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Direct α-Arylation of Ketones: The Reaction of Cyclic Ketone Enolates with Diphenyliodonium Triflate

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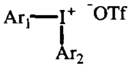
Abstract: Diphenyliodonium triflate **1a** reacts with the lithium enolates of cyclic ketones **2** (ring size = 5 - 8), in the presence of stoichiometric quantiites of copper cyanide, to afford the corresponding α-phenylated ketones **3** or α,α'-diphenylated ketones **4**. © 1997 Elsevier Science Ltd.

A number of methods have been developed for the production of an α-aryl ketone directly from the parent ketone. Included in these methods are the transition metal-catalysed reaction of enolate ions (or equivalents) with haloarenes,[1] and the reaction of an enolium (α-keto cation) synthon with electron rich aryl systems.[2] A seemingly more straightforward method is the $S_{RN}1$ reaction of ketone enolate ions with haloarenes, a process which involves a radical chain mechanism;[3] however, this type of procedure generally requires a large excess of ketone enolate in order to gain reasonable yields.[3b] In some cases, the intramolecular variant of this reaction is highly successful.[4] Closely related to these latter approaches is the reaction of ketone enolate ions (or equivalent) with electrophilic aromatic reagents of Bi^{V},[5] Pb^{IV},[6] and I^{III}.[3c,7] Variable yields were obtained using diphenyliodonium halides and the ketone enolates tested were restricted to the acyclic variety, or-1-indanone derivatives. We have developed efficient methods for the synthesis of a wide range of stable diaryliodonium triflates **1**,[7c,8] and we now report on the reactions of diphenyliodonium triflate **1a** with the enolates of a range of cyclic ketones **2**.[9]

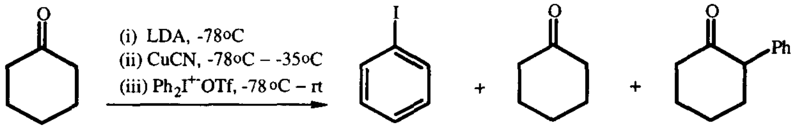


$$Ar_1{-}\overset{+}{I}(Ar_2)\ {}^{-}OTf$$

1

1a : Ar_1 , Ar_2 = Ph

A variety of reaction temperatures and enolate counterions were experimented with, using cyclohexanone **2c** as a typical cyclic ketone; however, efficient coupling could only be obtained using a copper enolate formed by reaction of the preformed lithium enolate with anhydrous copper cyanide (Table 1). Optimal conditions for formation of 2-phenylcyclohexanone **3c** entailed the use of one mole equivalent of copper cyanide (entry 5). In this case, ^{1}H NMR analysis of the crude reaction product showed it to consist of a *ca.* 2:1:1 mixture of iodobenzene, **2c** and **3c**.[10] Only trace amounts (<1%) of biphenyl could be detected, so presumably the other reduction product, benzene, is lost during work-up.[11]



2c **2c** **3c**

2 : 1 : 1

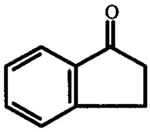
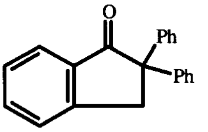
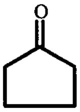
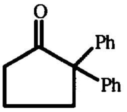
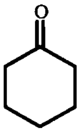
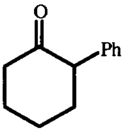
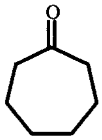
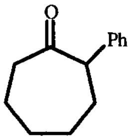
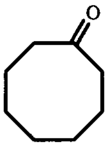
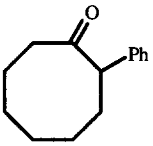
Table 1. The reaction of cyclohexanone **2c** with diphenyliodonium triflate **1a**[a]

entry	enolate	conditions for generation of enolate	yield of **3c**[b]
1	Li	1 equiv. LDA	<5%
2	Zn	(i) 1 equiv. LDA; (ii) 1 equiv. $ZnCl_2$	<5%
3	Cu	(i) 1 equiv. LDA; (ii) 1 equiv. CuI	<5%
4	Cu	(i) 1 equiv. LDA; (ii) 0.5 equiv CuCN	35%
5	Cu	(i) 1 equiv. LDA; (ii) 1 equiv. CuCN	50%
6	Cu	(i) 1 equiv. LDA; (ii) 2 equiv. CuCN	45%

[a] Typical Procedure: A solution of cyclohexanone **2c** (1.0 mmol) in THF (1 mL) was slowly added to a solution of LDA (1.0 mmol) in THF (10 mL), maintained under argon, at -78°C. The solution was stirred for 1 h at this temperature then the anhydrous salt ($ZnCl_2$, CuI or CuCN) was added in one portion. The mixture was allowed to warm to -35°C, stirred for 15 min at this temperature then recooled to -78°C. Diphenyliodonium triflate **1a** (1.0 mmol) was added, in one portion, resulting in the immediate formation of a bright yellow mixture. The reaction was maintained at -78°C for 15 min then allowed to slowly to warm to room temperature. After stirring for 1h at rt, the reaction mixture was partioned between ether and water, the combined ethereal extracts were dried ($MgSO_4$), filtered and concentrated to give a yellow oil. Purification by column chromatography (SiO_2, CH_2Cl_2) afforded 2-phenylcyclohexanone **3c** (50%) as an analytically pure, colourless oil. [b]Isolated yield of analytically pure material.

A survey of the reaction of a number of cyclic ketone enolates **2** with diphenyliodonium triflate **1a** in the presence of copper cyanide using the optimal reaction conditions described above is given in Table 2. Interestingly, the five-membered cyclic ketones **2a** and **2b** gave only α,α'-diphenylated products, **4a** and **4b**, respectively (entries 1 and 2). No mono-arylated products (**3a** or **3b**) could be detected in these cases. In contrast, the larger cyclic ketones **2c-e** (entries 3-5) gave only the respective mono-arylated products **3c-e**. In all cases, the balance of the crude reaction product was made up of iodobenzene and starting ketone.

Table 2. The α-arylation of the enolates of cyclic ketones, **2**, by diphenyliodonium triflate **1a** in the presence of copper cyanide.[a]

entry	starting material	product	product yield[b] (%)
1	 **2a**	 **4a**	35
2	 **2b**	 **4b**	38
3	 **2c**	 **3c**	50
4	 **2d**	 **3d**	46
5	 **2e**	 **3e**	55

[a] For typical procedure, see Table 1, entry 5. [b] Isolated yield of analytically pure material.

The yields obtained from these reactions are consistent, but limited by competing radical reduction processes. In principle, if the starting ketone was recovered, as it was for the case of cyclohexanone, the yields calculated at percentage conversion of the ketone would be greater than 80%, in each case. We have developed strategies for the synthesis of a range of diaryl- and bis(heteroaryl)-iodonium triflates,[8] therefore an investigation of the reaction of these species with copper (I) enolates, under the conditions described in this report, appears warranted. Furthermore, it is envisaged that useful selectivity may be observed for certain unsymmetrical diaryliodonium triflates. Such developments will be reported in due course.

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9. The arylation of ketone enolates with diphenyliodonium salts has been reported, but only in a dissertation: Manis, P. A. *The Synthesis and Reactions of Sterically Hindered Silyl Enol Ethers. The Reaction of α-Azido Esters with Base. The Phenylation of Ketone Enolates with Diphenyliodonium Salts*, Michigan State University, 1982.
10. The formation of cyclohexanone in these reactions is almost certainly due to radical reduction processes which compete with the desired coupling reaction. Attempts to quell these competing radical processes by the addition of radical chain inhibitors such as diphenylethylene[5] and styrene, were unsuccessful; the ratios of iodobenzene, **2c** and **3c** in the crude reaction product remained unchanged.
11. In accord with this proposal, the reaction of cyclohexanone with bis(2,4,6-trimethylphenyl)iodonium triflate under analogous conditions, gave only reduction, the reaction product consisting of a *ca.* 1:1:1 mixture of 1-iodo-2,4,6-trimethylbenzene, 1,3,5-trimethylbenzene and cyclohexanone.

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