Friedel-Crafts chemistry. Part 45: expedient new improved process for the synthesis of oxacarbazepine precursor 10,11-dihydro-10-oxo-5*H*-dibenz[*b*,*f*]azepine via Friedel-Crafts cycliacylations

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Abstract

An unprecedented efficient methodology for the synthesis of 10,11-dihydro-10-oxo-5*H*-dibenz[*b*,*f*]azepine via a three new synthetic pathways is described. The key steps of this approach are based on classical Friedel-Craft ring closures of three precursors 1-(2-(*N*-phenyl-*N*-tosylamino)phenyl)-2-bromoethanone, ethyl 2-(2-(*N*-phenyl-*N*-tosylamino)phenyl)acetate or 2-(2-(*N*-phenyl-*N*-tosylamino)phenyl)acetic acid, by using $AlCl_3/CH_3NO_2$ or $AlCl_3$ in dichloromethane. For the latter two precursors, P_2O_5 in toluene worked also well. The precursors were easily obtained in a two- or three -step reaction sequence. Overall, the described approach allows easy and efficient access to the tricyclic dibenzoazepinone ring system from easily accessible starting materials.

Keywords: Friedel-Crafts cycliacylations, oxacarbazepine, 10,11-dihydro-10-oxo-5*H*-dibenz[*b*,*f*]azepine, *o*-anilinoacetic acid, dibenzo[*b*,*f*]azepines

Introduction

The synthesis of dibenzo[*b*,*f*]azepines has been the focus of interest of many investigations during recent years. They are important synthetic intermediates[1] exhibit interesting biological activities[2] while substituted or reduced dibenzo[*b*,*f*]azepine skeletons are the core structures of several natural products[3] and pharmaceuticals[4,5] such as oxcarbazepine, carbamazepine, imipramine, desipramine, clomipramine and trimipramine exhibiting a diverse medical functions as antiviral, antidepressant, antiepileptic, anticonvulsant, antimicrobial, antimalarial and anticancer activities[5] (Fig. 1). Among the related dibenzoazepine derivatives, 10,11-dihydro-10-oxo-5*H*-dibenz[*b*,*f*]azepine **3** has a unique nitrogen-containing tricyclic structure which was the precursor in the develop of drug oxcarbazepine[6] (a second-generation of antiepileptic drug) sold under the trade name Trileptal®.

In spite of the large number of published synthetic routes to iminostilbene **2** and its reduced derivative **1**[7], to date, only a limited number of synthetic strategies have been successfully applied to the preparation of dibenzoazepinone **3**. This may be due to unfavorable entropic factors and transannular interactions encountered during the synthesis of medium-sized rings.[8]

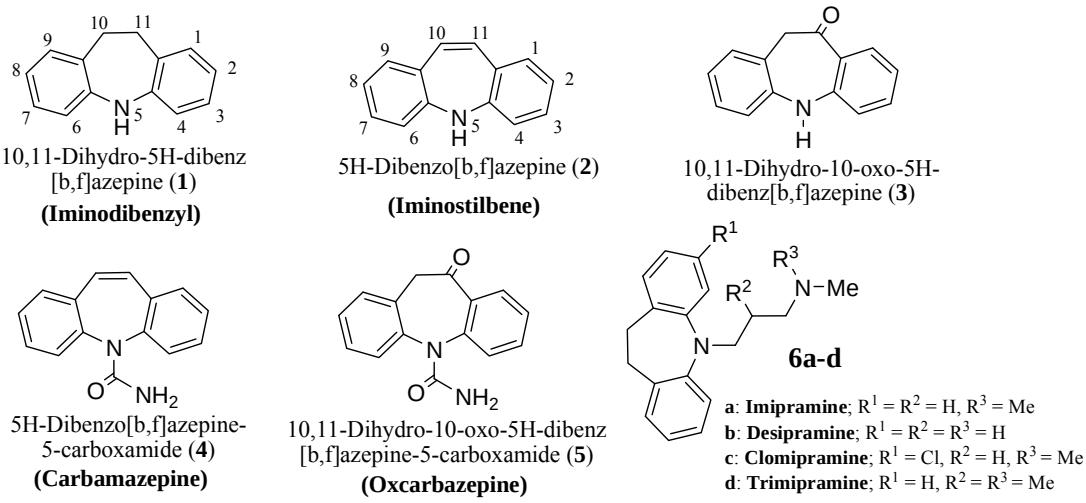
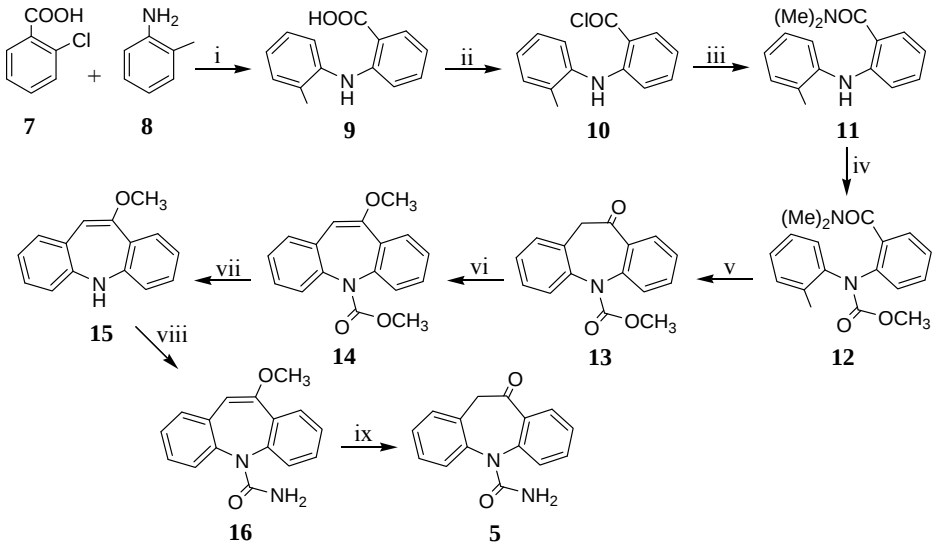


Figure 1. Dibenz[*b,f*]azepine templates containing drugs.

The most important synthetic strategies leading to dibenzoazepinones are as follows. In 1964 Geigy[9] synthesised compound **3** via the addition of bromine to 5-acety-5*H*-dibenz[*b,f*]azepine followed by dehydrohalogenation and hydrolysis of the remaining bromide under basic conditions. This strategy was found to be general, as it provided several derivatives of dibenzoazepinones. Fouche *et al*.[10] disclosed a convenient one-step regioselective synthesis of dibenzoazepinone **3** derivatives via hydrolysis followed by oxidation of 10-methoxydibenz[*b,f*]azepine. Later, Karusala *et al*.[11] and Gupta *et al*.[12] adopted the same strategy for the synthesis of 10-methoxy or 10-haloiminostilbene derivatives which involved sequential *N*-protection, halogenation and elimination sequence or alternatively by a dehydrohalogenation of a halomethoxyiminodibenzyl intermediate obtained by using 1,3-dihalodimethylhydantoin. By a different approach, Aufderhaar *et al*.[13] demonstrated a straightforward methodology for the construction of dibenzoazepinone **3** and consequently the synthesis of targeted oxcarbazepine **5** from iminodibenzyl by benzylic oxidation after a suitable *N*-functionalization. Lohse *et al.*[14] used a tandem remote metalation and cyclization of 2-carboxamido-2'-methyldiarylamines, prepared by palladium mediated Buchwald-Hartwig coupling of *o*-bromobenzamides with *o*-toluidine followed by *N*-deprotected and carbamoylated to afford oxcarbazepine **5**. Other widely used methodologies for the synthesis of oxcarbazepine **5** are, epoxidation of iminostilbene followed by hydrogenation and oxidation reactions,[15] iron-catalyzed reduction and acid hydrolysis of 10-nitroiminostilbene or its corresponding oximes respectively,[16] as the key steps in these

approaches. Both of theses processes, described in detail in Scheme 1, are industrial procedures for the development of oxcarbazepine **5** at Novartis.



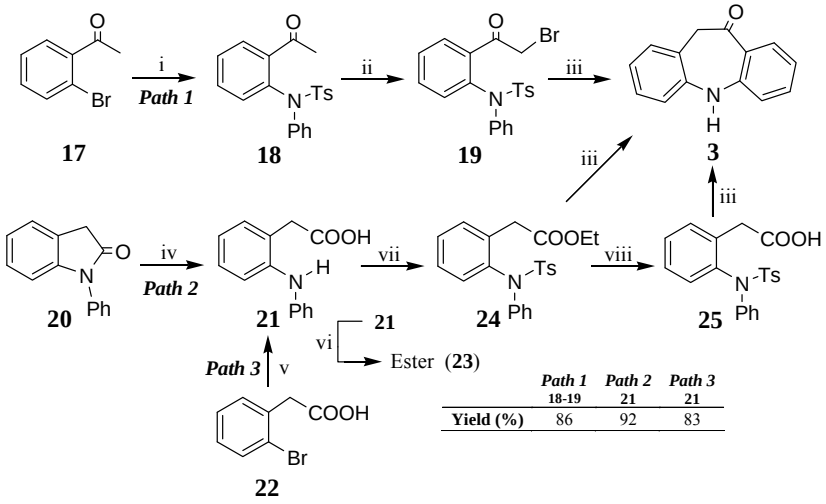
Scheme 1. Reagents and conditions: (i) CuO/K_2CO_3, 170 °C, 10h, (ii) $SOCl_2$, 80 °C, 2h, (iii) *aq.* Me_2NH, 1h, reflux, (iv) *n*-BuLi, $ClCOOCH_3$, (v) LDA, THF, 4h, (vi) $HC(OCH_3)_3$/ TsOH, MeOH, 5h, reflux, (vii) KOH, H_2O/PEG, 8h, reflux, (viii) *a*. NaOCN; *b*. $AcOH/H_2O$, 3h, (ix) HCl, 7h, reflux.

Further synthetic approaches to compound **5** involved intramolecular Friedel-Crafts acylation of 2-carboxymethyldiarylamine intermediate to give 10-methoxyiminostilbene which upon carbamoylation and hydrolysis furnished **5**.[17] Recently, a palladium-catalyzed sequential *N*-arylations reactions of substituted 2-(2-bromophenyl)-1-(2-(tosylamino)phenyl)ethanone was recently reported.[18] This strategy was applied to the synthesis of not only of oxcarbazepine **5** but also of several structural analogs which incorporate arene or heteroarene rings.

In recent communications we have demonstrated a very simple procedure for the synthesis of series of tricyclic keto derivatives of 10,11-dihydro-5*H*-dibenz[*b*,*f*]azepines (iminodibenzyls),[19,20] 5,6-dihydro-11*H*-benz[*f*]pyrido[2,3-*b*]azepines[20], 5,6,11,12-tetrahydro-5*H*-dibenz[*b*,*f*]azocines and 5,6,11,12-tetrahydro-6*H*-benz[*g*]pyrido[2,3-*c*]azocines, via cyclialkylations of suitably synthesized nitrogen-containing alkanols and carboxylic acids. The results sustain the broad significance and utility of Friedel-Crafts cyclialkylations chemistry[21] applied to the routine synthesis of difficult heterocyclic skeletons with the advantages of shorter reaction times and higher yields. In view of the above reports and in continuation of our interest in Friedel-Crafts ring closures[22] as expedient alternative synthetic routes of novel and known heterocyclic systems, herein, we report the synthesis of 10,11-dihydro-10-oxo-5*H*-dibenz[*b*,*f*]azepine **3** by three different facile synthetic routes starting with easily prepared precursors.

Results and Discussion

Our approaches to the desired 10,11-dihydro-10-oxo-5*H*-dibenz[*b,f*]azepine **3** involved three classical synthetic pathways (Scheme 2). *Path 1*, included the conversion of 1-(2-bromophenyl)ethanone **17**[23] to 1-(2-(*N*-phenyl-*N*-tosylamino)phenyl)-2-bromoethanone **19** via two consecutive steps: (i) *N*-alkylation of ketone **17** with *N*-tosylbenzenamine[24] in the presence of K_2CO_3 in DMF solution to give 1-(2-(*N*-phenyl-*N*-tosylamino)phenyl)ethanone (**18**) and (ii) bromination of the resulting ketone **18** with one equivalent of bromine in $CHCl_3$ afforded 2-bromoketone **19**. In the other two reaction paths, 2-(2-(phenylamino)phenyl)acetic acid (**21**) the key intermediate, obtained via *Path 2*, encompassed ring opening hydrolysis of 1-phenylindolin-2-one (**20**)[25] to acid **21** by refluxing with NaOH in ethanol and via *Path 3* from the base catalyzed Ullmann[26] *N*-coupling reaction of 2-(2-bromophenyl)acetic acid (**22**)[27] with aniline in the presence of K_2CO_3/Cu in pyridine at 110-20 °C. In the next step, the resulting *o*-anilinoacetic acid **21** was esterified[28] in the presence of ethanol and H_2SO_4 under reflux to furnish ethyl 2-(2-(phenylamino)phenyl)acetate **23**. The latter ester was converted to the *N*-tosylated ester **24** by reaction with tosyl chloride in pyridine which in turn was hydrolyzed with NaOH in methanol to carboxylic acid **25**. The structures of all new compounds were appropriately established by both elemental and spectral analyses (IR, ^{1}H NMR, MS).



	Path 1 18-19	Path 2 21	Path 3 21
Yield (%)	86	92	83

Scheme 2. Reagents and conditions: (i) PhNHTs, K_2CO_3, CuO, DMF, 170 °C, 15 h, (ii) Br_2, $CHCl_3$, 2 h, (iii) $AlCl_3$ or $AlCl_3/CH_3NO_2$ or $FeCl_3$ or P_2O_5 or PPA catalysts (Table 1), (iv) NaOH/ EtOH, 8 h, reflux, (v) $PhNH_2$, K_2CO_3/pyridine, Cu, 110-20 °C, 8 h, (vi) EtOH/H_2SO_4, 9 h, reflux, (vii) *p*-TosCl/pyridine/CH_2Cl_2, 80-90 °C, 11 h, (viii) NaOH/MeOH, rt, 10 h, reflux, HCl.

The IR spectrum of ketone **19** showed the characteristic absorption band for C=O group as at 1683 cm^{-1}. The ^{1}H NMR spectrum for compound **19** displayed three signals. The aromatic protons appear at δ 6.84-7.34, the aliphatic acyclic protons of the methyl and methylene groups

appear as two singlet at δ 2.47 and δ 4.48 respectively. The IR spectra of acid **25** showed a broad absorption band at 2700-2535 cm^{-1} for the OH group and a sharp band at 1717 cm^{-1} for the C=O group. The ^{1}H NMR data allowed an unambiguous results for the tosyl acid formation. Thus, the ^{1}H NMR spectrum displayed four signals, aromatic protons appear at δ 6.63-7.71 while the aliphatic protons of the two CH_3 and CH_2 groups of the new acid appeared at δ 2.27 and 3.45 respectively. The singlet at δ 10.28 corespounds to the carboxylic acid OH group.

In the final step, cycliacylation of bromoketone **19** ester **24** or aryl acids **25** proceeded smoothly in the presence of $AlCl_3$ or $FeCl_3$ or $AlCl_3/CH_3NO_2$ or PPA (polyphosphoric acid) or P_2O_5 catalysts[29] under different reaction conditions to provide tricyclic ketone 39 in good overall yields (Table 1 and Scheme 2).

From Table 1 it is evident that the cycliacylation of precursors **19**, **24** and **25** to product **3** depends on the catalyst, solvent and temperature used. Overall the best results are in the presence of Lewis acid catalysts. For example, treatment of **19** with $AlCl_3/CH_3NO_2$ in DCM for 24 hours at room temperature are the mildest conditions with the highest yield of compound **3**. For the cycliacylation of precursor **24** the use of $AlCl_3$ in DCM under reflux worked equally well (83% yield of **3**) when compared to the use of P_2O_5 in toluene under reflux (84% yield of **3**). On one the other hand, cycliacylation of precursor **25** worked by far the best when carried out in the presence of P_2O_5 in toluene under reflux (89% yield of **3**).

Table 1. Optimization of the Friedel-Crafts cycliacylations of **19**, **24** and **25** to tricyclic **3**

Entry	Substrate	Catalyst	Solvent	Temp. °C	Time (h)	Yield (%)[a]
1	**19**	$AlCl_3$[b]	DCE [c]	reflux	15	86
2	**19**	$AlCl_3/CH_3NO_2$[d]	DCM[e]	RT	24	90
3	**19**	$FeCl_3$ [f]	DCE	reflux	18	84
4	**24**	$AlCl_3$	DCE	reflux	10	83
5	**24**	P_2O_5 [g]	toluene	reflux	8	84
6	**24**	PPA	--	160-170	4	77
7	**25**	$AlCl_3$	DCE	reflux	8	84
8	**25**	$AlCl_3/CH_3NO_2$	DCM	RT	9	85
9	**25**	P_2O_5	toluene	reflux	5	89
10	**25**	PPA	--	160-170	5	74

[a] Crude isolated yield of ketone **3** refer to substrate. [b] With $AlCl_3$ catalyst reactant proportions were: carbinol or acid (3 mmol), $AlCl_3$ (6 mmol) and solvent (10 ml). [c] 1,2-dichloroethane.
[d] With $AlCl_3/CH_3NO_2$ catalyst reactant proportions were: carbinol (0.002 mole), $AlCl_3$ (0.0024 mole), CH_3NO_2 (0.024 mole), solvent (10 ml). [e] Dichloromethane. With $FeCl_3$ catalyst reactant proportions were: carbinol or acid (3 mmol), $AlCl_3$ (9 mmol) and solvent (10 ml). [f] With PPA catalyst reactant proportions were: carbinol or acid (0.5 g) and PPA (5 g).
[g] With P_2O_5 catalyst reactant proportions were: carbinol or acid (0.4 g) and P_2O_5 (4 g) in anhydrous toluene (15 mL).

A plausible acylation mechanism that accounted for the cycliacylation of **24** and **25** is the generation of acyl carbocation[30], either free or as an ion pair[31] which upon treatment with acidic catalysts losses water or alcohol. However, ring closures of **19** is explained to occur via an alkylation mechanism produce a primary carbocation.[32] The resulting acyl carbocation or carbocation then undergoes ring closure to dibenzazepinone **3**. The removal of the tosyl group occurs concurrently with the closure step as noted in other reported cases.[33]

It is noteworthy to comment about utility of Friedel-Crafts cycliacylations in the synthesis of medium-sized azacarbocycles which has received substantial support in the literature.[34] These reactions were observed for the synthesis of tetracyclic thiazocines, pyrrolothienodiazocine and benzodiazocines (Fig. 2).[35] The Friedel-Crafts reaction has been considered as one of the macrocyclization reactions (including carbocyclizations, macrolactonizations and macrolactamizations) for the synthesis of medium-sized rings characterized by small enthalpic cost and large entropic cost in the transition state but little to no entropic cost in the product cycle.[36] Furthermore, elimination of transannular interactions in the synthesis of medium-sized rings comes at the cost of minimized Baeyer and Pitzer strains which in turn could be diminished by applying more strenuous conditions.[37]

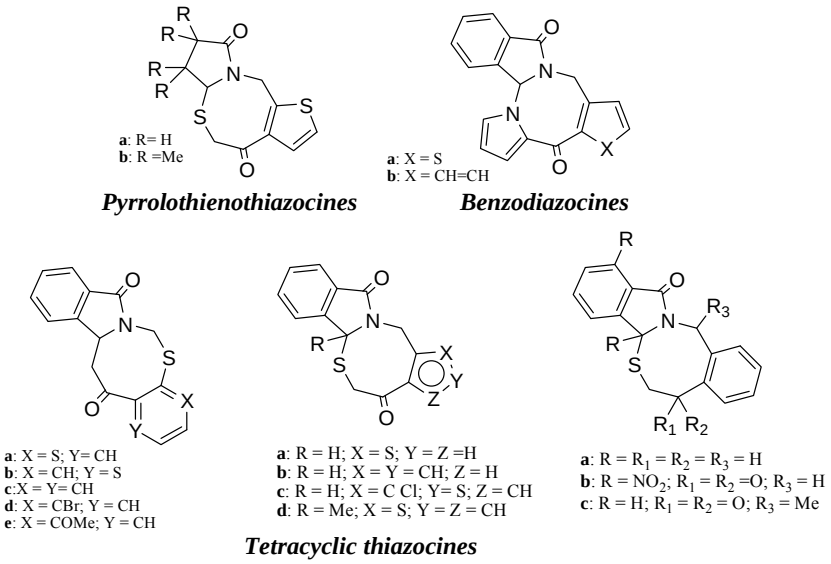


Figure 2. Heteropolycycles synthesized by Friedel-Crafts cycliacylations.

Conclusions

We have developed a simple and new synthetic routes to 10,11-dihydro-10-oxo-5*H*-dibenz[*b*,*f*]azepine in good yields by Friedel-Crafts ring closure of 1-(2-(*N*-phenyl-*N*tosylamino)phenyl)-2-bromoethanone, ethyl 2-(2-(*N*-phenyl-*N*-tosylamino)phenyl)acetate or 2-(2-(*N*-phenyl-*N*-tosylamino)phenyl)acetic acid by obtaining the best yields with $AlCl_3/CH_3NO_2$ and $AlCl_3$ in dichloromethane. For the latter two precursors, P_2O_5 in toluene worked also well.

The described approaches are an alternative to those previously reported for the synthesis of the dibenzazepinone ring system and provide the products in good yields with selectivity even during high temperatures and short reaction times. The results proved the significance of applying Friedel-Crafts ring closure reaction conditions for the synthesis of heteropolycycles.

Experimental Section

General. All reagents were purchased from Merck, Sigma or Aldrich Chemical Co. and were used without further purification. Melting points were measured on a digital Gallenkamp capillary melting point apparatus and are uncorrected. The IR spectra were determined with a Shimadzu 470 Infrared spectrophotometer using KBr wafer and thin film techniques (ν cm^{-1}). The ^{1}H NMR and ^{13}C NMR spectra were recorded on JEOL LA 400 MHz FT-NMR (400 MHz for ^{1}H, 100 MHz for ^{13}C) and on a Varian NMR (90 MHz) spectrometers using $CDCl_3$ solvent with TMS as internal standard. Chemical shifts (δ) and J values are reported in ppm and Hz, respectively. The mass spectra were performed by JEOL JMS 600 spectrometer at an ionizing potential of 70 eV using the direct inlet system. Refractive index was measured using an Abbe refractometer at sodium D-line wavelength (589.3 nm) at 25 °C (n_D^{25}). Elemental analyses were performed on a Perkin-Elmer 2400 Series II analyzer. Reactions were monitored by thin layer chromatography (TLC) using precoated silica plates visualized with UV light. Flash column chromatography was performed on silica gel or basic alumina.

Path 1. This route comprise two reaction steps starting with 1-(2-bromophenyl)ethanone (**17**)[23]

1-(2-(*N*-Phenyl-*N*-tosylamino)phenyl)ethanone (18). A solution of 1-(2-bromophenyl)-ethanone **17** (3.3 g, 17 mmol) in DMF (15 mL) was added slowly over 30 min to a stirred reaction mixture of *N*-tosylbenzenamine[24] (4.8 g, 20 mmol), CuO (0·05 g) and K_2CO_3 (6.2 g, 45 mmol) in DMF (20 mL). The mixture was stirred under reflux for 12 h and then cooled to room temperature, diluted with water (100 mL) and finally extracted with AcOEt (3×30 mL). The combined organic layer was washed successively with water, dried over $MgSO_4$ and the solvent was removed in *vacuo* to give (4.6 g, 77%) of crude ketone. Crystallization from benzene gave (4.3 g, 72%) of pure 1-(2-(*N*-phenyl-*N*-tosylamino)phenyl)ethanone (**18**) as white crystals; mp 162 °C; IR (KBr) ν_{max} 3084, 2952, 1680, 1605, 1586, 1510, 1442, 1360, 1275, 1164, 764 cm^{-1}. ^{1}H NMR (90 MHz, $CDCl_3$, ppm), δ 2.35 (3H, s, CH_3), 2.75 (3H, s, CH_3), 7.45-8.45 (13H, m, Ar-H). MS (EI, 70 eV) *m/z* (%), 366 (M^++1, 18), 365 (M^+, 66), 364 (100), 350 (43), 322 (21), 288 (53), 245 (25), 210 (37), 195 (36), 169 (62), 132 (15), 91 (20) 76 (6). Anal. Calcd. for $C_{21}H_{19}NO_3S$ (365); C, 69.04; H, 5.20; N, 3.83; S, 8.76. Found; C, 69.15; H, 5.27; N, 3.74; S, 8.60%.

1-(2-(*N*-Phenyl-*N*-tosylamino)phenyl)-2-bromoethanone (19). To an ice-cold solution of substituted acetophenone **18** (3.6 g, 10 mmol) in chloroform (25 mL) was gradually added a solution of bromine (1.9 g, 12 mmol) in chloroform (10 mL) over 30 minutes with continuous stirring. After the addition was complete, the reaction mixture was slowly brought to the room

temperature and stirring was continued for another 2h until the evolution of hydrogen bromide gas ceased. Afterwards, the solvent was removed in *vacuo* to give (3.7 g, 86%) of crude product. Crystallization from ethanol gave (3.4 g, 80%) of pure 1-(2-(*N*-phenyl-*N*-tosylamino)phenyl)-2-bromoethanone **19** as white crystals; mp 105 °C; IR (KBr) ν_{max} 3075, 2964, 1683, 1600, 1568, 1511, 1455, 1268, 1177, 687 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, ppm), δ 2.47 (3H, s, CH_3), 4.48 (2H, s, CH_2), 6.84-7.34 (13H, m, Ar-H). MS (EI, 70 eV) *m/z* (%), 445 (M^++1, 32), 444 (M^+, 43), 367 (42), 364 (100), 350 (20), 322 (16), 287 (78), 272 (51), 180 (62), 168 (38), 105 (27), 90 (14) 77 (9). Anal. Calcd. for $C_{21}H_{18}BrNO_3S$ (444); C, 56.75; H, 4.05; N, 3.15; S, 7.20; Br, 18.01. Found; C, 56.60; H, 4.17; N, 3.20; S, 7.34; Br, 17.82%.

2-(2-(Phenylamino)phenyl)acetic acid (21). This compound was synthesized via two different pathways: *path 2* starting with 1-phenylindolin-2-one (**20**)[25] and *path 3* starting with 2-(2-bromophenyl)acetic acid (**22**).[27]

Path 2. Hydrolysis of 1-phenylindolin-2-one (20).

To a refluxed solution of oxindole **20** (4.2 g, 20 mmol) in ethanol (20 mL, 90%), was slowly added NaOH solution (10 N, 5 mL) and reflux is continued for 6 h. The solution is cooled to about 30 °C and treated slowly with HCl solution (40 mL, 20 %). The obtained suspension is then left to stand at refrigerator for overnight. The crystals are collected by filtration, washed with water and dried giving (4.1 g, 92%) of crude acid. Crystallization from methanol gave (3.7 g, 84%) of pure 2-(2-(phenylamino)phenyl)acetic acid **21** as white crystals; mp 147 °C; IR (KBr) ν_{max} 3395, 3063, 2955, 2564, 1725, 1600, 1580, 1463, 1445, 1374, 1180, 749 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, ppm), δ 3.57 (2H, s, CH_2), 5.24 (1H, s, NH), 6.71-7.90 (9H, m, Ar-H), 11.14 (1H, s, COOH). Anal. Calcd. for $C_{14}H_{13}NO_2$ (227); C, 74.00; H, 5.72; N, 6.16. Found; C, 73.85; H, 5.85; N, 6.14%.

Path 3. Ullmann coupling reaction of 2-(2-bromophenyl)acetic acid (22) with aniline

A mixture of acid **22** (2.1 g, 10 mmol), aniline (1.8 g, 20 mmol), K_2CO_3 (3.4 g, 25 mmol), pyridine (2 mL) and activated copper powder (0.4 g) was heated with continuous stirring for 8 h at 110-20 °C. The resulting slightly brownish mixture was diluted with water (50 mL), filtered while hot and washed with water (40 ml). The filtrate was cooled to room temperature and extracted with hexane (3×20 mL). The aqueous layer was separated and decolorizing carbon (5 g) was added and then the whole mixture was boiled for 10 min then filtered on hot. The clear cold filtrate was acidified using HCl solution (30 mL, 20%) until the pH 1-2. The resultant precipitate was collected, washed with water and dried to give (1.8 g, 83%) of the crude acid. Recrystallization from ethanol gave the pure product that's physical and spectral data are similar to that obtained from *path 2*.

Ethyl 2-(2-(phenylamino)phenyl)acetate (23). A mixture of acid **21** (4.5 g, 20 mmol), absolute ethanol (40 mL) and concentrated sulfuric acid (4 mL) was refluxed for 10 h. The excess alcohol removed by distillation and the residue was diluted with water (50 mL), basified with Na_2CO_3 solution (20 mL, 30%) and extracted with ether (2×20 mL). The ethereal layer was separated, washed with water, dried over $MgSO_4$ and the solvent was removed in *vacuo* to give (4.5 g, 90 %) of crude oily ester **23**. Purification by flash column chromatography (basic alumina,

EtOAc/n-hexane, 2/1) gave (4.1 g, 82%) of pure ethyl 2-(2-(phenylamino)phenyl)acetate (**23**) in the form of pale yellow oil; n_D^{25} 1.588; IR (Film) ν_{max} 3386, 3065, 2973, 1745, 1600, 1560, 1490, 1455, 1340, 1174, 748 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$, ppm), δ 1.35 (3H, t, *J* 7.5 Hz, CH_3), 3.50 (2H, s, CH_2), 4.25 (2H, s, *J* 7.5 Hz, CH_2), 4.90 (1H, s, NH), 6.50-7.90 (9H, m, Ar-H); MS (EI, 70 eV) *m/z* (%), 255 (M^+, 25), 240 (27), 210 (100), 195 (33), 164 (19), 148 (37), 119 (12), 91 (8), 90 (16), 77 (5). Anal. Calcd. for $C_{16}H_{17}NO_2$ (255); C, 75.29; H, 6.66; N, 5.49. Found; C, 75.35; H, 6.54; N, 5.62%.

Ethyl 2-(2-(*N*-phenyl-*N*-tosylamino)phenyl)acetate (24). To a solution of ester **23** (5.1 g, 20 mmol) in a mixture of pyridine (9.5 ml, 120 mmol) in dichloromethane (25 ml) was added *p*-toluenesulfonyl chloride (4.7 g, 25 mmol) slowly in small portions over 10 minutes. The reaction mixture was stirred at room temperature for 16 h and then heated for 30 min on water bath at 80-90 °C. After cooling, water (100 mL) was added and the mixture was extracted with AcOEt (3×30 mL). The combined organic layer was washed with HCl (2×30 mL, 5%), with $NaHCO_3$ soln (3×30 mL) and finally with water. The organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated in *vacuo* to afford (7.5 g, 92%) of crude tosylated ester **24**. Crystallization from aqueous acetone gave (6.8 g, 84%) of pure ethyl 2-(2-(*N*-phenyl-*N*-tosylamino)phenyl)acetate (**24**) as white crystals; mp 153-55 °C (Lit.[20] mp 152-3 °C). IR (KBr) ν_{max} 3070, 2980, 1742, 1585, 1520, 1455, 1440, 1390, 1333, 1160, 745 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$, ppm), δ 1.30 (3H, t, *J* 7.5 Hz, CH_3), 2.35 (3H, s, CH_3), 3.65 (2H, s, CH_2), 4.25 (2H, s, *J* 7.5 Hz, CH_2), 6.45-7.90 (13H, m, Ar-H); MS (EI, 70 eV) *m/z* (%), 410 (M^++1, 12), 409 (M^+, 31), 364 (100), 254 (83), 209 (50), 181 (66), 163 (31), 118 (17), 90 (24) 77 (9). Anal. Calcd. for $C_{23}H_{23}NO_4S$ (409); C, 67.48; H, 5.62; N, 3.42; S, 7.82. Found; C, 67.40; H, 5.72; N, 3.57; S, 7.96%.

2-(2-(*N*-Phenyl-*N*-tosylamino)phenyl)acetic acid (25). To a stirred solution of tosylated ester **24** (4.0 g, 10 mmol) in methanol (25 mL) was added in small increments with swirling NaOH solution (5 mL, 10%). The reaction mixture was efficiently stirred for15 h at room temperature and the resultant clear solution was diluted with water (500 mL) then poured with into an ice-cold HCl solution (25 mL, 10%). The crude precipitate was filtered off and dissolved with slight warming in $NaHCO_3$ solution (40 mL, 20%), filtered and acidified with HCl solution (10%). The precipitated acid was collected, washed and dried to give (3.2 g, 84%) of crude acid **25**. Crystallization from methanol gave (3.0 g, 79%) of pure 2-(2-(*N*-Phenyl-*N*-tosylamino)phenyl)acetic acid (**25**) as white crystals; mp 154-55 ºC (Lit.[20] mp 152-4 °C); IR (KBr) ν_{max} 3105, 2974, 2700-2535, 1717, 1580, 1460, 1440, 1395, 1230, 747 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, ppm), δ 2.27 (3H, s, CH_3), 3.45 (2H, s, CH_2), 6.63-7.71 (13H, m, Ar-H), 10.28 (s, 1, COOH); MS (EI, 70 eV) *m/z* (%), 381 (M^+, 32), 364 (24), 363 (43), 336 (100), 304 (31), 260 (57), 259 (27), 226 (75), 206 (34), 183 (82), 178 (17), 168 (13), 104 (18), 91 (9), 77 (5). Anal. Calcd. for $C_{21}H_{19}NO_4S$ (381); C, 66.14; H, 4.98; N, 3.67; S, 8.39. Found; C, 66.18; H, 4.83; N, 3.72; S, 8.52%.

Friedel-Crafts cycliacylation procedures

The procedures described for cyclialkylation of heteroarylalkanols with $AlCl_3$ or $AlCl_3/CH_3NO_2$

$FeCl_3$ or P_2O_5 or PPA were essentially followed.[29] In all reactions, the crude products were purified firstly by flash column chromatography (basic alumina, EtOAc/n-hexane, 2/1) to give the pure product. The conditions and yields for the cyclic dibenzazepinone **3** are shown in Table 1 while the physical and spectral data are given in the following.

10,11-Dihydro-10-oxo-5*H*-dibenz[*b,f*]azepine (3). White needles; mp 143-44 °C (Lit.[9] mp 145-6 °C. Lit.[20] mp 141-3 °C) (Benzene). IR (KBr) ν_{max} 3380, 3064, 2975, 1743, 1600, 1586, 1450, 1440 1385, 1285, 1070, 750 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, ppm), δ 3.77 (2H, s, CH_2), 6.41-7.52 (8H, m, Ar-H), 9.53 (1H, s, NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.2, 118.4, 119.0, 119.5, 119.8, 123.0, 128.2, 128.8, 129.3, 132.2, 136.8, 140.7, 145.6, 198.5; MS (EI, 70 eV) *m/z* (%), 210 (M^++1, 28), 209 (M^+, 19), 208 (100), 194 (62), 181 (83), 177 (27), 167 (48), 151 (31), 109 (57), 91 (35), 77 (15). Anal. Calcd. for $C_{14}H_{11}NO$ (209); C, 80.38; H, 5.26; N, 6.69. Found; C, 80.45; H, 5.33; N, 6.52%.

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