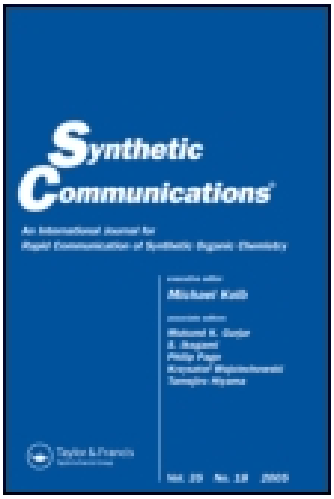

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SYNTHESIS OF ISOQUINOLINE DERIVATIVES FROM β-HYDROXYARYLETHANAMIDES

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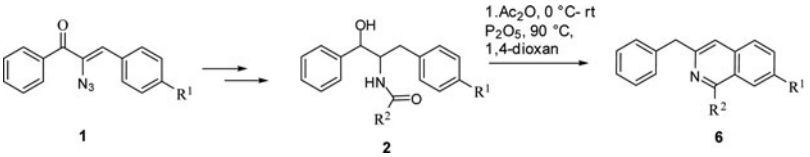
GRAPHICAL ABSTRACT



Abstract *A simple and efficient protocol for the construction of medicinally important substituted isoquinolines through intramolecular cyclization of* β*-hydroxyarylethanamides using acetic anhydride and phosphorous pentoxide in dioxane has been described. The chemo- and regioselectivities due to the influence of different catalysts were investigated and optimized for good to excellent yields. All the synthesized compounds have been characterized by NMR and mass spectral analyses.*

Keywords β-Hydroxyarylethanamide; intramolecular cyclization; isoquinolines; phosphorous pentoxide; selectivity

INTRODUCTION

The isoquinoline nucleus is a common skeleton present in different classes of alkaloids that exhibit important biological activities.[1] They also serve as building blocks in pharmaceutical compounds[2] and find application in the preparation of chiral ligands for transition-metal catalysts.[3] Many popular drugs such as emetine, morphine, papaverine, and quinocarcin contain the isoquinoline nucleus. The available methods for the construction of isoquinoline ring include the Pomeranz–Fritsch reaction,[4] Bischler–Napieralski reaction,[5] and Pictet–Splengler reaction.[6] Homophthalaldehyde, which can readily be obtained by the ozonolysis of indene, can be cyclized with ammonia to form the isoquinoline derivative in good yields.[7] Palladium-catalyzed reaction of *o*-bromoarylaldehyde with an alkyne and subsequent

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reaction with ammonia can also produce the isoquinoline derivative.[8] Recently, a new method for the synthesis of isoquinoline derivative from 2-azido-3-arylacrylates by treating them with an α-diazocarbonyl compound in the presence of triphenylphosphine has been described. The reaction involves a Wolff rearrangement, an aza-Wittig reaction, and an electrocyclic ring closure.[9] A mild and efficient one-step synthesis of substituted dihydro- and tetrahydroisoquinoline has been developed by the ferric chloride–catalyzed intramolecular cyclization of benzylamino-substituted propargylic alcohols.[10] A method has been developed for the cyclization of *N*-phenylethylbenzamide involving trifluoromethane sulfonic anhydride and 2-chloropyridine, providing 3,4-dihydroisoquinoline in good yield.[11] 3-Arylisoquinoline derivatives are potent antitumor agents. The structure–activity relationship (SAR) studies of the 3-aryl isoquinolones and 3-arylisoquinolamine show potent in vitro cytotoxicity.[12] These significant properties prompted us to synthesize novel isoquinoline derivatives through a simple route.

RESULTS AND DISCUSSION

A protocol for the generation of isoquinoline from β-acetoxyarylethanamide employing acetic anhydride and phosphorous pentoxide is described in this article. We have already described the synthetic utility of α-azido chalcones **1** in generating heterocyclic compounds.[13] β-Hydroxyarylethanamide **2,** derived from the chalcones **1,** have also been exploited by us to construct new rings[14] and it has been shown that the nature of the acid employed has emphatically dictated the course of cyclization. Thus titatinum tetrachloride–catalyzed cyclization has led to isoxazolines **3** [Fig. 1; Eq. (1)], whereas trifluoromethane sulfonic acid–catalysed cyclization has led to indane derivatives **4** [Fig. 1; Eq. (2)].[14] The Lewis and Brønsted acidic characters of the reagents employed have a telling effect on the course of the reactions in these cases, providing hard and soft nature. In continuation of this work, we decided to investigate the effect of attempting cyclization on the protected hydroxyl amide **5,** β-acetoxyarylethanamide. The acetyl derivatives **5** were obtained as a mixture of

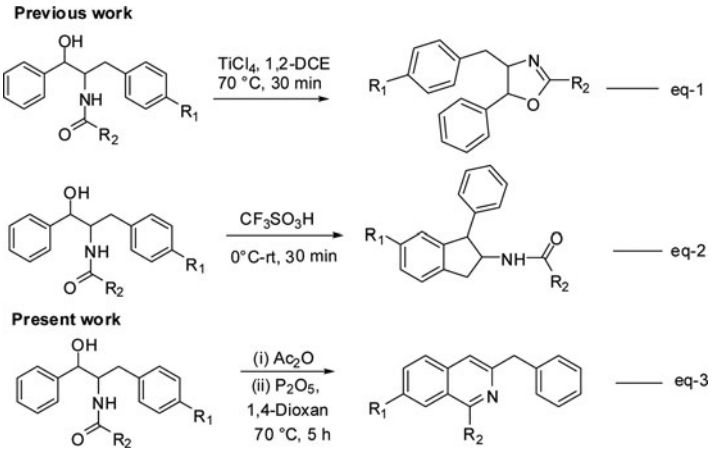
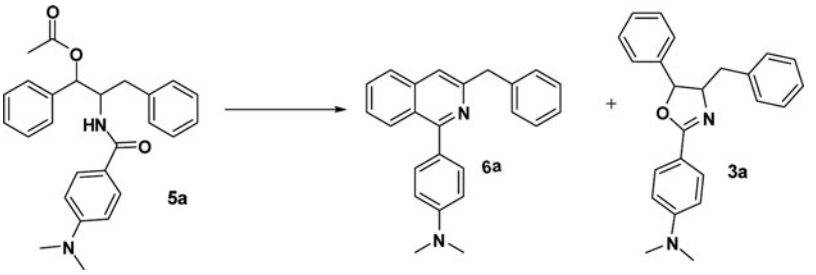


Figure 1. Synthetic utility of β-hydroxylarylethanamides.

Table 1. Screening impact of the reagents and solvents for the selective formation of isoquinolines

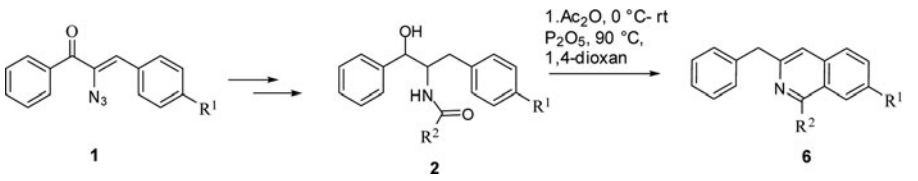


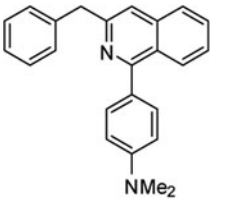
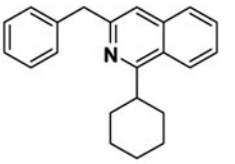
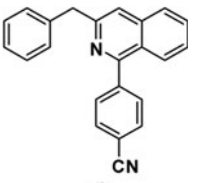
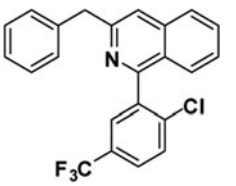
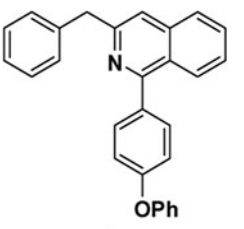
Entry	Reaction conditions	Yield **6a** (%)[a]	Yield **3a** (%)[a]
1	$POCl_3$, 1,2-dichloroethane, 80 °C, 3 h	—	88
2	Eaton's reagent, 90 °C, 5 h	—	74
3	$TiCl_4$, 1,2-dichloroethane, 80 °C, 30 min	—	92
4	Polyphosphoric acid, 90 °C, 5 h	—	71
5	$Ti(^iOPr)_4$, 1,2-dichloroethane, 80 °C, 5 h	—	—
6	$AlCl_3$, 1,2-dichloroethane, 80 °C, 5 h	—	—
7	ZnI, 1,2-dichloroethane, 80 °C, 5 h	—	—
8	P_2O_5, xylene, 140 °C, 6 h	35	28
9	P_2O_5, 1,2-dichloroethane, 90 °C, 5 h	38	37
10	P_2O_5, 1,2-dichlorobenzene, 120 °C, 6 h	30	41
11	P_2O_5, toluene, 110 °C, 6 h	42	27
12[b]	**P_2O_5, 1,4-dioxan, 90 °C, 5 h**	**78**	**5**

[a]Isolated yield.
[b]Optimized reaction condition: β-acetoxy amide (1 eq), P_2O_5 (4 eq) in 1,4-dioxan, 90 °C, 5 h.

the diastereomers from the respective hydroxyl compounds **2**. Compound **5a** was reacted with various reagents, in anticipation of a different course of cyclization, as the acetate is a relatively better leaving group than the hydroxyl group. The details of the reagents treated with compound **5a** are listed in Table 1. Use of polyphosphoric acid, Eatons reagent, phosphorous oxychloride, and titanium chloride resulted in oxazoline **3a** as the major cyclization product. When compound **5a** was treated with phosphorous pentoxide in xylene, 35% of isoquinoline **6a** was obtained along with 28% of oxazoline **3a** (Table 1). Toluene, benzene, 1,2-dichloroethane, and *o*-dichlorobenzene are not much effective for this conversion, whereas 1,4-dioxan is found to be effective as a solvent for this conversion. Titanium isopropoxide, aluminum chloride, and zinc iodide have also been tried but the reaction did not proceed in these cases. Finally, it was found that the reaction of **5a** with phosphorus pentoxide in 1,4-dioxane at 90 °C delivered 78% of isoquinoline derivative, **6a**. The procedure has been simplified by allowing the hydroxyamide **2a** to react with 1 equivalent of acetic anhydride in 1,4-dioxan at 0 °C to rt and then adding phosphorous pentoxide to the reaction mixture without isolating the intermediate. The resulting mixture was heated to 90 °C for 5 h to furnish the isoquinoline **6a** [Fig. 1; Eq. (3)]. The reaction has been carried out under the optimized conditions (Ac_2O, P_2O_5, 1,4-dioxane, 90 °C; Table 2) for various substrates. Amides containing both the electron-releasing groups and electron-withdrawing groups led to the corresponding isoquinoline derivatives with good to excellent yield. Cyclohexyl carboxylamide also yielded the corresponding isoquinoline under

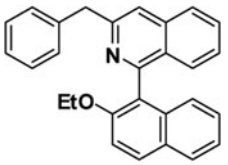
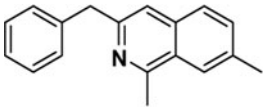
Table 2. Synthesis of 3-benzyl isoquinoline derivatives

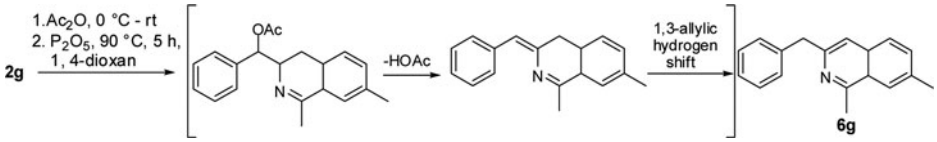


Entry	R^1	R^2	Isoquinolines	Yield (%)
1	H	4-N,N-Dimethylaminophenyl	 **6a**	78
2	H	Cyclohexyl	 **6b**	67
3	H	4-Cyanophenyl	 **6c**	79
4	H	2-Chloro-5-trifluoromethylphenyl	 **6d**	60
5	H	4-Phenoxyphenyl	 **6e**	76

(Continued)

Table 2. Continued

Entry	R^1	R^2	Isoquinolines	Yield (%)
6	H	2-Ethoxynaphth-1-yl	 **6f**	64
7	CH_3	Methyl	 **6g**	75



Scheme 1. Proposed mechanism for the regioselective formation of isoquinoline derivative.

the optimized condition. The details are provided in Table 2. In both the single-step reaction and the two-step reaction, the yields were almost the same.

Initially the mechanism of the reaction was considered to be simple: the acid-catalyzed cyclization occurs at the aryl group geminal to the acetoxy followed by the elimination of acetic acid. But we realized that the mechanism of this reaction is not as simple as proposed. When **5 g,** which has two different aryl groups at geminal to acetoxy and at benzyl end, was subjected to the reaction, the isoquinoline formed has been shown to be 1,7-dimethyl-3-benzylisoquinoline and not 1-methyl-3-(4-methylbenzyl)isoquinoline (Table 2, entry 7). This is confirmed by the presence of a singlet at 7.85 ppm accounting for one hydrogen, apart from the C4-H singlet at 7.17 ppm in the ^{1}H NMR spectrum of **6 g**. This clearly indicates that the cyclization has not taken place in the ring geminal to the acetoxy as concluded earlier. The cyclization has taken place on the other ring, followed by the elimination of acetic acid, resulting in the formation of an exocyclic double bond. Then 1,3-allylic shift could have taken place, the driving force being the aromaticity towards isoquinoline.

It is clear that the cyclization takes place prior to the elimination–tautomerization sequence. If the elimination–tautomerization takes place initially, the cyclization could have occurred anywhere as the olefin is now symmetrical. The initial cyclization takes place preferentially at the aryl ring, which is not geminal to acetoxy, probably due to steric reason. The mechanism is shown in Scheme 1.

CONCLUSION

In summary, a regioselective formation of isoquinolines from β-hydroxyarylethanamides with phosphorous pentoxide in 1,4-dioxan has been described.

EXPERIMENTAL

All solvents were purchased from commercial sources and used without further purification. ^{1}H NMR spectra were recorded at 400 MHz and ^{13}C NMR spectra were recorded at 100 MHz in dimethylsulfoxide (DMSO-d_6) or $CDCl_3$ using a 300- or 400-MHz spectrometer. Chemical shifts are reported in δ (ppm) relative to tetramethylsilane (TMS). Elemental analyses were performed on a Perkin-Elmer 2400 series II Elemental CHNS analyzer. Silica-gel G plates (Merck) were used for thin-layer chromatography (TLC).

Typical Procedure for the Synthesis of 1-Substituted-3-benzylisoquinoline (6a–g)

Acetic anhydride (0.279 mmol, 1 eq) was added to a solution of β-hydroxy amide **2** (0.279 mmol, 1 eq.) in 1,4-dioxane (5 mL) at 0 °C. The resulting mixture was stirred at room temperature for 1 h. Phosphorus pentoxide (1.11 mmol, 4 eq) was added to the reaction mixture and it was stirred at 90 °C for 5 h. The reaction mixture was then quenched with 10% sodium carbonate solution and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over sodium sulfate, and concentrated in vacuum. The crude product was purified by column chromatography using 10% ethyl acetate in hexane as the solvent to give isoquinoline derivatives **6**.

Selected Spectral Data for 4-(3-Benzylisoquinolin-1-yl)-N,N-dimethylaniline (6a)

Pale yellow viscous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.06 (s, 6H, -N(Me)$_2$), 4.39 (s, 2H, -CH$_2$), 6.89 (d, $J = 8.8$ Hz, 2H, Ar-H), 7.26–7.44 (m, 7H, Ar-H), 7.59 (t, $J = 8.0$ Hz, 1H, Ar-H), 7.66 (d, $J = 8.8$ Hz, 2H, Ar-H), 7.71 (d, $J = 8.0$ Hz, 1H, Ar-H), 8.18 (d, $J = 8.4$ Hz, 1H, Ar-H);^{13}C NMR (100 MHz, $CDCl_3$) δ: 40.5, 44.4, 112.1, 117.0, 125.2, 126.1, 126.2 (2C), 126.6 (2C), 127.8, 128.5, 129.5, 129.7, 131.2, 137.8, 140.0, 150.8, 153.6, 160.5; UPLC (M + 1) 339.4. Anal. calcd. for $C_{24}H_{22}N_2$: C, 85.17; H, 6.55; N, 8.28%. Found C, 85.11; H, 6.50; N, 8.24%.

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SUPPORTING INFORMATION

Full experimental details and ^{1}H and ^{13}C NMR spectra for this article can be accessed on the publisher's website.

REFERENCES

1. (a) Bentley, K. W. *The Isoquinoline Alkaloids*; Hardwood Academic: Amsterdam, 1998; vol. 1; (b) Scott, J. D.; Williams, R. M. Chemistry and biology of the tetrahydroisoquinoline antitumor antibiotics. *Chem. Rev*. **2002**, *102*, 1669–1730; (c) Chrzwadowska, M. D. Asymmetric synthesis of isoquinoline alkaloids. *Chem. Rev*. **2004**, *104*, 3341–3370.
2. (a) Kletsas, D.; Li, W.; Han, Z.; Papadopoulos, V. Peripheral-type benzodiazepine receptor (PBR) and PBR drug ligands in fibroblast and fibrosarcoma cell proliferation: Role of ERK, c-Jun, and ligand-activated PBR-independent pathways. *Biochem. Pharmacol*. **2004**, *67*, 1927–1932; (b) Mach, U. R.; Hacking, A. E.; Perachon, S.; Ferry, S.; Weremuth, C. G.; Schwartz, J.-C.; Sokoloff, P.; Stark, H. Development of novel 1,2,3,4-tetrahydroisoquinoline derivatives and closely related compounds as potent and selective dopamine D_3 receptor ligands. *Chembiochem* **2004**, *5*, 508–518.
3. (a) Durola, F.; Sauvage, J.-P.; Wenger, O. S. Sterically non-hindering endocyclic ligands of the bi-isoquinoline family. *Chem. Commun*. **2006**, 171–173; (b) Sweetman, B. A.; Muller-Bunz, H.; Guiry, P. J. Synthesis, resolution, and racemisation studies of new tridentate ligands for asymmetric catalysis. *Tetrahedron Lett*. **2005**, *46*, 4643–4646; (c) Lim, C. W.; Tissot, O.; Mattison, A.; Hooper, M. W.; Brown, J. M.; Cowley, A. R.; Hulmes, D. I.; Blacker, A. J. Practical preparation and resolution of 1-(2′-diphenylphosphino-1′-naphthyl)isoquinoline: A useful ligand for catalytic asymmetric synthesis. *Org. Process Res. Dev*. **2003**, *7*, 379–384; (d) Alcock, N. W.; Brown, J. M.; Hulmes, G. I. Synthesis and resolution of 1-(2-diphenyl phosphino-1-naphthyl) isoquinoline, a P-N chelating ligand for asymmetric catalysis. *Tetrahedron: Asymmetry* **1993**, *4*, 743–756.
4. (a) Birch, A. J.; Jackson, A. H.; Shannon, P. V. R. A new modification of the Pomeranz–Fritsch isoquinoline synthesis. *J. Chem. Soc. Perkin Trans. 1* **1974**, 2185–2190; (b) Larghi, E. L.; Kaufman, T. S. Preparation of N-benzylsulfonamido-l,2-dihydroisoquinolines and their reaction with Raney nickel: A mild, new synthesis of isoquinolines. *Tetrahedron Lett*. **1997**, *38*, 3159–3162.
5. (a) Nagubandi, S.; Fodor, G. The mechanism of the Bischler–Napieralski reaction. *J. Heterocycl. Chem*. **1980**, *17*, 1457–1463; (b) Banwell, M. G.; Bissett, B. D.; Busato, S.; Cowden, C. J.; Hockless, D. C. R.; Holman, J. W.; Reed, R. W.; Wu, A. W. Trifluoromethanesulfonic anhydride–4-(N,N-dimethylamino)pyridine as a reagent combination for effecting Bischler–Napieraiski cyclisation under mild conditions: Application to total syntheses of the amaryllidaceaealkaloids N-methylcrinasiadine, anhydrolycorinone, hippadine, and oxoassoanine. *J. Chem. Soc., Chem. Commun*. **1995**, 2551–2553; (c) Fitton, A. O.; Frost, J. R.; Zakaria, M. M.; Andrew, G. Observations on the mechanism of the Pictet–Gams reaction. *J. Chem. Soc., Chem. Commun*. **1973**, 889–890.
6. Venkov, A. P.; Statkova-Abeghe, S. M. Synthesis of 3,4-dihydroisoquinolines, 2-alkyl(acyl)-1(2H)-3,4-dihydroisoquinolinones, 2-alkyl-1(2H)-isoquinolinones, and 1-alkyl-2(2H)-quinolinones by oxidation with potassium permanganate. *Tetrahedron* **1996**, *52*, 1451–1460.
7. Miller, R. B.; Frincke, J. M. Synthesis of isoquinolines from indenes. *J. Org. Chem*. **1980**, *45*, 5312–5315.
8. Sakamoto, T.; Konda, Y.; Miura, N.; Hayashi, K.; Yamanaka, H. Condensed heteroaromatic ring systems, XI: A facile synthesis of isoquinoline N-oxides. *Heterocycles* **1986**, *24*, 2311–2314.

9. Yang, Y. Y.; Shou, W. G.; Chen, Z. B.; Hong, D.; Wang, Y. G. A tandem approach to isoquinolines from 2-azido-3-arylacrylates and α-diazocarbonyl compounds. *J. Org. Chem* **2008**, *73*, 3928–3930.
10. Huang, W.; Shen, Q.; Wang, J.; Zhou, X. One-step synthesis of substituted dihydro- and tetrahydroisoquinolines by $FeCl_3 \cdot 6H_2O$-catalyzed intramolecular Friedel–Crafts reaction of benzylamino-substituted propargylic alcohols. *J. Org. Chem*. **2008**, *73*, 1586–1589.
11. Movassaghi, M.; Hill, M. D. A versatile cyclodehydration reaction for the synthesis of isoquinoline and β-carboline derivatives. *Org. Lett*. **2008**, *10*, 3485–3488.
12. Khadka, D. B.; Cho, W. J. 3-Arylisoquinolines as novel topoisomerase. *Bioorg. Med. Chem*. **2011**, *19*, 724–734.
13. Suresh, R.; Muthusubramanian, S.; Nagaraj, M.; Manickam, G. Indium trichloride–catalyzed regioselective synthesis of substituted pyrroles in water. *Tetrahedron Lett*. **2013**, *54*, 1779–1784.
14. Suresh, R.; Muthusubramanian, S.; Boominathan, M.; Manickam, G. Acid-controlled generation of indanes and oxazolines from β-hydroxyarylethanamide. *Tetrahedron Lett*. **2013**, *54*, 2315–2320.