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A NON-ACYL AZIDE ROUTE TO ISOQUINOLIN-1(2*H*)-ONE DERIVATIVES VIA β-STYRIL CARBAMATES

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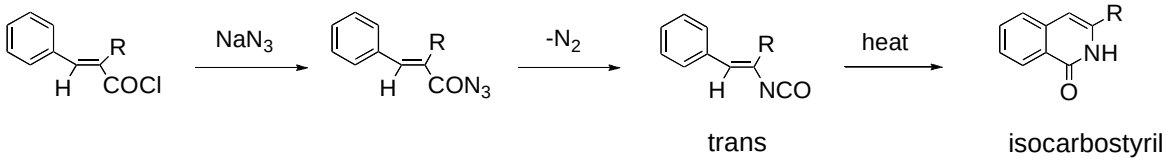
Abstract – The efficient reactions of the phenyl acetaldehydes **1a-e** and the enol ethers of benzyl ketones **1o-s** with ethyl urethane lead to the formation of the β-styril carbamates **2**, which are excellent precursors for generating isoquinolin-1(2*H*)-ones **4**. Upon thermolysis at 230 °C in an inert organic solution, the carbamates decomposed into the transient β-styril isocyanate intermediates **3**. The resulting isoquinolin-1(2*H*)-ones obtained were in good yields (65-93 %). This synthetic methodology allows the convenient preparation of isoquinolin-1(2*H*)-ones via a non-phosgene and non-acyl azide route from readily accessible starting materials.

INTRODUCTION

Isoquinoline-1(2*H*)-ones are prominent structural features in a variety of natural products and compounds of medicinal interest.[1] They are also potentially useful as optical-electro-intermediates in DVD and Polymer Light Emitting Diode (PLED) applications because of their conjugated UV absorption bands and high thermal stability.[2] There are several methodologies available for synthesizing compounds possessing Isoquinoline-1(2*H*)-one moieties including the followings: ring expansion of indanones with alkyl nitrites,[3] cyclization of 2-cyanobenzyl phenyl ketones with concentrated sulfuric acid,[4] and photocyclization of 3-chlorobenzo[*b*]thiophenes.[5] Most of these routes result in poor yields. In 2001, Usifoh reported an alternative approach for the synthesis of 3-substituted isoquinoline-1(2*H*)-one through the transformation of *o*-toluic acid chloride with methyl amine followed by ring closure reaction of tolyl methylamide with *n*-butylithium. Although this methodology appears to be quite efficient, the reactions require a chloride-containing reagent and further must be carried out at a low temperature (–63 °C) with

butyllithium.[6] As a result, the Usifoh route can be unattractive even though the synthesis is simple and straightforward. Recently, several examples of transition metal-catalyzed routes to heterocyclic compounds have been demostrated in the literature.[7] However, only several examples applicable to the synthesis of isoquinoline-1(2*H*)-one have appeared.[8] Therefore, the search continues for an efficient, high yielding, and eco-friendly method of isoquinoline-1(2*H*)-one synthesis.

A synthetic approach for producing isoquinoline-1(2*H*)-ones which uses a β-styril isocyanate route, reported by Boyer and Mikol in 1972, attracted our interest because it provides overall high yields (Scheme 1).[9] One major problem with this approach however, is that the preparation of the β-styril isocyanate via an acyl azide is obtained through the reaction of NaN_3 and trans-cinnamoyl chloride. This reaction is not appealing from a safety or green chemistry standpoint. With our continuing interest in non-chlorine routes for isocyanate synthesis,[10] we developed a new alternative methodology based on carbamates as precursors to isocyanates.

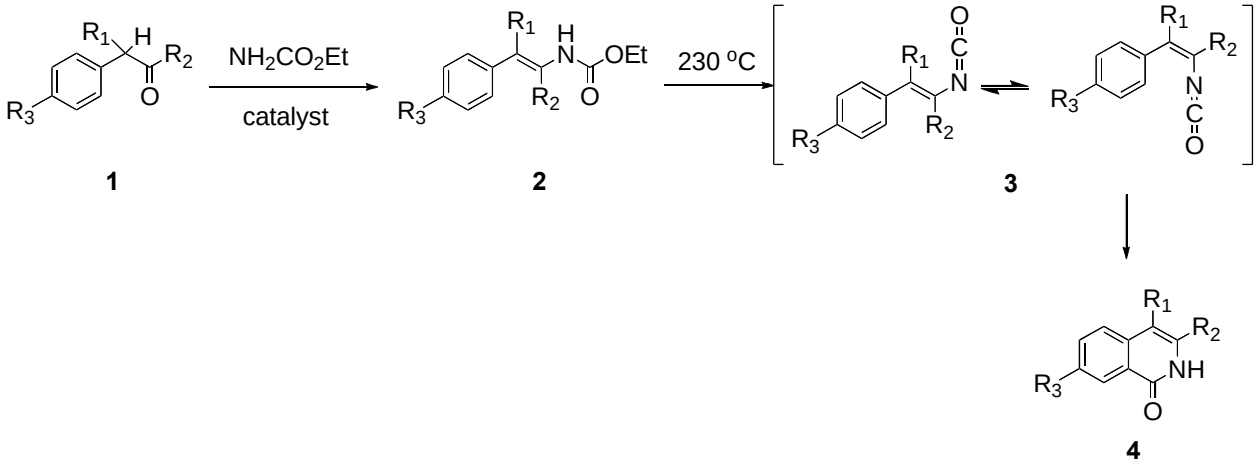


Scheme 1. Boyer's synthesis of isoquinoline-1(2*H*)-ones through β-styril isocyanate.[9]

Our present non-azide route (Scheme 2) toward isoquinoline-1(2*H*)-ones is an improvement upon past methodologies.[9] It involves the synthesis of β-styril carbamates **2** using readily available ethyl urethane and benzyl carbonyl compounds **1** as raw materials.[11] In the first step, condensation of ethyl urethane with the phenyl acetaldehydes **1a–e** or with the ketals/enol ethers of benzyl ketones **1o–s** produces their respective β-styril carbamates **2**. The generation of the trans-styril isocyanates **3**, their trans-to-cis isomerization and subsequent cyclization to isoquinoline-1(2*H*)-ones **4** were accomplished in one pot through thermolysis at ca. 230 °C. This carbamate route does not require any chlorine- or azide-based reagents. Additionally, pure isoquinolin-1(2*H*)-ones can be isolated from the reaction solutions directly in good yields.

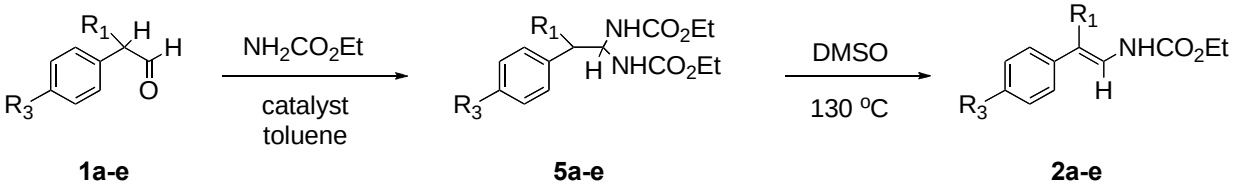
RESULTS AND DISCUSSION

Synthesis of β-styril carbamates 2a-e from phenyl acetaldehydes 1a-e: We developed a general synthesis of the isoquinoline-1(2*H*)-ones **4a–e** from several phenyl acetaldehydes **1a–e** using ethyl urethane as the common reagent. Then, we applied the approach to the synthesis of other carbonyl compound such as the benzyl ketone **1o-s** to obtain both α- and β-substituted isoquinoline-1(2*H*)-ones



Scheme 2. Carbamate route to isoquinoline-1(2*H*)-ones **4**

4o–s. In the first step, β-styril carbamates **2a-e** are obtained via acid-catalyzed condensation reactions (Scheme 3). The parent compound, phenyl acetaldehyde **1a**, condenses readily with two moles of ethyl urethane at room temperature in a toluene solution containing conc. H_2SO_4 as the catalyst. The biscarbamate **5a** precipitated in 70% yield from the reaction mixture after ca. 30 min at room temperature.[12] We converted this biscarbamate selectively into the pure trans-β-styril carbamate **2a** in 70% yield upon heating in DMSO at ca. 120 °C, i.e., through the loss of one mole of ethyl urethane. Selective isolation of the trans-β-styril carbamate suggests that **2a** is the preferred isomer in this mild thermolysis condition. The syntheses of the corresponding β-styril carbamates **2b** and **2c** from 2-phenyl-2-methylacetaldehyde **1b** and 2,2-diphenylacetaldehyde **1c**, respectively, occurred at ambient temperature and showed loss of ethyl urethane more facile than that from biscarbamate **5a**. For instance, the acid-catalyzed condensation of diphenylacetaldehyde with ethyl urethane can led directly to the β-styril carbamate **2c** in 60–70% yield when ethyl urethane was used at just slightly over one molar equivalent.[13] It appears that the presence of the two phenyl groups in 2,2-diphenylacetaldehyde **1c** facilitates the formation of its β-styril carbamate **2c**. In addition, the asymmetrical and substituted phenyl acetaldehydes **1d** and **1e** were also converted directly (i.e., one-step syntheses) into their corresponding β-styril carbamates as in the cases of **2d** and **2e**, respectively shown in Table 1. Most of the pure β-styril carbamates **2a-e** are crystalline compounds at room temperature. They show characteristic IR



Scheme 3. Preparation of the β-styril carbamates **2a**–**e** from the phenylacetaldehydes **1a**–**e**

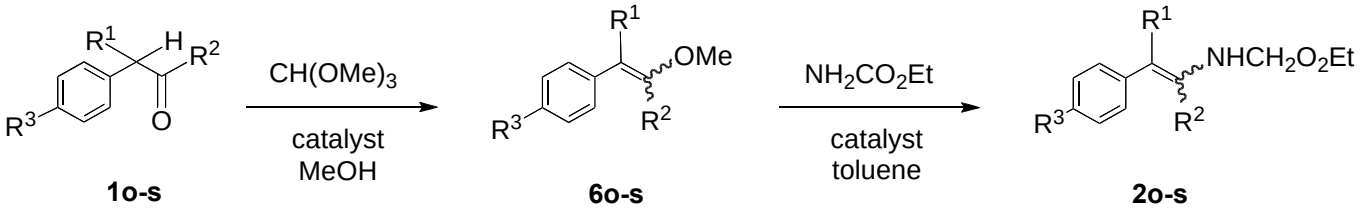
Table 1. Yields of β-styril carbamates **2a-e** obtained from the phenylacetaldehydes **1a-e**

entry	product	R^1	R^2	R^3	**5**		**2**	
					Yield[a] (%)	mp (°C)	Yield[a] (%)	mp (°C)
1	**a**	H	H	H	70	158–159	70	85–87
2	**b**	Me	H	H	60	160–161	72	Oil
3	**c**	Ph	H	H	50	162–164	64	68–69
4	**d**	*p*-ClPh	H	Cl	39	215–217	51	110–112
5	**e**	*p*-BrPh	H	Br	–	–	54[b]	126–129

a) Isolated yields. b) **2e** was obtained in a one-pot synthesis from **1e**.

spectroscopic absorptions at 1710–1730 cm^{-1} for their urethane group.

Synthesis of β-styril carbamates 2o-s from the benzyl ketones 1o-s: We also investigated the use of the benzyl ketones **1o–s** as potential raw materials for the synthesis of substituted isoquinoline-1(2*H*)-ones (Scheme 4). All of these benzyl ketones are less reactive than the phenylacetaldehydes since they did not undergo condensation with ethyl urethane directly under acidic conditions. In contrast, their ketal derivatives and better yet, enol ethers such as the (*E*)- and (*Z*)-2-methoxy-1-phenyl-1-propenes **6o** and methoxy-1,2-diphenylethene **6r**, prepared from the corresponding ketones and methyl orthoformate,[14] served as appropriate starting materials. We performed the condensations of urethane with the enol ethers of the benzyl ketones in the presence of an acid catalyst (e.g., toluenesulfonic acid, TsOH) under vacuum to both facilitate the removal of methanol and promote the forward conversions into α-styril monocarbamates. Using this approach, we converted several representative benzyl ketones 1o–s into their corresponding β-styril carbamates **2o–s** (50–75% yields), which we characterized in terms of their urethane absorptions at 1710–1730 cm^{-1} in IR spectra. Apart from the β-styril carbamate **2s**, which we isolated as oil containing two stereoisomers, the other β-styril carbamates derived from ketones **2o-r** were obtained as crystalline solids (Table 2).



Scheme 4. Preparation of the β-styril carbamates **2o-s** from the ketals of benzyl ketones **1o–s**

Table 2. Yields of β-styril carbamates **2o-s** obtained from the ketals of benzyl ketones **1o-s**

entry	product	R^1	R^2	R^3	Yield[a] (%)	mp (°C)
1	**2o**	H	CH_3	H	60	85-90[c]
2	**2p**	H	CH_2Ph	H	66	115[c]
3	**2q**	Ph	CH_3	H	75	59-61
4	**2r**	H	Ph	H	50	127-129
5	**2s**	$–R^1–R^2– = –(CH_2)_4–$		H	–[b]	Oil

a) Isolated yields. b) Pure 2s was not isolated. c) Boiling point of the product at 0.1 mm.

Thermolysis of β-styril carbamates 2 into isoquinoline-1(2*H*)-ones 4: To effect the formation of β-styril isocyanates from corresponding β-styril carbamates **2**, we added the β-styril carbamates **2** to a hydrocarbon solvent having a boiling point of greater than 230 °C (e.g., phenylcyclohexane). The formation of the isocyanates began at a temperature above 200 °C with a rapid cis-to-trans isomerization of styryl isocyanate **3**. At a temperature of ca. 230 °C however, the formation of cis-styril isocyanates and their cyclization into isoquinoline-1(2*H*)-ones **4** were very rapid. The whole transformation was complete within 4 h. Because the isoquinoline-1(2*H*)-ones are more polar than phenylcyclohexane, they readily crystallized from their solutions upon cooling. We directly isolated the pure solid isoquinoline-1(2*H*)-ones **4** in one-crop (in yields consistently greater than 65%) from the reactions of all of the β-styril carbamates **2**.

To further simplify the overall synthesis, we found that the crude β-styril carbamates prepared from the condensation of ethyl urethane could be used directly for thermolysis. In particular, β-styril carbamates **2** made from phenylacetaldehyde **1a-e** or the enol ethers of benzyl ketones **1o-s** were carried out in this manners. For instance, we converted 2-phenyl-2-methylacetaldehyde **1b** and 2-phenyl-1-cyclohexanone **1s** into their β-styril carbamates (**2b** and **2s**, respectively) using the described procedure and then thermolyzed the crude products directly without purification. After cooling the thermolysis solutions to room temperature, the isoquinoline-1(2*H*)-ones **4b** and **4s**, respectively, were isolated as pure crystalline products in 73 and 65% yield, respectively (Table 3). The yields and isolation process were unaffected when using this simplified process. As a result, the overall procedure is less tedious.

Complications in isoquinoline-1(2*H*)-one 4a formation during thermolysis of β-styril carbamate 2a: A detailed thermolysis study of the parent β-styril carbamate **2a** examined the formation and disappearance of the intermediates using HPLC and FTIR spectroscopy. In this case, we also isolated an interesting by-product that resulted along with major product isoquinoline-1(2*H*)-ones **4a**. Based on its physical (mp > 350 °C), HPLC analysis and spectral characteristics, we identified this by-product as 5-phenyluracil **7**. The formation of 5-phenyluracil **7** presumably arose through the initial dimerization

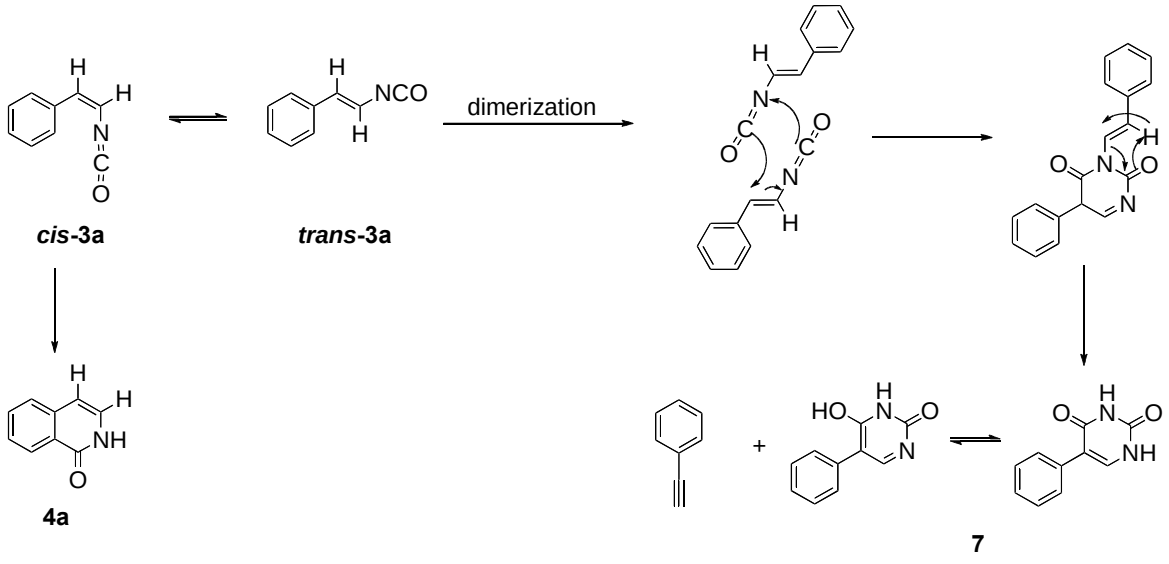
Table 3. Yields of isoquinoline-1(2*H*)-ones **4** derived from the β-styril carbamates **2**

entry	product	R^1	R^2	R^3	Yield[a] (%)	mp (°C)
1	**4a**	H	H	H	73	205–206
2	**4b**	Me	H	H	73	171–173
3	**4c**	Ph	H	H	80	237–239
4	**4d**	*p*-ClPh	H	Cl	79	285–286
5	**4e**	*p*-BrPh	H	Br	83	312–314
6	**4o**	H	Me	H	86	213–215
7	**4p**	H	CH_2Ph	H	66	188–190
8	**4q**	Ph	Me	H	93	275–276
9	**4r**	H	Ph	H	79	201–202
10	**4s**	$–R^1–R^2– = –(CH_2)_4–$		H	65	253–255

a) Isolated yields.

of trans-styril isocyanate followed by expulsion of phenyl acetylene. The postulated mechanism is outlined in Scheme 5.

This dimerization by-product can arise from a Diels–Alder reaction between two trans-styril isocyanates **3a**. Thus, to optimize the yields of the major product isoquinoline-1(2*H*)-one **4a**, the thermally induced



Scheme 5. Mechanism of 5-phenyluracil **7** fromation from the Diels-Alder reaction of styril isocyanate **3a**

Table 4. Yields of products from the thermolysis of β-styril carbamates **2a** under various conditions.

Entry	reaction conditions			Yield[a] (%)	
	2a (g)	phenylcyclohexane (mL)	temperature (°C)	**4a**	**7**
1	1	20	240	53	2
2	2	20	200	15	17
3	2	20	220	26	12
4	2	20	240	37	4
5	3	20	240	29	33

a) Reported yields determined through HPLC analysis.

bimolecular reaction of the trans-styril isocyanates **3a** during the thermolysis of the β-styril carbamates should be minimized as much as possible thereby avoiding production of the dimerization by-product. The bimolecular reaction can be minimized through either dilution or slow addition of the starting material to the heated solution. From a study of the thermolysis of β-styril carbamates **2a** at 230 °C, the yield of the isoquinoline-1(2*H*)-ones **4a** increased from 29 to 53% while that of 5-phenyluracil **7** decreased from 33 to 2% when we decreased the concentration of β-styril carbamates **2a** in phenylcyclohexane from 0.15 to 0.05 g/mL (see Table 4). Therefore, improved yields can be achieved when using a dilution strategy. Apart from the reaction of β-styril carbamates **2a**, pure isoquinoline-1(2*H*)-one **4a** were the only products isolated, meaning no by-products similar to 5-phenyluracil **7** were observed in any of the other cases. Synthetic implication aside, this dimerization mechanism might also be implicated to explain the formation of the mystery dimers of styril isocyanate **3a** isolated previously by Boyer and Mikol.[9]

CONCLUSIONS

We have developed a general and straightforward synthetic route for the preparation of isoquinolin-1(2*H*)-ones **4** through the thermolysis of β-styril carbamates **2**. Although the formation of styril isocyanates occur only in transit, styril isocyanates **3** cyclize smoothly into their corresponding isoquinolin-1(2*H*)-ones at 230 °C. Thus, styril carbamates can replace the styril isocyanates used previously as precursors in isoquinolin-1(2*H*)-one synthesis. In addition to the good general yields of the products, this methodology has an advantage over the Boyer synthesis because it is a green process.[9] Moreover, phenylacetaldehydes and benzyl ketones can be obtained from a variety of sources using well-known synthetic techniques, allowing further structural modifications of the isoquinolin-1(2*H*)-ones.

For instance, the 2,2-dichloro and -dibromo derivatives of diphenylacetaldehydes (**1d** and **1e**, respectively) can be synthesized using the corresponding benzophenones as raw materials according to Mackinney's procedure[15] via Darzen's syntheses.[16] Another good source of the starting carbonyl compounds (e.g., **1a**–**c**) is the isomerization of epoxides. Phenylacetaldehydes and diphenylacetaldehydes are in particular readily accessible through the rearrangement of styrene oxides or stilbene oxides catalyzed by Lewis acids,[17] acidic zeolite catalysts,[18] bismuth catalysts,[19] and alumina-silica catalysts.[20] In short, we suspect that a wide range of isoquinolin-1(2*H*)-ones will be available using this versatile urethane synthesis methodology.

EXPERIMENTAL

*Synthesis of β-styril carbamate **2a-e** from phenylacetaldehyde **1a-e*:**

*Biscarbamate **5a** from phenyl acetaldehyde **1a**.* This is an modified process of Grow's original procedure,[12] except con. Sulfuric acid was used to enhance the overall yield. Phenylacetaldehyde (14.1 g, 10 mmol) and ethyl urethane (20 g, 22 mmol) was added into a 250-mL triple-neck round-bottom flask containing toluene (30 mL). The solution was stirred magnetically to form a homogenous solution, and then three drops of conc. H_2SO_4 were added at room temperature. After a mild exothermic reaction, the stirring was stopped and the solution was left to stand at room temperature. White crystalline precipitate gradually formed. After 5 h, the solution was cooled to 0 °C and the precipitate collected through suction filtration and washed with cold toluene to give the biscarbamate **5a** (19.4 g, 70%); mp 158–159 °C; IR (KBr) 3346, 1706, 1657 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ = 1.09 (t, 6H), 2.82 (d, 2H), 3.89 (q, 4H), 5.10 (q, 1H), 7.15–7.26 (m, 5H), 7.47 (d, 2H) ppm.

*β-Styril carbamates **2a** from the biscarbamate **5a**.* Biscarbamate **5a** (5g, 17.8 mmol) was dissolved in DMSO (50 mL) in a 100-mL triple-neck round-bottom flask equipped with a thermometer. The solution was heated in an oil bath at 120 °C with stirring for 2 h until complete disappearance of the carbonyl peak (1672 cm^{-1}), as monitored using FTIR spectroscopy; at the same time, new peaks at 1658 and 1700 cm^{-1} became the major signals in the C=O absorption regions of the spectra of the reaction mixtures. After cooling the solution to room temperature, trans-styril carbamate **2a** was isolated by pouring the mixture into ice water and filtering off the solid, which was recrystallized from MeOH (2.3 g, 70%): mp 85–87 °C; ^1H NMR (200 MHz, acetone-d_6): δ = 1.03 (t, 3H), 1.18 (t, 3H), 1.30 (d, 2H), 3.23 (t, 1H), 3.80 (q, 2H), 4.00 (q, 2H), 5.23 (q, 1H), 6.20 (s, 1H), 6.48 (s, 1H), 7.05–7.40 (m, 5H) ppm.

*Synthesis of Substituted phenylacetaldehydes **1d** and **1e*:** These aldehydes were obtained from the appropriate benzophenones via Darzen's glycidic ester synthesis, according to procedures reported by Horton *et al*. and Counsell *et al*.[16] The general method is illustrated by the preparation of 2,2-bis(*p*-chlorophenyl)acetaldehyde **1d**. Sodium hydride (12 g, 24 mmol, 50% dispersion) was added with stirring

over a 4 h period to a solution of ethyl chloroacetate (15 mL, 15.4 mmol) and 2,2-dichlorobenzophenone (20.0 g, 80.0 mmol) in anhydrous benzene (50 mL) under N_2. The reaction mixture was stirred for 16 h at room temperature and then it was poured into ice-cold 25% HCl solution (100 mL). The resulting mixture was extracted with benzene (3 × 100 mL); the combined extracts were dried (Na_2SO_4) and evaporated to dryness. The partially solidified residue was recrystallized from MeOH to afford Ethyl β,β-di(*p*-chlorophenyl)glycidate (18.4 g, 67%) as a white crystalline solid; mp 110–112 °C; spectral data for major compound: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.02 (t, *J* = 7.2 Hz, 3H), 3.94 (s, 1H), 4.04 (q, 2H), 7.18–7.42 (m, 8H) ppm. Ethyl β,β-di(*p*-chlorophenyl)glycidate (21.7 g, 6 mmol) was dissolved in EtOH (120 mL) and the resulting solution was heated under reflux for 6 h in the presence of 30% aqueous NaOMe solution (solution in MeOH, 14.2 g). The solvent was removed through rotary evaporation and the residue was diluted with distilled water (50 mL) and extracted with Et_2O (3 × 50 mL). The aqueous phase was heated on a steam bath to remove residual ether, left to cool, and acidified with 20% HCl. The mixture was extracted with Et_2O (2 × 50 mL); the combined extracts were washed with distilled water, dried (Na_2SO_4), and concentrated to an oily residue, which was heated in an oil bath at 150 °C under reduced pressure (water aspiration). Distillation of the crude decarboxylated product afforded 2,2-bis(*p*-chlorophenyl)acetaldehyde (**1d**, 10.2 g, 60%); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.85 (s, 1H), 7.14 (d, *J* = 8.0 Hz, 4H), 7.33 (d, *J* = 7.6 Hz, 4H), 9.87 (s, 1H) ppm.

2,2-Bis(*p*-bromophenyl)acetaldehyde **1e** was prepared was in 70% yield using the same procedure; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.82 (s, 1H), 7.08 (d, *J* = 8.2 Hz, 4H), 7.49 (d, *J* = 8.2 Hz, 4H), 9.88 (s, 1H) ppm.

*β-Styril biscarbamate **5d** from phenylacetaldehyde **1d.*** 2,2-bis(*p*-chlorophenyl)acetaldehyde (**1d**, 7.9 g, 3 mmol) and ethyl carbamate (5.35 g, 6 mmol) were dissolved in toluene (50 mL) and then conc. H_2SO_4 (2 mg) was added while churning under ice-cooling. The solution was maintained under the same conditions for 1 h. The resulting yellow solid precipitate was removed through filtration and the solution was evaporated to dryness. The partially solidified residue was recrystallized from MeOH to afford Ethyl β,β-bis(*p*-chlorophenylvinyl)biscarbamate (**5d**, 5.1 g, 39%) as a white crystalline solid; mp 215–217 °C. Spectral data for the major compound: ^{1}H NMR (200 MHz, acetone-d_6): δ = 1.05 (t, *J* = 6.4 Hz, 3H), 3.94 (q, 2H), 4.67 (d, *J* = 11.6 Hz, 1H), 5.99 (q, 1H), 6.66 (s, 1H), 7.31 (d, *J* = 8.6 Hz, 4H), 7.37 (d, *J* = 8.6 Hz, 4H) ppm. Anal. Calcd for $C_{20}H_{22}Cl_2N_2O_4$: C, 56.48; H, 5.21; N, 6.59. Found: C, 56.60; H, 5.29; N, 6.95.

Ethyl β,β-bis(*p*-chlorophenylvinyl)biscarbamate (**5d**, 12.7 g, 3 mmol) was heated in DMSO (38 mL) at 130 °C for 4 h. The reaction mixture was distilled in vacuo at 70 °C to leave a yellow oily residue, which was recrystallized (toluene/cyclohexane) to give β-Styril carbamate (**2d**, 8.7 g, 51%); mp 110–112 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27 (t, *J* = 7.6 Hz, 3H), 4.20 (q, 2H), 6.44 (d, *J* = 11.5 Hz, 1H), 7.09 (d, *J*

= 8.6 Hz, 2H), 7.18–7.20 (m, 2H), 7.22–7.30 (m, 2H), 7.42 (d, *J* = 8.4 Hz, 2H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): δ = 14.5, 61.9, 119.9, 122.0, 127.7, 128.6, 129.7, 131.3, 132.5, 133.9, 138.4, 153.5 ppm.

One-pot synthesis of β-styril carbamate ***2a-e*** *from phenylacetaldehyde* ***1a-e*****:** The general method is illustrated by the preparation of Ethyl β,β-bis(*p*-bromophenylvinyl)carbamate **2d**. 2,2-Bis(*p*-bromophenyl)acetaldehyde (**1e**, 0.93 g, 3 mmol) and ethyl urethane (0.53 g, 6 mmol) were added to a 100-mL round-bottom flask containing toluene (6 mL) and then conc. H_2SO_4 (1 drop) was added with stirring while cooling in a water-bath. After initial precipitation of yellowish solid products, the mixture was heated slowly to 80 °C under vacuum (0.1 mm) to remove excess ethyl urethane from the mixture, resulting in brown oil. The reaction mixture was cooled and then recrystallized from cyclohexane (10 mL) to obtain β-styril carbamate (**2e**, 0.6 g, 54%); mp 126–129 °C. Spectral data for the major compound: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27 (t, *J* = 7.2 Hz, 3H), 4.20 (q, 2H), 6.45 (d, *J* = 11.2 Hz, 1H), 7.04 (d, *J* = 6.8 Hz, 2H), 7.12 (d, *J* = 8.3 Hz, 2H), 7.37 (d, *J* = 6.8 Hz, 2H), 7.59 (d, *J* = 8.3 Hz, 2H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): δ = 14.4, 61.9, 119.9, 120.5, 122.0, 122.1, 128.0, 131.4, 131.5, 131.6, 131.7, 132.7, 138.8, 153.5 ppm.

β-Styril carbamate **2a**[21] was prepared was in 70% yield using the same procedure; mp 85–87 °C; ^{1}H NMR (200 MHz, acetone-d_6): δ = 1.03 (t, 3H), 1.18 (t, 3H), 1.30 (d, 2H), 3.23 (t, 1H), 3.80 (q, 2H), 4.00 (q, 2H), 5.23 (q, 1H), 6.20 (s, 1H), 6.48 (s, 1H), 7.05–7.40 (m, 5H) ppm. Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 68.80; H, 6.88; N, 7.12.

β-Styril carbamate **2c**[13] was prepared was in 64% yield using the same procedure; mp 68-69 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.26 (t, 3H), 4.19 (q, 2H), 6.45 (s, 1H), 6.97–7.51 (m, 11H) ppm. Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.23; H, 6.48; N, 5.01.

Synthesis of β-styril carbamate ***2o-s*** *from phenyl acetones and the benzyl ketone* ***1o-s*****:**

The general method is illustrated by the preparation of ethyl-(1,2-diphenylvinyl)carbamate **2r**. *p*-Toluenesulfonic acid monohydrate (0.05 g) was added to a solution of benzyl phenyl ketone (1r, 20.0 g, 10.2 mmol) and trimethyl orthoformate (21.7 g, 20.4 mmol) in dry MeOH (30 mL). The reaction mixture was heated under reflux at 60 °C while stirring for 30 h. The reaction mixture was distilled in vacuo (0.1 mm) at 130 °C to leave a colorless oily residue. The resulting residue was recrystallized from hexane to afford (*Z*)-1-methoxy-1,2-diphenylethene (**6r**, 18.5 g, 86%) as a white solid; mp 50–52 °C. Spectral data for the major compound: ^{1}H NMR (200 MHz, acetond-d_6): δ = 3.61 (s, 3H), 6.22 (s, 1H), 7.16–7.77 (m, 10H) ppm; Anal. Calcd for $C_{15}H_{14}O$: C, 85.71; H, 6.67. Found: C, 84.89; H, 6.70. The ethyl carbamate (5.1 g, 6 mmol) and *p*-toluenesulfonic acid monohydrate (0.6 g) were dissolved in toluene (50 mL). The reaction mixture was stirred for 15 min at 40 °C and then (*Z*)-1-methoxy-1,2-diphenylethene (**6r**, 10.0 g) was added. The solvents were evaporated in vacuo (water pump) for 10 min at 70 °C to give a yellow residue, which was recrystallized from cyclohexane to afford β-Styril carbamate (**2r**,[22] 10.3 g, 50 %) as a

yellow-white solid; mp 127–129 °C. Spectral data for the major compound: ^{1}H NMR (400 MHz, acetond-d_6): δ = 1.12 (br t, 3H), 4.03 (q, 2H), 6.61 (s, 1H), 6.61 (s, 1H), 7.19–7.59 (m, 10H), 7.85 (br s, 1H) ppm; ^{13}C NMR (400 MHz, DMSO-d_6): δ = 15.0, 61.3, 123.0, 126.9, 128.0, 128.9, 129.0, 129.2, 129.3, 129.4, 129.7, 135.8, 136.0, 137.5, 140.6, 155.4 ppm; MS (EI+ mode): m/z 267 (M+, 100%), 268 (20), 194 (56); Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.41; H, 5.98; N, 5.26. Found: C, 76.38; H, 6.41; N, 5.24.

β-Styril carbamate **2o** was prepared was in 60% yield using the same procedure; bp 85-90 °C (0.1 mm); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.23 (t, 3H), 20.3, 2.29 (d, 3H), 4.11 (q, 2H), 5.56, 6.71 (s, 1H), 6.20, 6.62 (s, 1H), 7.00–7.40 (m, 5H) ppm. Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 68.83; H, 7.24; N, 6.89.

β-Styril carbamate **2p** was prepared was in 66% yield using the same procedure; bp 115 °C (0.1 mm); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.18 (t, 3H), 3.71, 3.92 (s, 2H), 4.05 (q, 2H), 5.75 (s, 1H), 5.85, 6.40 (1H), 6.70–7.40 (m, 10H) ppm. Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 77.45; H, 7.01; N, 5.40.

β-Styril carbamate **2q** was prepared was in 75% yield using the same procedure; mp 59-61 °C (0.1 mm); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.17 (t, 3H), 2.25 (s, 3H), 4.05 (q, 2H), 6.28 (s, 1H), 6.85-7.45 (m, 10H) ppm. Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 77.03; H, 6.81; N, 4.77.

β-Styril carbamate **2s** was prepared using the same procedure; pure compound was not isolated; oil compound; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.16 (t, 3H), 1.40-2.80 (m, 8H), 4.03 (q, 2H), 5.92 (s, 1H), 6.95-7.50 (m, 5H).

*Thermolysis of β-styril carbamates **2** into isoquinoline-1(2H)-ones **4*:**

The general method is illustrated by the preparation of 7-chloro-4-(*p*-chlorophenyl)isoquinoline-1(2*H*)-one **4d**. Ethyl β,β-bis(*p*-chlorophenylvinyl)carbamate (**2d**, 4.0 g, 1 mmol) was heated in phenylcyclohexane (4 mL) at 230 °C for 4 h and the crude 7-chloro-4-(*p*-chlorophenyl)isoquinoline-1(2*H*)-one **4d** was solidified after cooling. The solid was washed with phenylcyclohexane and recrystallized from acetone to give 7-chloro-4-(*p*-chlorophenyl) isoquinoline-1(2*H*)-one (**4d**, 2.8 g, 79%); mp 285–286 °C. Spectral data for the major compound: ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.17 (d, J = 5.6 Hz, 1H), 7.43–7.45 (dd, J = 6.4, 6.8 Hz, 2H), 7.49 (d, J = 8.8 Hz, 1H), 7.54 (d, J = 8.4 Hz, 2H), 7.71–7.74 (dd, J = 8.8, 8.8 Hz, 1H), 8.21 (s, 1H), 11.70 (br d, 1H) ppm; ^{13}C NMR (400 MHz, DMSO-d_6): δ = 115.7, 126.3, 126.5, 127.1, 128.7, 128.7, 131.3, 131.6, 132.4, 132.4, 132.7, 134.6, 135.1, 160.3 ppm; MS (EI+ mode): m/z 289 (M+, 100%), 290 (20), 291 (65); HRMS (EI+ model): m/z calcd for M+ 289.0061, found 289.0070; Anal. Calcd for $C_{15}H_{11}NO$: C, 62.09; H, 3.13; N, 4.83. Found: C, 62.00; H, 3.37; N, 4.79.

One-pot preparation of isoquinoline-1(2H)-one from phenyl acetaldehydes. Conc. H_2SO_4 (2 mg) was

added to a solution of 2,2-bis(*p*-chlorophenyl)acetaldehyde (1d, 7.9 g, 3.0 mmol) and ethyl carbamate (5.35 g, 6.00 mmol) in toluene (50 mL) and churned while cooling in ice for 1 h. The solvents were distilled off under vacuum (0.1 mm) at 80 °C to leave a yellow oily residue. After the residue cooling to 40 °C, cyclohexane (100 mL) was added. The solvent was evaporated under vacuum (0.1 mm) at 80 °C and then phenylcyclohexane (100 mL) was added. The reaction mixture was then heated at 230 °C for 4 h and the crude 7-chloro-4-(*p*-chlorophenyl)isoquinoline-1(2*H*)-one **4d** was solidified after cooling. The solid was washed with phenylcyclohexane and recrystallized from acetone to give 7-chloro-4-(*p*-chlorophenyl)isoquinoline-1(*2H*)-one (**4d**, 6.3 g, 73 %).

The isoquinoline-1(2H)-one ***4a*** was prepared in 70% yield according to the general procedure; mp 205–206 °C (lit.,[23] 203–205 °C). ^{1}H NMR (200 MHz, DMSO-d_6): δ = 7.08–7.79 (m, 4H), 8.12–8.23 (d, 1H), 6.55 (d, *J* = 7.6 Hz, 1H), 11.22 (br, 1H) ppm. Anal. Calcd for C_9H_7NO: C, 74.48; H, 4.83; N, 9.66. Found: C, 73.43; H, 5.24; N, 9.66.

The 4-methylisoquinoline-1(2H)-one ***4b*** was prepared in 73% yield according to the general procedure; mp 171–173 °C (lit.,[24] 172–173 °C). ^{1}H NMR (400 MHz, acetone-d_6): δ = 2.26 (s, 3H), 10.48 (s, 1H), 8.36 (d, *J* = 8.0 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.52 (t, *J* = 8.0 Hz, 1H), 7.75 (t, *J* = 8.0 Hz, 1H), 7.08 (s, 1H) ppm; ^{13}C NMR (400 MHz, DMSO-d_6): δ = 15.3, 111.7, 124.3, 127.0, 127.1, 127.5, 128.4, 133.2, 139.4, 163.1 ppm.

The 4-phenylisoquinoline-1(2H)-one ***4c*** was prepared in 80% yield according to the general procedure; mp 237–239 °C (lit.,[25] 240–241 °C); ^{1}H NMR (200 MHz, DMSO-d_6): δ = 7.3–7.6 (m, 7H), 7.6–7.8 (t, 1H), 8.2–8.4 (d, 1H), 7.1–7.2 (s, 1H), 11.4–11.6 (s 1H) ppm. Anal. Calcd for $C_{15}H_{11}NO$: C, 81.26; H, 5.03; N, 6.35. Found: C, 81.45; H, 4.98; N, 6.33.

7-Bromo-4-(p-bromophenyl)isoquinoline-1(2H)-one ***4e*** was prepared in 83% yield according to the general procedure; mp 312–314 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.19 (d, *J* = 5.6 Hz, 1H), 7.37–7.39 (dd, *J* = 6.8, 6.8 Hz, 2H), 7.43 (d, *J* = 8.8 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 2H), 7.83–7.86 (dd, *J* = 8.8, 8.8 Hz, 1H), 8.36 (s, 1H), 11.71 (br d, 1H) ppm; ^{13}C NMR (400 MHz, DMSO-d_6): δ = 115.8, 119.6, 120.9, 126.6, 127.4, 128.8, 129.4, 131.7, 131.9, 134.9, 135.4, 160.1 ppm; EI-MS: m/z 379 (M^+); FTIR (KBr): ν = 1629 (C=C), 1676 (C=O), 3173 (NH), 3050–3350 cm^{-1}. Anal. Calcd for $C_{15}H_{11}NO$: C, 47.53; H, 2.39; N, 3.70. Found: C, 47.49; H, 2.59; N, 3.60.

The 3-methylisoquinoline-1(2H)-one ***4o*** was prepared in 86% yield according to the general procedure; mp 213–215 °C (lit.,[26] 214–216 °C); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.43 (s, 3H), 6.35 (s, 1H), 7.20–7.80 (m, 3H), 8.42 (d, *J* = 8.0, Hz 1H), 11.85 (s, 1H) ppm. Anal. Calcd for $C_{10}H_9NO$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.43; H, 5.83; N, 8.68.

The 3-benzylisoquinoline-1(2H)-one ***4p*** was prepared in 66% yield according to the general procedure; mp 188–190 °C (lit.,[27] 190–191 °C). Anal. Calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95. Found: C,

81.75; H, 5.60; N, 5.89.

The 3-methyl-4-phenylisoquinoline-1(2H)-one ***4q*** was prepared in 93% yield according to the general procedure; mp 275–276 °C (lit.,[28] 279–280 °C). Anal. Calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.63; H, 5.67; N, 5.76.

The 3-phenylisoquinoline-1(2H)-one ***4r*** was prepared in 79% yield according to the general procedure; mp 201–202 °C (lit.,[29] 199.5–200 °C); ^{1}H NMR (200 MHz, DMSO-d_6): δ = 6.91 (s, 1H), 7.24–7.49 (m, 4H), 7.63 (d, J = 7.2 Hz, 1H), 7.69 (t, J = 7.2 Hz, 1H), 7.69–7.77 (m, 2H), 8.42 (d, J = 8.0 Hz, 1H), 11.60 (br s, 1H) ppm. Anal. Calcd for $C_{15}H_{11}NO$: C, 81.43; H, 5.01; N, 6.33. Found: C, 81.20; H, 5.68; N, 6.39.

The phenanthridinone ***4s*** was prepared in 65% yield according to the general procedure; mp 253–255 °C (lit.,[30] 250–255 °C). Anal. Calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.34; H, 6.70; N, 6.90.

The 5-phenyluracil ***7***; mp >300 °C (lit.,[31] >300 °C); ^{1}H NMR (200 MHz, DMSO-d_6): δ = 7.20-7.59 (m, 5H), 7.62 (s, 1H), 11.05-11.26 (br, 2H); EI-MS: m/z 188 (M^+). 99% ee by HPLC analysis (HYPERSIL-100 C18 column, 0.46 cm x 25 cm, flow rate = 0.5 mL/min, 100% acetonitrile, detection wavelength = 254 nm). Retention times = 5.74 min.

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