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Received: An Easy, Stereoselective Synthesis of Hexahydroisoindol-4-ones under Phosphine Catalysis

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Abstract. A new synthetic approach to hexahydroisoindol-4-ones is reported, based on the formal [3+2] cyclization reaction between N-arylsulfonylimines and cyclic conjugated dienes, under phosphine catalysis. Key substrates are 3-vinylcyclohex-2-enones with electron-withdrawing substituents (ester, amido, cyano, phosphoryl and keto groups) on the exocyclic double bond, which afford the three atom synthons for the construction of the pyrroline ring. Total syn stereoselectivity is observed in these annulations. The scope of the reaction has been demonstrated and mechanistic issues are considered, based on deuterium experiments and DFT calculations.

Keywords: phosphine organocatalysis; conjugated dienes; imines; hexahydroisoindolones;[3+2] annulations

1 Introduction

Isoindoline units are commonly found in biologically relevant compounds and drug candidates displaying a remarkable variety of activities.\cite{1} The related perhydroisoindol-4-ones have also found applications as core scaffolds or synthetic intermediates in medicinal chemistry.\cite{2} Common synthetic strategies toward saturated fused bicyclic amines of this class mainly involve the 1,3-dipolar cycloaddition of azomethine ylides on suitable cyclic olefins\cite{3,4} or Diels-Alder type reactions on maleimide.\cite{5,6}

Scheme 1 Synthetic approaches to perhydroisoindol-4-one scaffolds.

A new, alternative and practical synthesis of hexahydro-4H-isoinol-4-one derivatives is reported hereafter, based on phosphine catalyzed [3+2] cyclizations\cite{7} which involve imines and dienes as the two atom and three atom components respectively. The method has been unexpectedly brought to light while expanding the scope of the recently disclosed reaction between electron-poor conjugated dienes and imines, under phosphine catalysis, shown in Scheme 2.\cite{6} In this reaction, starting from acyclic conjugated dienes properly activated by electron-withdrawing groups on both ends, 3-pyrrolines were produced.\cite{6} The cyclization took place selectively on the double bond substituted by the ester function, following to formal activation of this bond by the nucleophilic phosphine.

Scheme 2. Synthesis of pyrrolines from conjugated dienes and imines under phosphine catalysis.\cite{6}

As a logical extension of this previous work, the same strategy has been applied then to conjugated dienes where one of the double bonds is embedded in a cyclic moiety. These experiments have allowed an
efficient access to the hexahydroisoindol-4-one scaffolds 3 to be implemented, as shown hereafter.

2 Results and Discussion

With the purpose of expanding the scope of the phosphine promoted annulations reactions between imines and conjugated dienes shown in Scheme 2,[7] we have considered the known 3-(2-methoxy-carbonylvinyl)-2-cyclo-hexenone 1a[9] as a model substrate for initial studies. Diene 1a has been reacted with N-tosyl-benzaldimine in the presence of trivalent phosphines as nucleophilic catalysts (Scheme 3). A clean reaction took place indeed, leading to the bicyclic pyrroline 3a, whose formation has been optimized by a rapid screening of catalysts (PBu₃, PMe₃, PMe₂Ph, PMePh₂, PPh₃, P(t-Bu)₃) and reaction conditions. The optimized conditions include the use of PBu₃ as the catalyst, a 2:1 imine:diene ratio, polar solvents (methyl ethyl ketone or t-BuOH) and a reaction temperature of 80°C. In MEK, with a 10 mol% amount of the phosphorus catalyst, total conversion could be attained after 18h.

Scheme 3. Phosphine promoted annulation between the cyclic diene 1a and imine 2a.

The molecular structure of 3a has been assigned at first by NMR and unambiguously established then by X-ray crystallography on the corresponding hydrazone 3a' (Figure 1).[10] NMR and structural data indicate that the reaction affords exclusively the syn isomer of the bicyclic fused pyrroline, with total chemo- and stereoselectivity.

Figure 1. X-ray crystal structure of hydrazone 3a'.

The outcome of this cyclization reaction highlights a striking chemodivergent behaviour of the cyclic diene 1a with respect to the acyclic analogue I, as far as cyclization takes place on the enone function of 1a while it was shown to take place on the enone function of I. This result rises some mechanistic concerns which will be discussed briefly in final section of this paper.

Since a variety of hexahydroisoindol-4-ones might be easily available from simple starting materials following the synthetic strategy typified in Scheme 1, we next examined the scope of this catalytic process. Representative results are depicted in Table 1. The cyclization reaction can be performed with tosylimines bearing substituted aryls, heteroaryls (entry 3) and alkyl groups (entry 7). It also tolerates p-chloro- and p-nitro phenylsulfonyl activating groups on the nitrogen atom (entries 8, 9), while N-DPP imines failed to react. Most reactions take place at 80°C with a 10 mol% amount of PBu₃, but in some cases it may be advantageous to increase the catalyst amount or the temperature in order to increase the conversion rates. Both methyl ethyl ketone (MEK) and t-BuOH are suitable solvents. According to NMR analyses, the crude final mixtures contain 3 and, possibly, some residual starting material, with only minor amounts of side products.

Table 1. Phosphine promoted synthesis of the hexahydroisoindol-4-ones 3: variations of the imine partner.

<table>
<thead>
<tr>
<th>Imine</th>
<th>R</th>
<th>R'</th>
<th>PBu₃ %</th>
<th>Prod.</th>
<th>Yield %[a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2b</td>
<td>4-Cl-C₆H₄</td>
<td>Ts</td>
<td>10</td>
<td>3b</td>
</tr>
<tr>
<td>2</td>
<td>2c</td>
<td>4-CF₃-C₆H₄</td>
<td>Ts</td>
<td>30</td>
<td>3c</td>
</tr>
<tr>
<td>3</td>
<td>2d</td>
<td>2-thienyl</td>
<td>Ts</td>
<td>10</td>
<td>3d</td>
</tr>
<tr>
<td>4</td>
<td>2e</td>
<td>4-MeO-C₆H₄</td>
<td>Ts</td>
<td>30</td>
<td>3e</td>
</tr>
<tr>
<td>5</td>
<td>2f</td>
<td>1-naphthyl</td>
<td>Ts</td>
<td>10</td>
<td>3f</td>
</tr>
<tr>
<td>6</td>
<td>2g</td>
<td>p-N-O₂-C₆H₄</td>
<td>Ts</td>
<td>30</td>
<td>3g</td>
</tr>
<tr>
<td>7</td>
<td>2h</td>
<td>i-Pr</td>
<td>Ts</td>
<td>30</td>
<td>3h</td>
</tr>
<tr>
<td>8</td>
<td>2i</td>
<td>Ph</td>
<td>4-Cl-PhSO₂</td>
<td>10</td>
<td>3i</td>
</tr>
<tr>
<td>9</td>
<td>2j</td>
<td>Ph</td>
<td>4-NO₂-PhSO₂</td>
<td>10</td>
<td>3j</td>
</tr>
</tbody>
</table>

[a] Conditions: reactions have been performed at a 0.3 mmol scale, under Ar, in degassed MEK (1 mL, entries 1-5 and 8) or t-BuOH (1 mL, entries 6, 7, 9); diene:imine ratio = 1:1.5, unless otherwise stated. [b] Reaction temperature: 100°C. [c] diene:imine ratio = 1:2. [d] Diene:imine ratio = 1:3

The fused bicyclic pyrrolines 3b-j were obtained as single isomers which have been assigned as the syn isomers by analogy to 3a, based on their typical ¹H NMR pattern. The two NCH units display signals at δ = 5.6 (d, J ~ 1.2 Hz, NCHAr) and 5.0 ppm, while the chemical shifts of the CH₂-CO₂Me units are at about
3 ppm (AB system with $J_{HH}$ = 16 Hz, $J_{HH}$ = -4 and -8 Hz).

Further efforts have been directed then toward modulation of the withdrawing group of the diene moiety (Scheme 4). Dienes 5a-e bearing keto, amido, cyano and diethylphosphoryl functions on the external double bond, have been prepared by Heck reaction from either 3-tosyloxy- or 3-bromo-2-cyclohexenones and suitably functionalized olefins. They have been reacted then with N-tosylbenzaldimine in the presence of PBu$_3$ in MEK.

![Scheme 4](image)

Scheme 4. Synthesis of hexahydroisoindol-4-ones with various functional groups tethered to the 1-position.

Compared to 1a, the new dienic substrates 5 displayed lower reactivity, nevertheless the desired hexahydroisoindol-4-ones 6 could be obtained in moderate to good yields for reactions carried out at 100°C, with about 30 mol% catalyst.$^{[11]}$ In these reactions also, the final products were isolated as single isomers.

In additional experiments, variation of the ring size of the dienic substrate has been attempted by considering the five-member cyclic diene 7 as a possible reaction partner. Diene 7 has been prepared by Heck reaction between methyl acrylate and 3-iodocyclopent-2-enone,$^{[12]}$ with Pd(OAc)$_2$/Ph$_3$P(CH$_2$)$_2$PPh$_2$ as the catalyst. In the usual conditions, the reaction of 7 with N-tosylbenzaldimine failed to give the expected pyrrole displaying a bicyclo[3.3.0] scaffold. It produced however the aza-Morita-Baylis-Hillman adduct 8 in 70% yield.

![Scheme 5](image)

Scheme 5. Aza-Morita-Baylis-Hillman type reaction of vinylcyclopentenone 7 and N-tosylbenzaldimine.

The aza-MBH reaction takes place selectively on the enone function, despite the fact that this will involve formal activation of a trisubstituted double bond by the phosphorus nucleophile. As far as we know, this is an unprecedented example of phosphine promoted aza-MBH reaction on a $\beta$-substituted cyclic enone.

In summary, results in Scheme 5 show that, in the case of cyclopentenone derivatives, the annulation reaction is no longer competitive with the direct elimination of the phosphine leading to the classical aza-MBH adduct. Therefore, the application field of our method is restricted so far to the synthesis of the [4.3.0]-bicyclic moiety of isoindolines.

Finally, in order to expand the synthetic utility of the method, we have checked the feasibility of nitrogen deprotection in the final bicyclic product. To this end, we have considered the $N$-nosyl protected tetrahydrosindolone 3j, since mild deprotection protocols are known for the nosyl group. The nosyl group could be removed actually by reaction of 3j with thiophenol in the presence of sodium carbonate (Scheme 6).$^{[13]}$

![Scheme 6](image)

Scheme 6. Removal of the nosyl protecting group from isoindoline 3j.

The final secondary amine has been isolated from the crude reaction mixture, in pure form and good yield (66%), by extraction in acid solution. NMR data show that the bicyclic pyrroline ring is retained during the deprotection procedure.

**Mechanistic considerations**

On a mechanistic point of view, the most straightforward pathway for building the tetrahydrosindolines 3 (or 6) would involve addition of the phosphorus nucleophile to the intracyclic double bond of 1 or 5 (path a in Scheme 7), followed by nucleophilic addition of A to the imine. Intermediate A1 should undergo then an intramolecular Michael type addition leading to A2. A formal [1,4]-proton shift will then convert A2 into A3 and create a negative charge $\beta$-to the phosphorus centre. The phosphine elimination step achieves the cyclization process. This mechanism implies the preferential activation of the internal, trisubstituted double bond of the starting diene, vs. activation of the disubstituted enolate function via intermediate B (Scheme 7b). This is rather unexpected, especially when considering that the related phosphine promoted aza-Morita-Baylis-Hillman reactions seldom apply to $\beta$-substituted Michael acceptors.$^{[14,15]}$
Therefore, in order to get additional information on possible reaction intermediates, the cyclization between 5a and 2a has been performed in the presence of excess D₂O, as shown in Scheme 8. Since H-shifts are known to be mediated by traces of water,[10] deuterium is expected to be incorporated on all positions involved in H-shift processes.

Scheme 8. Cyclization reaction in the presence of D₂O

The sample of 6a isolated from this experiment contains a significant amount of deuterium (70%) at the methylene carbon α to the COMe group. This was fully anticipated, due to the postulated formation of intermediate A2. However, deuterium has been partially incorporated also at the C1 carbon of 6a (30%) while the C3 moiety contains only protons. The mechanism shown in Scheme 7a does not account, by itself, for the observed deuterium distribution, since it does not involve H-exchanges at the C1 carbon. Therefore, less straightforward mechanisms can’t be excluded so far, which might involve initial addition of the phosphorus catalyst to other sites of the dienic moiety.

According to Hückel and quantum chemical calculations, the LUMO orbital of conjugated dienes such as 1a or 5a is distributed along the dienic unit, with roughly identical coefficients on the four atoms (Figure 2).

Figure 2. LUMO coefficients for the dienic carbon atoms at the HF and Hückel (in bracket) levels (top) and qualitative view of the LUMO at the DFT level (bottom) for A) 1a and B) 5a.

Consequently, the zwitterionic species B, C and D (Scheme 7b) might also be formed by addition of the nucleophilic phosphate to the α, γ and δ positions of the dienic ketone. They might enter a catalytic cycle or, alternatively, their reversible formation might induce H/D exchange reactions accounting for the observed D-distribution in the final product 6a (Scheme 8).

The reversible addition of tributylphosphate to the diene has been evidenced by the H/D exchange experiment shown in Scheme 9.

Scheme 9. PBu₃-promoted, H/D exchange reactions.

When 5a was stirred at r.t. in the presence of PBu₃ and D₂O, deuterium has been incorporated in comparable amounts on the α, γ and δ carbons of the starting dienic unit. Thus, experimental data and calculations support the hypothesis of an initial, reversible addition of the phosphorus nucleophile to various positions of the dienic substrate generating different zwitterionic adducts. The reaction outcome will be determined then at a later step of the catalytic cycle. Additional studies are required to enlighten the precise mechanism of these cyclization reactions.

3 Conclusion

This work demonstrates that the phosphine-mediated organocatalytic annihilations between 3-vinylcyclohexenones and N-arylsulfonylimines produce hexahydroisoindol-4-ones with various functional groups connected to the C1-carbon by a CH₂ spacer. This represents a new, easy and
stereoselective access to isoidoline derivatives with an unprecedented substitution scheme. Insights into the reaction mechanism have been obtained from deuteration experiments and DFT calculations which demonstrate the reversible addition of the phosphorus catalyst to the dienic unit.

The method proved unsuitable for the direct synthesis of the analogous 2-aza-bicyclo[3,3,0] units from cyclpentenone derivatives. Cyclic substrates with different ring sizes are now considered in ongoing studies.

**Experimental Section**

**Synthesis of the conjugated dienes 1, 5 and 7 via Heck reactions.** (a) Dienes 1a and 5a,c,e have been prepared from tosylate 4a according to the reported method.[3] Representative procedure: A mixture of tosylate 4a (4.0 g, 15 mmol), a suitable olefine H₂C=CH₂ (22 mmol), Et₃N (3.3 mL, 24 mmol), Pd(OAc)₂ (50.6 mg, 0.22 mmol) and PPh₃ (50.6 mg, 0.22 mmol) in degased N,N-dimethylacetamide (11 mL) / DMF (4.5 mL) was heated at 105°C under argon for 24 h. The reaction mixture was then concentrated to a small volume. The final product was purified by column chromatography on silica gel.

(E)-N,N-dimethyl-3-(3-oxocyclohex-1-enyl)acrylamide (5c) has been obtained in 59% yield (0.85 g, 4.4 mmol) from tosylate 4a (2.0 g, 7.5 mmol) and N,N-dimethyl acrylamide (1.1 g, 11 mmol) (Method a). The final product has been purified by column chromatography with ethyl acetate (Rₑ = 0.2) as the eluent. ¹H NMR (CDCl₃): δ 7.27 (d, J = 15.6 Hz, 1H), 6.69 (d, J = 15.6 Hz, 1H), 6.11 (s, 1H), 3.10 (s, 3H), 3.01 (s, 3H), 2.50-2.39 (m, 4H), 2.09-2.00 (m, 4H), 3.10 (s, 3H), 2.40-2.29 (m, 4H), 2.24-2.00 (m, 4H).

Phosphine promoted cyclization reactions. General Procedure: PBu₃ (25-75 μmol) was added to a mixture of diene (0.25 mmol) and imine (0.50 mmol) in methyl ethyl ketone (or t-BuOH) (1mL) under argon. The mixture was heated overnight (18h) at the given temperature (see Schemes 3, 4 and Table 2). Conversion rates were determined on the crude mixture by ¹H NMR, with 1,3,5-trimethoxybenzene as the internal standard. After evaporation of the solvent, the final product was purified by column chromatography on silica gel.

Methyl 2-(3-phenyl-4-oxo-2-tosyl-2,3,4,5,6,7-hexahydro-1H-isindol-1-yl)acetate (3a). Compound 3a was obtained in 90% yield (98 mg) after purification with an heptane/ethyl acetate gradient (Rₑ = 0.3 in heptane/ethyl acetate 1:1). ¹H NMR (CDCl₃): δ 6.66 (d, J = 8.2 Hz, 2H), 7.3-7.2 (7H), 5.61 (d, J = 1.2 Hz, 1H, N-CH₂), 5.03 (br, m, NCH), 3.74 (s, 3H, OMe), 3.17 (dd, J = 15.9 and 4.0 Hz, 1H, CH₂-O-Me), 2.93 (d, J = 15.9 and 7.9 Hz, 1H, CH₂-CH₂-Me), 2.42 (s, Me), 2.4-2.2 (m, 4H), 2.0-1.9 (m, 2H); ¹³C NMR (CDCl₃): δ 194.4 (CO), 170.7 (CO-Me), 158.5 (C=C-CO), 144.0 (C), 139.9 (C), 135.0 (C), 134.4 (C), 129.8, 127.8, 127.7, 127.6, 68.2 (NCH₂Ph), 65.6 (NCH), 32.1 (O-Me), 40.1 (CH₂-CO-Me), 37.7 (CH₂-CO), 23.6, 22.9, 21.5 (Me) ppm. HRMS (ESI) calc. for C₂₃H₂₂NO₂ [M+Na]⁺: 462.1351, found: 462.1360. IR (neat) ν = 1732, 1673 cm⁻¹.

Methyl 2-(3-(4-chlorophenyl)-4-oxo-2-tosyl-2,3,4,5,6,7-hexahydro-1H-isindol-1-yl)acetate (3b). Compound 3b was obtained in 93% yield (110 mg) after purification with an heptane/ethyl acetate gradient (Rₑ = 0.3 in cyclohexane/ethyl acetate 1:1). ¹H NMR (CDCl₃): δ 7.65 (d,
Methyl 2-(4-oxo-2-tosyl-3-(4-(trifluoromethyl)phenyl)-2,3,4,5,6,7-hexahydro-1H-isindol-1-yl)acetate (3c) was obtained in 78% yield after purification with an heptane/ethyl acetate gradient. 1H NMR (CDCl₃): δ 7.55 (d, J = 8.2 Hz, 2H), 7.41 (d, J = 8.5 Hz, 2H), 7.34 (d, J = 8.5 Hz, 2H), 7.20 (d, J = 8.2 Hz, 2H), 5.58 (br, m, 1H, N-CHAr), 5.0 (br, m, 1H NCH), 3.70 (s, 3H, OMe), 3.13 (dd, J = 16.0 and 4.1 Hz, 1H, CH₂CO₂Me), 2.97 (dd, J = 16.0 and 7.4 Hz, 1H, CH₂CO₂Me), 2.36 (s, 3H, Me), 2.3-2.2 (m, 4H), 2.0-1.9 (m, 2H); 13C NMR (CDCl₃): δ 194.4 (CO), 170.7 (CO₂Me), 159.2 (C=CH₂Ar), 144.6 (C=CH₂), 135.0 (C), 134.7 (C), 130.0 (C), 127.8, 127.0, 126.6, 125.2, 65.5 (NCHAr), 65.2 (NCH), 52.2 (OMe), 40.4 (CH₂CO₂Me), 37.8 (CH₂CO₂), 23.8, 23.0, 21.6 (Me) ppm. HRMS (ESI) calc. for C₂₃H₂₆F₃NO₃S [M+Na]+: 496.0961, found: 496.0950. IR (neat) ν 1732, 1675 cm⁻¹.

Methyl 2-(3-(naphthalen-1-yl)-4-oxo-2-tosyl-2,3,4,5,6,7-hexahydro-1H-isindol-1-yl)acetate (3f) was obtained in 83% yield (101 mg) after purification with an heptane/ethyl acetate gradient. 1H NMR (CDCl₃): δ 8.22 (d, J = 8.6 Hz, 1H), 7.66 (d, J = 8.6 Hz, 1H), 7.57 (d, J = 7.5 Hz, 1H), 7.46 (d, J = 8.6, 6.9 and 1.6 Hz, 1H), 7.4-7.3 (m, 3H), 7.2-7.1 (m, 2H), 6.85 (d, J = 8.6 Hz, 2H), 6.36 (br, m, 1H, N-CHAr), 5.20 (br, m, 1H NCH), 3.71 (s, 3H, OMe), 3.23 (dd, J = 15.9 and 3.8 Hz, 1H, CH₂CO₂Me), 3.06 (dd, J = 15.9 and 7.9 Hz, 1H, CH₂CO₂Me), 2.4-2.2 (m, 4H), 2.15 (s, 3H, Me), 2.0-1.9 (m, 2H); 13C NMR (CDCl₃): δ 194.2 (CO), 171.1 (CO₂Me), 157.5 (C=CH₂Ar), 143.7 (C), 136.5 (C), 136.2 (C), 134.4 (C), 133.6 (C), 131.4 (C), 129.2, 128.5, 128.0, 126.0, 125.6, 125.0, 123.4, 65.4 (NCHAr), 63.2 (NCH), 52.2 (OMe), 40.1 (CH₂CO₂Me), 37.8 (CH₂CO₂), 23.8, 23.3, 21.5 (Me) ppm. HRMS (ESI) calc. for C₂₃H₂₆F₃NO₃S [M+Na]+: 512.1508, found: 512.1500. IR (neat) ν 1734, 1677 cm⁻¹.

Methyl 2-(3-(4-nitrophenoxy)-4-oxo-2-tosyl-2,3,4,5,6,7-hexahydro-1H-isindol-1-yl)acetate (3g) was obtained in 47% yield (57 mg) after purification with an heptane/ethyl acetate gradient. 1H NMR (CDCl₃): δ 8.04 (d, J = 8.8 Hz, 2H), 7.59 (d, J = 7.6 Hz, 2H), 7.46 (d, J = 8.8 Hz, 2H), 7.21 (d, J = 7.6 Hz, 2H), 5.59 (d, J = 2.4 Hz, 1H, N-CHAr), 4.96 (br, m, 1H NCH), 3.72 (s, 3H, OMe), 2.96 (dd, J = 16.1 and 3.9 Hz, 1H, CH₂CO₂Me), 3.15 (dd, J = 16.1 and 7.3 Hz, 1H, CH₂CO₂Me), 2.38 (d, J = 3.9 Hz, 1H, CH₂CO₂Me), 2.15-2.0 (m, 4H), 2.0-1.9 (m, 2H); 13C NMR (CDCl₃): δ 194.3(CO), 170.7 (CO₂Me), 159.7 (C=CH₂Ar), 147.3 (C), 144.8 (C), 134.3 (C), 133.8 (C), 130.2 (C), 128.9, 128.1, 123.6, 67.7 (NCHAr), 65.9 (NCH), 52.4 (OMe), 39.8 (CH₂CO₂Me), 37.7 (CH₂CO₂), 23.8, 22.9, 21.7 (Me) ppm. HRMS (ESI) calc. for C₂₃H₂₆NO₃S [M+Na]+: 507.1202, found: 507.1187. IR (neat) ν 1733, 1676 cm⁻¹.

Methyl 2-(3-(4-isopropylthio)-4-oxo-2-tosyl-2,3,4,5,6,7-hexahydro-1H-isindol-1-yl)acetate (3h) was obtained in 71% yield (72 mg) after purification with an heptane/ethyl acetate gradient. 1H NMR (CDCl₃): δ 7.67 (d, J = 8.3 Hz, 2H), 7.26 (d, J = 8.3 Hz, 2H), 4.76 (dd, J = 8.9, 4.0 and 1.2 Hz, 1H), 4.57 (d, J = 2.2 Hz, 1H, N-CHAr), 3.72 (s, 3H, OMe), 3.04...
(dd, J = 16.3 and 4.2 Hz, 1H, CH$_2$CO$_2$Me), 2.66 (dd, J = 16.3 and 8.8 Hz, 1H, CH$_2$OH), 2.38 (s, 3H Me), 2.3-2.2 (m, 1H), 1.9-1.8 (m, 1H), 0.97 (d, J = 7.0 Hz, 3H, Me) 0.97 (d, J = 0.7 Hz, 3H, Me) 13C NMR (CDCl$_3$): δ 195.2 (CO), 171.2 (CO$_2$Me), 159.2 (C=C-CO), 144.1 (C), 135.2 (C), 133.8 (C), 130.0, 128.0, 71.1 (NCHAr), 65.7 (CO), 52.3 (OMe), 40.6 (CH$_2$CO$_2$Me), 37.9 (CO), 32.8, 23.1, 21.7, 19.7, 18.8 (Me ppm). HRMS (ESI) calcd. for C$_{32}$H$_{39}$N$_2$O$_7$S [M+Na$^+$]: 428.1508; found: 428.1501. IR ( neat) v 1735, 1672 cm$^{-1}$.

1-(2-Oxo-2-phenylethyl)-3-phenyl-2-tosyl-2,3,4,5,6,7-hexahydro-1H-isooindol-4(5H)-one (6b) was obtained in 47% yield (57 mg) after purification with an heptane/ethyl acetate gradient ($R_f$ = 0.3 in cyclohexane/ethyl acetate 1:1). 1H NMR (CDCl$_3$): δ 7.9-7.8 (m, 1H), 7.7-7.6 (m, 1H), 7.6-7.5 (m, 2H), 7.5-7.4 (m, 1H), 7.4-7.3 (m, 2H), 7.3-7.1 (m, 7H), 5.47 (d, J = 1.7, 1H, N-CH$_2$Ar), 5.17 (dd, J = 8.9 and 3.0 Hz, 1H, NCH), 3.76 (dd, J = 17.4 and 3.1 Hz, 1H, CH$_2$CO$_2$Ar), 3.44 (dd, J = 17.4 and 8.9 Hz, 1H, CH$_2$CO$_2$Ar), 2.29 (s, 3H Me), 2.2-2.1 (m, 4H), 2.0-1.8 (m, 2H). 13C NMR (CDCl$_3$): δ 197.4 (COAr), 194.6 (CO), 159.8 (C=C- CO), 144.2 (C), 140.4 (C), 134.0 (C), 130.1 (C), 129.0, 128.5, 128.0, 127.7, 126.6, 68.2 (NCHAr), 65.2 (NCH), 45.3 (CH$_2$CO$_2$Ar), 37.9 (CH$_2$CO$_2$), 24.2, 23.1, 21.7 (Me ppm). HRMS (ESI) calcd. for C$_{32}$H$_{39}$N$_2$O$_7$S [M+Na$^+$]: 508.1539; found: 508.1582. IR ( neat) v 1671 cm$^{-1}$.

N,N-Dimethyl-2-(4-oxo-3-phenyl-2-tosyl)-2,3,4,5,6,7-hexahydro-1H-isooindol-1-ylacetamide (6c) was obtained in 68% yield (77 mg) after purification with an heptane/ethyl acetate gradient ($R_f$ = 0.3 in cyclohexane/ethyl acetate 1:1). 1H NMR (CDCl$_3$): δ 7.68 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.0 Hz, 1H), 7.3-7.1 (m, 5H), 6.86 (d, J = 8.0Hz, 1H), 5.44 (br, m, 1H, N-CH$_2$Ar), 4.90 (br, m, 1H, NCH), 3.0-2.9 (m, 2H, CH$_2$CONMe$_2$), 2.90 (s, 3H, NMe$_2$), 2.64 (s, 3H, NMe$_2$), 2.55 (s, 3H, Me$_2$), 2.2-1.8 (m, 6H). 13C NMR (CDCl$_3$): δ 194.7 (CO), 169.5 (CH$_2$CONMe$_2$), 160.7 (C=C-CO), 144.3 (C), 140.4 (C), 134.3 (C), 133.7 (C), 130.1 (C), 128.3, 128.0, 127.9, 68.1 (NCHAr), 66.9 (NCH), 39.1 (CH$_2$CONMe$_2$), 37.8 (NMe$_2$), 35.7 (NMe$_2$), 24.3, 23.1, 21.7 (Me ppm). HRMS (ESI) calcd. for C$_{32}$H$_{39}$N$_2$O$_7$S [M+Na$^+$]: 475.1668; found: 475.1662. IR ( neat) v 1674, 1643 cm$^{-1}$.

2-(4-Oxo-3-phenyl-2-tosyl-2,3,4,5,6,7-hexahydro-1H-isooindol-1-ylacetamidinonitrile (6d) was obtained in 32% yield (32 mg) after purification with an heptane/ethyl acetate gradient ($R_f$ = 0.3 in cyclohexane/ethyl acetate 1:1). 1H NMR (CDCl$_3$): δ 7.44 (d, J = 8.3 Hz, 2H), 7.3-7.2 (m, 2H), 7.1-7.0 (m, 5H), 5.46 (d, J = 2.3 Hz, 1H, N-CH$_2$Ar), 4.73 (br, m, 1H, NCH), 3.0-2.9 (m, 2H, CH$_2$CN), 2.26 (s, 3H, Me), 2.2-2.1 (m, 4H), 2.0-1.9 (m, 2H). 13C NMR (CDCl$_3$): δ 194.0 (CO), 154.9 (C=C-CO), 144.6 (C), 138.8 (C), 136.7 (C), 134.3 (C), 130.0 (C), 128.4 128.2, 128.1, 127.9, 116.7 (CN), 68.7 (NCHAr), 64.6 (NCH), 37.9 (CH$_2$CN), 23.9, 23.1, 21.7 (Me ppm). HRMS (ESI) calcd. for C$_{32}$H$_{39}$N$_2$O$_7$S [M+Na$^+$]: 429.1249; found: 429.1258. IR ( neat) v 1676, 2220 cm$^{-1}$.
Diethyl (4-Oxo-3-phenyl-2-tosyl-2,3,4,5,6,7-hexahydro-1H-isooindol-1-yl)methylphosphonate (6e) was obtained in 41% yield (53 mg) after purification with an heptane/ethyl acetate gradient (RI = 0.3 in cyclohexane/ethyl acetate 1:1). H NMR (CDCl3): δ 5.77 (d, J = 8.4 Hz, 2H), 7.2-7.1 (m, 3H), 5.44 (br, m, 1H, N-CH=N), 4.76 (br, m, 1H, NCH), 4.1-3.9 (m, 4H, OCH3), 2.7-2.5 (m, 2H, CH3-PO(=O)(Et)), 2.29 (s, 3H, Me), 2.2-2.0 (m, 4H), 1.3-1.2 (m, 6H, OCH2CH2), 1.55 (t, J = 8.4 Hz, 3CH3), 1.59 (t, J = 8.4 Hz, 3CH3), 1.49 (t, J = 8.4 Hz, 3CH3), 1.48 (t, J = 8.4 Hz, 3CH3), 1.47 (t, J = 8.4 Hz, 3CH3), 1.46 (t, J = 8.4 Hz, 3CH3). C NMR (CDCl3): δ 194.7 (CO), 159.5 (C=O), 144.2 (C), 140.0 (C), 135.3 (C), 134.3 (C), 130.1 (C), 128.4, 128.0, 127.9, 127.7, 68.0 (NCH=N), 64.3 (NCH3), 62.0 (d, J = 6.6 Hz, OCH3), 37.8, 34.2, 32.4 (CH3-PO(=O)(Et)), 29.8, 24.1, 23.2, 16.4 (d, J = 6.0 Hz, Me), 16.3 (d, J = 6.0 Hz, Me), ppm. 31P NMR (CDCl3): 25.5. HRMS (ESI) calcd. for C17H16NO5PS [M+Na]+: 540.1586, found: 540.1597. IR (neat) ν 1676 cm⁻¹.

N-Deprotection procedure: Synthesis of methyl (1S*,3R*)-4-oxo-3-phenyl-2,3,4,5,6,7-hexahydro-1H-isooindol-1-yl-acetate (3j). To a solution of methyl [(1S*,3R*)-2-[(4-nitrophenoxy)sulfonyl]-4-oxo-3-phenyl-2,3,4,5,6,7-hexahydro-1H-isooindol-1-yl]acetate 3j (30 mg, 0.06 mmol) and K2CO3 (35 mg, 0.25 mmol, 4.0 equiv.) in CH3CN-DMSO (95:5) (1 mL) at room temperature was added PhSH (23 μL, 0.22 mmol). The reaction mixture was heated at 40°C for 2 h. The crude mixture was diluted with AcOEt (10 mL) and HCl 1N (10 mL) and the layers were separated. The aqueous layer was basified with solid K2CO3 (pH 10-11) and extracted with AcOEt (3×10 mL). The combined organic extracts were dried over MgSO4, filtered, and concentrated in vacuo to provide 3j (12 mg, 66%). H NMR (CDCl3): δ 7.34 (d, J = 7.1 Hz, 2H), 7.30 (d, J = 7.1 and 6.9 Hz, 2H), 7.22 (t, J = 6.9 Hz, 1H), 7.25 (s, 1H, N-CPh3), 4.39 (dq, J = 4.4 and 4.1 Hz, 1H, NCH3), 3.71 (s, 3H, OMe), 2.79 (dq, J = 15.6 and 4.1 Hz, 1H, CH2-COMe), 2.60 (dd, J = 15.6 and 4.1 Hz, 1H, CH2-COMe), 2.51-2.30 (m, 4H), 2.22 (br, s, NH), 1.55-1.26 (m, 2H). C NMR (CDCl3): δ 195.6 (CO), 171.8 (CO2Me), 162.3 (C=CO), 143.6 (C), 138.2 (C), 128.2, 127.5, 127.2, 65.7 (NCHPh), 63.1 (NCH), 51.9 (OMe), 41.0 (CH2-COMe), 38.2 (CH2-COMe), 23.8, 23.5 ppm. HRMS (ESI) calcd. for C12H12N2O2 [M+H]+: 286.1443, found: 286.1449. IR (neat) ν 1733, 1669 cm⁻¹.

Computational methods. Geometry optimization was carried out on the B97-D level of theory using the def2-TZVP basis set. These calculations were accelerated using the Multipole Accelerated Resolution of Identity for J (MARI-J) approximation method, as implemented in Turbomole 6.2. LUMO energies have been determined using the gOpenMol 3.00 package. The molecular orbital coefficients have been computed at the HF/STo3-G level, based on the DFT gas-phase geometries. Hückel calculations were carried out with the Hückel simple program.[25]

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References


[10] CCDC-786106 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax (+44) 1223-336033; e-mail deposit@ccdc.cam.uk) or via www.ccdc.cam.ac.uk/data_request/cif

[11] Portionwise addition of the phosphine, i.e. 15-20 mol% at the beginning of the reaction and again after 8h heating, can be applied to increase conversion rates.


An Easy Stereoselective Synthesis of Hexahydroisoindol-4-ones under Phosphine Catalysis.


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