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An approach to substituted dihydroisoquinolin-1(*2H*)-ones from Baylis–Hillman adducts

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Abstract—In this communication we describe an easy and straightforward alternative method for the preparation of 3,4-substituted isoquinolin-1(*2H*)-ones, using Baylis–Hillman adducts as starting material.
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Isoquinolinones are important compounds from both the synthetic and applied points of view. Their structures are incorporated in several alkaloids[1] and other pharmacologically important compounds.[2] Isoquinolinones have already been employed as useful intermediates in the synthesis of indenoisoquinolines,[3] protoberberines,[4,5] and dibenzoquinolizines[5] and are also of interest in medicinal chemistry.[6]

Due to their biological and pharmacological importances, several methods have been reported for the synthesis of isoquinolinones.[1d] Most of these methods involve the use of either a preformed isoquinoline or homophthalic acid, which is in turn obtained by a several step sequence.[7] Isoquinolines are converted into isoquinolinones by a further two-step sequence either through isoquinolium salts and their oxidation with different reagents,[8] or by photolysis of isoquinoline N-oxide.[9] Homophthalic acids are transformed into isoquinolinones via isocoumarins or isoquinolone-4-carboxylic acid,[7] or via homophthalimide.[7f,10]

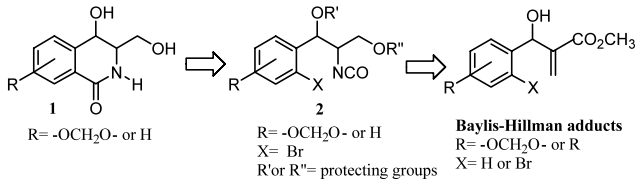
Lithiated phthalides undergo cyclocondensation reactions with benzaldimines to give isoquinolinones with good chemical yields. This strategy has been used to prepare a mixture of *cis*/*trans* 3,4-disubstituted dihydroisoquinolinones.[11] Intermolecular Diels–Alder reactions were also used as the key step for the preparation of substituted isoquinolinones.[11c,d]

In an ongoing research program directed to the utilisation of Baylis–Hillman adducts as versatile starting materials for the synthesis of different classes of natural and non-natural products[12] we envisaged developing an alternative strategy to prepare substituted isoquinolinones.

The widespread occurrence of the isoquinolinone unit in several classes of alkaloids, associated with the medicinal interest in this class of compounds, easily justifies the need for new approaches for the synthesis of isoquinolinones. In this comunication, we describe an alternative, easy and direct method for the preparation of 3,4-disubstituted isoquinolinones from Baylis–Hillman adducts.

The reaction sequence to achieve our target is outlined in Scheme 1. 3,4-Disubstituted dihydroisoquinolinones such as **1** could be easily prepared via an intramolecular acylation with isocyanate **2**, which in turn could be readily produced from a Baylis–Hillman adduct in a 6 steps sequence.

The Baylis–Hillman reaction[13] of piperonal (**3**), 6-bromopiperonal (**4**) and 2-bromobenzaldehyde (**5**) with methyl acrylate, in the presence of ultrasound[14] provides the adducts **6**, **7** and **8**, with good chemical yields (Scheme 2 and Table 1). In the next step of our



Scheme 1. Retrosynthetic analysis towards the dihydroisoquinolinone core.

Keywords: Baylis–Hillman; dihydroisoquinolinone; heterocycles.
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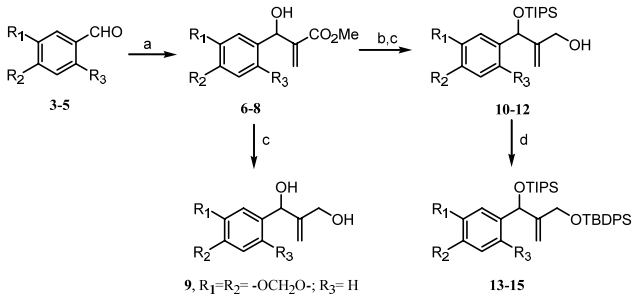
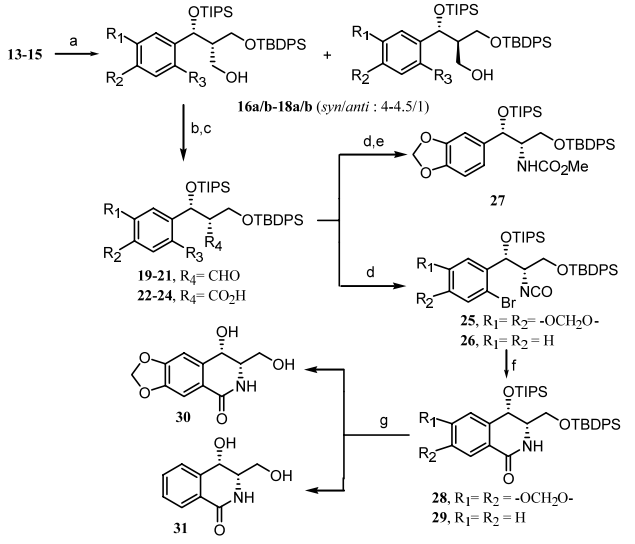


Scheme 2. Preparation of the Baylis–Hillman adducts. *Reagents and conditions*: (a) methyl acrylate, ultrasound, rt, 24–72 h; (b) TIPSOTf, Et_3N, CH_2Cl_2 or 2,6-lutidine, rt, 2 h; (c) DIBAL-H, CH_2Cl_2, −78°C, 2 h; (d) TBDPSCl, DMF, imidazole, rt, 14 h.

sequence, the methyl ester group of Baylis–Hillman adducts were chemoselectively reduced. Attempts to run this reduction with DIBAL-H without protection of the secondary hydroxyl groups furnished the desired diol **9**, however with only a 50% chemical yield (Scheme 2). This problem was easily solved by protecting the secondary hydroxyl group as a silyl ether (triisopropylsilyl). Subsequent reduction with DIBAL-H provided the allyl alcohols **10**, **11** and **12**, with very good overall chemical yields (Table 1).

The preparation of the lactam ring exhibited in the isoquinolinone structures could be readily secured by an intramolecular acylation reaction using a carbamate or an isocyanate as acylating agent.[8a] Then, the allyl alcohols **10**–**12** were treated with *t*-butyldiphenylsilyl chloride in the presence of DMF to give the silyl ethers **13**, **14** and **15** (Scheme 2 and Table 1 for yields).

Subsequent hydroboration reaction of the double bond of these silyl ethers with 9-BBN gave alcohols **16a/b**, **17a/b** and **18a/b** (Scheme 3 and Table 1), as a mixture of diastereoisomers, in which the *syn* is always the major one.[12c] After separation,[15] the alcohols (**16a**, **17a** and **18a**) were treated with TPAP in the presence of NMO[16] to furnish the corresponding aldehydes **19**–**21**, which were treated with sodium chlorite to provide the acids **22**–**24** in a very good overall chemical yields (see



Scheme 3. Synthesis of dihydroisoquinolinones. *Reagents and conditions*: a. (i) 9-BBN, THF, 0°C→rt, 16–18 h; (ii) NaOH 3 mol/L, 30% H_2O_2, 0°C→rt, 1.5 h; b. TPAP, NMO, CH_2Cl_2, MS 4 Å, rt, 1 h; c. $NaClO_2$, NaH_2PO_4, *t*-BuOH, 2-methyl-but-2-ene, 0°C→rt, 4 h; d. (i) ethyl chloroformate, acetone, Et_3N, 0°C, 45 min; (ii) NaN_3, rt, 2 h; (iii) refluxing toluene, 2 h; e. refluxing methanol, 12 h; f. *t*-BuLi, THF, −78°C, 30 min; g. TBAF, THF, rt, 2 h.

Table 1. Chemical yields for the preparation of the dihydroisoquinolinones.

R_1–R_3		$R_1=R_2=CH_2OCH_2$; $R_3=H$	$R_1=R_2=CH_2OCH_2$; $R_3=Br$	$R_1=R_2=H$; $R_3=Br$
Baylis–Hillman reaction	Product	**6**	**7**	**8**
	Yield (%)[a]	73	80	78
DIBAL-H reduction	Product	**10**	**11**	**12**
	Yield (%)[a,b]	86	83	88
TBDPS protection	Product	**13**	**14**	**15**
	Yield (%)[a]	90	91	94
Hydroboration reaction	Product	**16a/b** *syn:anti*	**17a/b** *syn:anti*	**18a/b** *syn:anti*
	Yield (%)[a]	89	77	77
Oxidation reactions	Product	**22**	**23**	**24**
	Yield (%)[a,c]	86	81	88
Carbamate/isoquinolinone formation	Product	**27**	**28**	**29**
	Yield (%)[a]	60[d]	40[e]	40[e]

[a] All yields are for isolated and purified products.
[b] Yield for two steps (TIPS protection and reduction).
[c] Yields for two oxidation steps.
[d] Preparation of carbamate, overall yield for 4 steps.
[e] Overall yield for the preparation of the dihydroisoquinolinones, 4 steps.

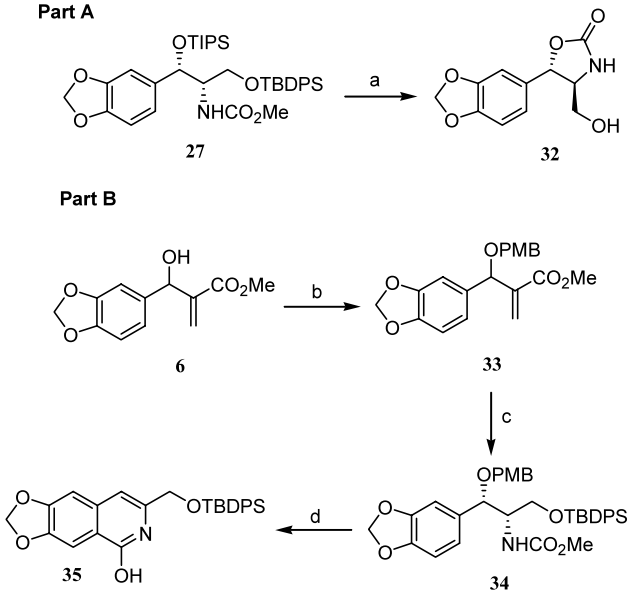
Table 1 and Scheme 3).[12c,17] Attempts to perform the oxidation directly to the corresponding carboxylic acids failed.[12c]

The acids **22**–**24** were then submitted to a Curtius rearrangement[18,19] in order to incorporate the nitrogen atom exhibited by the isoquinolinone unit. Thus, treatment of acids **22**–**24** successively with ethyl chloroformate and sodium azide gave the acylazide intermediates, which were rearranged to the corresponding isocyanates (not isolated) by refluxing in toluene.

After evaporation of the toluene, isocyanates **25** and **26** were treated in situ with *t*-butyl lithium in ethyl ether at −78°C to furnish the products **28** and **29**, with overall yields of 40% from the acids **23**/**24** (4 steps, Table 1). Removal of the protective groups with TBAF in THF at room temperature gave the 3,4-disubstituted dihydroisoquinolin-1(*2H*)-ones **30** and **31** in 76% yields (Scheme 3).[20]

Alternatively, the isocyanate generated from acid **22** was treated in refluxing methanol to give the carbamate **27** with an overall yield of 60% from the corresponding acid (4 steps). To promote the internal acylation, carbamate **27** was then treated with triflic anhydride in the presence of DMAP.[21f] The only product detected in this reaction was the disubstituted oxazolin-2-one (**32**) (Scheme 4, Part A).

To drive this reaction in the direction of the protected dihydroisoquinolin-1(*2H*)-one (**28**) we tried several different Bischler–Napieralski[12c] experimental protocols (e.g. $POCl_3$/py, $POCl_3$/toluene; P_2O_5/$POCl_3$, etc), however we were unable to detect the formation of compound **28**. Due to the lability of the silyl group in the Bischler–Napieralski protocols, we decided to change the secondary hydroxyl protective group. Instead of a silyl ether, the secondary hydroxyl of the Baylis–Hillman adduct **6** was protected as a PMB–ether (**33**). Using the same reaction sequence described above, PMB-ether (**33**) was transformed into the carbamate **34**. Attempts to perform the Bischler–Napieralski reaction with **34** gave as the only product the isoquinolol **35**, in a chemical yield of 42% (Scheme 4, Part B).



Scheme 4. Oxazolidinone and isoquinolol syntheses. *Reagents and conditions*: a. (i) Tf_2O, DMAP, CH_2Cl_2, 0°C→rt, 18 h; (ii) HCl, dioxane, rt 10 h, 45%; b. PMB trichloroacetimidate, CSA, CH_2Cl_2, 12 h, rt, 76%; c. see conditions in Schemes 2 and 3; d. $POCl_3$/Py, toluene, reflux, 1 h, 42%.

These results clearly demonstrate that it is possible to prepare disubstituted dihydroisoquinolin-1(*2H*)-ones from the Baylis–Hillman adducts **7** and **8**. The sequence is very simple, however it shows a poor to reasonable diastereoselectivity. The preliminary results obtained in our laboratory also demonstrate that this sequence can be easily scaled up. On an experimental scale, reactions with 3–10 g can be conveniently carried out. The 3,4-disubstituted dihydroisoquinolin-1(*2H*)-ones **30** and **31** were prepared in 9 steps using a multistep sequence in an overall yield of 14%.

As far as we know this is also the first report relating to the preparation of 3,4-disubstituted dihydroisoquinolin-1(*2H*)-ones from a Baylis–Hillman adduct.[22] An additional reductive step on the carbonyl group of **30** and **31** could also permit access to dihydroisoquinolines using the same sequence. Efforts to optimize some steps of this sequence are ongoing in our laboratory. Applications toward specific natural products and the further development of an asymmetric version of this strategy are currently underway and will be reported in due course.

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20. All the spectral data recorded for **30**/**31** are compatible with the proposed structure. (*syn* diastereoisomer). **30**: IR (film, ν_{max}) 3423, 3196, 1669, 1611 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 7.28 (s, 1H), 6.99 (s, 1H), 6.1 (s, 2H, CH_2OCH_2), 4.61 (d, $J=4.76$ Hz, 1H), 3.63 (br s, 2H), 3.34–3.7 (m, 1H); ^{13}C NMR (75.4 MHz, DMSO-d_6) δ 163.6, 150.9, 147.6, 137.2, 122.8, 107.9, 107.0, 102.3, 65.6, 62.3, 59.7; HRMS (70 eV, m/z) calcd. for $C_{11}H_{11}NO_5$ 237.063722; Found 237.06371; **31**: IR (film, ν_{max}): 3417, 2956, 2922, 2850, 1660, 1026, 825, 764 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 7.82 (m, 1H), 7.47 (m, 3H), 5.71 (d, $J=6$ Hz, 1H), 4.67 (d, $J=4$ Hz, 1H), 3.50 (m, 3H); ^{13}C NMR (75.4 MHz, DMSO-d_6) δ 163.9, 140.84, 140.80, 131.99, 131.92, 128.5, 127.9, 127.8, 127.7; 127.2, 126.8, 126.84, 64.76; 64.63, 59.94, 58.85; HRMS (70 eV, m/z) calcd. for $C_{10}H_{11}NO_5$ 193.2027; Found 193.1981.
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