In Table 1, several β-substituted cycloalkenones were converted to the corresponding α-iodocycloalkenones in moderate to high yields. However the yield of **13** is relatively low, which is probably due to the presence of the terminal double bond.

In conclusion, we have developed an efficient method for the preparation of α-iodoenones with or without β-substituent, which opens new directions to use β-substituted cycloalkenones as important synthetic intermediates in organic synthesis.[7]

References and Notes:

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5. Sha, C.-K.; Shen, C.-Y.; Jean, T.-S.; Chiu, R.-T.; Tseng, W.-H. *Tetrahedron Lett.* **1993**, *34*, 7641.
6. A standard procedure to prepare β-substituted α-iodocycloalkenones: 2-iodo-3-butyl-2-cyclohexen-1-one **8**. To a solution of 3-butyl-2-cyclohexen-1-one (100 mg, 0.66 mmol) in dichloromethane (1 mL) was added freshly distilled trimethylsilyl azide (152 mg, 1.32 mmol) at 0 °C. After the mixture was stirred at 0 °C for 2 h, a solution of iodine (335 mg, 1.32 mmol) in dichloromethane (1 mL) and pyridine (1 mL) was added slowly at 0 °C. The mixture was allowed to warm to room temperature and stirred for 12 h. The mixture was then diluted with diethyl ether (25 mL). The organic layer was washed with water (15 mL), HCl (10%, 15 mL), saturated $NaHCO_3$ (15 mL), $Na_2S_2O_3$ (10%, 20 mL) and brine, and dried over anhydrous $MgSO_4$. Filtration, concentration and chromatography gave 2-iodo-3-butyl-2-cyclohexen-1-one **8** (147 mg, 80%).

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