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Carbonyl Transposition of α-Hydroxyamidals Mediated by Triphenylphosphine-Iodine. A New Entry to Tetrahydroisoquinolin-4-ones

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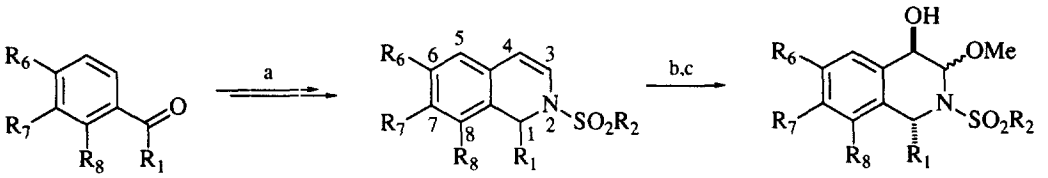
Abstract: Carbonyl transposition of 2-sulfonyl-3-methoxy-4-hydroxy-tetrahydroisoquinolines with the triphenylphosphine-iodine reagent provides a new access to tetrahydroisoquinolin-4-one derivatives.

Tertiary phosphine-dihalides and related reagents have been extensively used[1] for the selective cleavage of acetals,[2a,b] ketals[2b] and ethers,[2c,d] as well as for the conversion of alcohols,[2e,f] protected alcohols[2g,h] and other functional groups[2i] into halides under mild, neutral and non-aqueous conditions. In addition, the adducts of tertiary phosphines with hydrogen halides have been used as glycosylation[2j] and acetalization[2k] catalysts.

Recent reports on carbonyl transposition of α-hydroxyacetals[3a] and α,β-epoxysulfoxides[3b] mediated by $Ph_3P.I_2$ prompted us to study this couple as a reagent to achieve the yet unreported carbonyl transposition of α-hydroxyamidals. This transformation is important since the transposition of carbonyls is a challenging problem that has received considerable attention over the years, because the need to relocate this functional group within a molecule occurs frequently,[4,5] and the relocation of masked carbonyls has been scarcely studied.[3]

In this letter we disclose the one-step 1,2-carbonyl transposition of α-hydroxyamidals promoted by $Ph_3P.I_2$, leading to the synthesis of tetrahydroisoquinolin-4-ones in high yield. The latter have been employed as key intermediates for the elaboration of various complex natural products and, accordingly, their synthesis has been accomplished by different means, including intramolecular Friedel-Crafts acylation of *N*-benzyl glycines,[6a,b] Dieckmann condensation[6c,d] and photochemical Mannich cyclization.[6e]



1 2 3

Scheme 1. *Reagents and conditions:* a. Jackson isoquinoline synthesis (ref. 7); b. OsO_4(cat.), NMO, Me_2CO-^{t}BuOH-H_2O (4:2:1), RT, 80-85%; c. $HC(OMe)_3$, MeOH, TsOH (cat.), CH_2Cl_2, RT, 95-100%

As shown in Scheme 1, the starting α-hydroxyamidals (**3**) were obtained in 75-80% overall yields by

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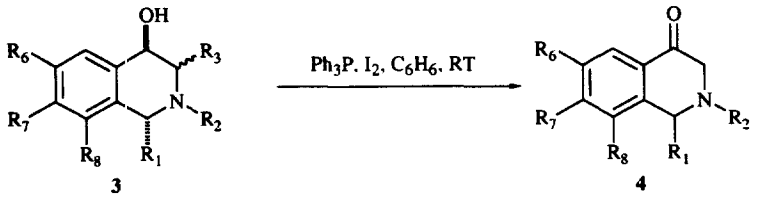
dihydroxylation of *N*-tosyl-1,2-dihydroisoquinolines (**2**), easily available from aromatic aldehydes and ketones (**1**), employing the synthetic protocol developed by Jackson,[7] followed by trimethyl orthoformate-mediated acetalization of the resulting hemiamidals.

Upon reaction with $PPh_3.I_2$ in benzene at room temperature,[8] the α-hydroxyamidals (**3**) were smoothly converted to the related tetrahydroisoquinolin-4-ones (**4**) in high yield, as shown in the Table. Generally, the transformations were clean and fast, being completed in 0.5-2 h. Interestingly, α-hydroxyhemiamidals like **3a** are capable of undergoing the same transformation (entry 1); however, less efficiently than the related amidals **3b** and **3c** (entries 2 and 3). Different substituents and substitution patterns are tolerated, including phenolic and aliphatic ethers, potentially susceptible to cleavage,[2c] and the transformation is insensitive to the configuration of the 3-methoxy group relative to the neighbouring hydroxyl (entries 2 vs. 3, 4 vs. 5, 6 vs. 7).

It was also observed that the reaction is catalytic in iodine, smoothly proceeding to completion in 8 h when only 10 mol % of the halogen is added, and that other reagents such as Ph_3P-NBS and $(PhO)_3PMeI$, employed for the iodination and dehydration of alcohols,[9] are capable of efficiently accomplishing the same transformation. The ^1H NMR study of the reaction progress (NMR tube, C_6D_6) evidenced rapid formation of MeI and Ph_3PO as reaction products, the mixture turning slightly acidic (HI formation),[3] when 0.5 equiv. of I_2 were employed; however, when catalytic amounts of I_2 were added, formation of Ph_3PO was negligible.

Table. Carbonyl transposition mediated by $Ph_3P.I_2$. Synthesis of tetrahydroisoquinolin-4-ones.



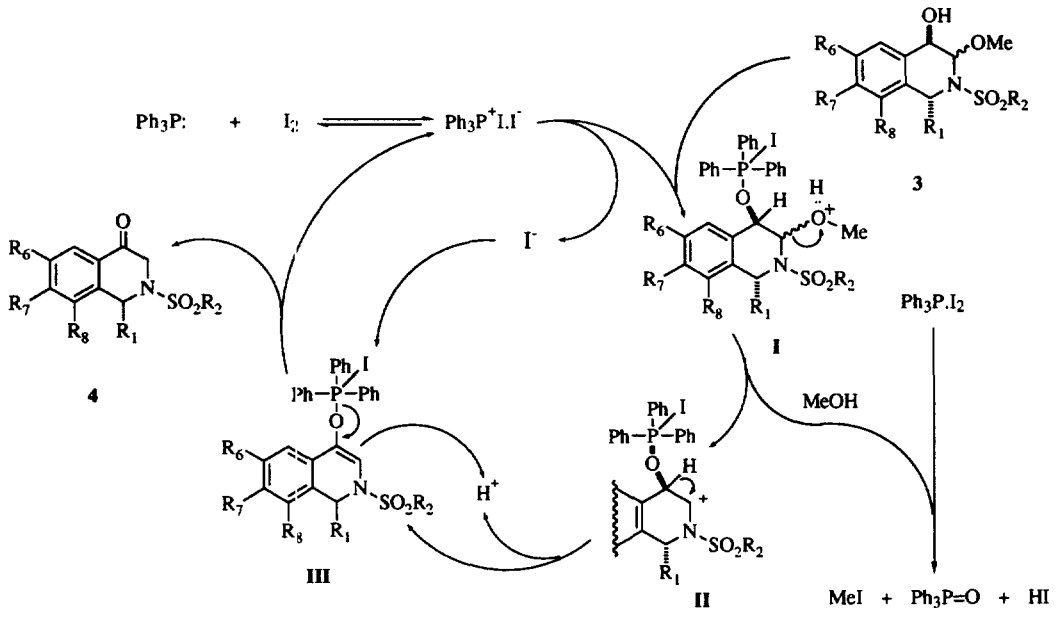
3 **4**

Entry	Amidal	R_1	R_2[a]	R_3	R_6	R_7	R_8	Ketone	Yield (%)
1	**3a**	H	Ts	~~OH	OMe	OMe	H	**4a**	50
2	**3b**	H	Ts	—OMe	OMe	OMe	H	**4a**	75
3	**3c**	H	Ts	····OMe	OMe	OMe	H	**4a**	80
4	**3d**	H	Ts	—OMe	H	OMe	OMe	**4b**	86
5	**3e**	H	Ts	····OMe	H	OMe	OMe	**4b**	98
6	**3f**	H	Ts	—OMe	H	OMe	OBn	**4c**	100
7	**3g**	H	Ts	····OMe	H	OMe	OBn	**4c**	95
8	**3h**	Me	Bs	····OMe	OMe	OMe	H	**4d**	86
9	**3i**	H	Cs	····OMe	H	OMe	OBn	**4e**	84
10	**3j**	CH_2OBn	Ts	····OMe	H	NHAc	OMe	**4f**	87

[a] Ts= tosyl; Bs= benzylsulfonyl; Cs= (+)-10-camphorsulfonyl

A possible reaction mechanism to account for the above observations is depicted in Scheme 2. As shown, reaction of Ph_3P with iodine gives the known electrophilic $Ph_3P.I_2$ adduct[1,2c,d] which, once attacked by the α-hydroxyamidal liberates hydrogen iodide,[3] capable of protonating the oxygen in the amidal moiety (**I**).[2j] Next, loss of MeOH with concomitant formation of a carbocationic intermediate (**II**), could be followed by deprotonation to give an enol-phosphine derivative (**III**).[3b] Finally, conversion of the enol to its related ketone could be achieved by iodide attack to the pentacoordinated phosphorus,[3b] regenerating the $Ph_3P.I_2$ adduct. Formation of MeI by reaction with MeOH,[1] which substracts iodide and the fact that $(PhO)_3PMeI$ also mediates the transposition, indicate that $Ph_3P.I_2$ may not be the only promoter present in the reaction medium.

The mechanistic details are speculative and the mechanistic picture oversimplified, since alternative routes may also be envisioned; however, that involving reaction of the $Ph_3P.I_2$ reagent with the amidal moiety to give an intermediate tosyliminium ion, which could rearrange to the enolic form of **3**, was discarded because no 3-allyl tetrahydroisoquinoline derivative was formed when excess allylTMS was added to the reaction mixture and, moreover, no transposition products were detected when α-hydroxyamidals **3b** and **3c** were reacted with Lewis acids, such as $BF_3.Et_2O$, ZnI_2 and $MgBr_2$, known to produce these intermediates.[7b] In addition, that the phosphine-halogen adduct reacts with the carbinolic oxygen was inferred from analysis of the ^1H NMR spectrum of the intermediate from the reaction of **3b** with $(Me_2N)_3P$-CCl_4, which displayed its H-4 signal [δ 5.64 (d, J = 2.3 Hz)] coupled only with H-3. The benzylic character of H-4 and the steric hindrance around C-4[10] probably facilitate the transposition pathway over the halide formation reaction.[2e,f]



Scheme 2.

The high yield and simplicity of this minimal time consuming procedure suggest that the protocol serves as a promising means for effecting the 1,2-migration of the carbonyl group in α-hydroxyamidals and that this reaction may find further use in organic synthesis.

Acknowledgements

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8. In a typical procedure, to a stirred solution of the α-hydroxyamidal (0.6 mmol) in dry benzene (3 mL) were successively added PPh_3 (2 equiv.) and a freshly prepared solution of I_2 in benzene (0.5 equiv.). The characteristic colour of the halogen faded rapidly and the reaction mixture was stirred at room temperature until complete disappearance of the starting material was assessed by TLC (0.5 - 2 h). The solvent was removed under reduced pressure and the remaining oil was flash chromatographed (hexane-EtOAc). All new compounds were satisfactorily characterized by spectral and analytical means.
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