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Synthetic application of in situ generation of *N*-acyliminium ions from α-amido *p*-tolylsulfones for the synthesis of α-amino nitriles

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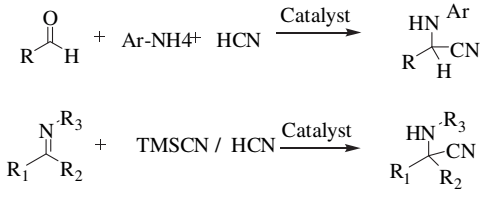
ABSTRACT

In the presence of catalytic amount of bismuth bromide (5 mol %) the α-amido *p*-tolylsulfones are converted into *N*-acyliminium ions, which undergo the nucleophilic addition of trimethylsilyl cyanide (TMSCN) to provide the *N*-protected α-amino nitriles in very good yield. A variety of α-amido *p*-tolylsulfones were prepared from aromatic as well as aliphatic aldehydes for the synthesis of α-amino nitriles.

1. Introduction

α-Amino nitriles have shown the broad interest in recent years because of their synthetic utility when transferring their functionality into the bioactive and natural products.[1] α-Amino nitriles can be readily converted into α-amino acids and various nitrogen containing heterocycles, such as imidazoles and thiadiazoles.[2] α-Amino acids manifest biological and economical significance due to their use in chemistry and biology.[3] One of the most important reactions for the production of α-amino nitriles is the catalytic cyanation of imines (Scheme 1). Another method for the synthesis of α-amino nitriles is the one-pot three-component reaction of carbonyl compounds, aromatic amines and HCN or TMSCN in the presence of the catalyst. In addition to HCN and TMSCN, other cyanating agents, such as tributyltin cyanide,[4a] diethyl phosphorocyanidated (DEPC),[4b] acetyl cyanide,[4c] and diethyl aluminum cyanide[4d] have been also reported under various reaction conditions. TMSCN is a safe and easy to handle reagent, and more effective cyanide source for the Strecker reactions as compared to hydrogen cyanide, sodium or potassium cyanides.



Scheme 1. Synthesis of α-amino nitriles via Strecker reaction.

α-Amino nitriles have been prepared with carbonyl compounds, amines, and TMSCN by numerous catalytic systems[5a,b] using such as vanadyl triflate,[5c] rhodium iodide,[5d] $Fe(Cp)_2PF_6$,[5e] ionic liquid,[5f] β-cyclodextrin,[5g] thallium chloride,[5h] and iodine.[5i] Along with the catalytic systems, Strecker reactions are also reported without help of the catalyst.[6] Recently several authors demonstrate the use of phase transfer catalysts for the asymmetric Strecker reactions of α-amido *p*-tolylsulfones. Ooi et al. have reported the synthesis of *N*-arylsulfonyl α-amino nitriles from α-amido *p*-tolylsulfones in aqueous potassium cyanide in presence of quaternary ammonium salt.[7a] Herrera et al. describe the enantioselective Strecker reactions of α-amido *p*-tolylsulfones with the help of acetone cyanohydrin as a cyanating agent.[7b] The synthesis of recemic α-amino nitrile from α-amido *p*-tolylsulfones in presence 10 mol % of indium chloride has been also reported.[8]

α-Amido *p*-tolylsulfones are considered stable precursor to produce *N*-acyliminium ion **2** that can further react with various types of nucleophiles (Scheme 2).[9]

The reaction of *N*-acyliminium ions has been employed for the synthesis of *N*-homoallylic amines,[10a] α,β-dipeptides,[10b] α-amino phosphonates,[10c] β-amino carbonyl compounds,[10d] and (1-alkyl-1-aryl)methyl

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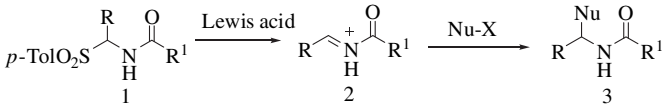


Scheme 2. Nucleophilic substitution of α-amido *p*-tolylsulfones through *N*-acyliminium ions.

phenylsulfones.[10e] Ballini et al. have reported that the Montmorillonite K-10 could be an efficient catalyst for the Friedel–Crafts reactions of α-amido *p*-tolylsulfones with indoles.[10f] Kim et al. demonstrate that $InBr_3$ is an effective catalyst for the synthesis of triaryl methanes and 3-(1-arylsulfonylalkyl)indole from α-amido *p*-tolylsulfones.[10g] Gianelli et al. have utilized the amino catalyst for the *anti*-Mannich reaction of aldehydes with α-amido *p*-tolylsulfones.[10h]

With increasing environmental concern, the need for environmentally benign method has become of significant importance. According to the principle of green chemistry, synthetic method should be designed to use substances that exhibit little or no toxicity to human health and environment.[11] In this regard, bismuth salts have recently attracted considerable attention because bismuth salts are remarkably nontoxic, stable, and cost less.[12] Bismuth salts have been reported as the catalyst for various organic transformation, such as Friedel–Craft reactions,[13a] deprotection of ketoximes,[13b] coupling of carbonyl compounds with alkoxysilane,[13c] synthesis of homoallylic amines,[13d] silylation of alcohols,[13e] and allylation of aldehydes.[13f]

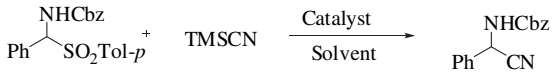
2. Results and discussions

In light of the success in developing several catalytic systems for the cyanosilylation of carbonyl compounds,[14,15] we extend our studies to cyanation of α-amido *p*-tolylsulfones with TMSCN. We wish to herein report a simple and mild method for the synthesis *N*-protected α-amino nitriles from α-amido *p*-tolylsulfones.

The investigations involving the reaction of *N*-benzyloxycarbonylamino phenyl *p*-tolylsulfone with TMSCN in presence of heterogeneous catalysts such as Nafion-SAC-13, Nafion-NR-50, Montmorillonite K-10 (30 mg) and PMA (10 mol %) show no reactivity for the cyanation reaction. Strong Lewis acid $B(C_6F_5)_3$ is enable to produce only 30% yield of the product within 6 h reaction time. Among the other Lewis acid, rhodium iodide is unable to produce the desired product but $FeCl_3$, $FeBr_3$, and thallium chloride are able to yield 48, 33, and 17% of the products, respectively. Fortunately, 10 mol % $BiBr_3$ gives 90% yield of desired product within 3 h reaction time. The reduction of catalyst amount up to 5 mol % shows similar effect on the reactivity. But further decrease in catalyst loading up to 3 mol % gives the lower yield (64%) in 8 h reaction time. The reactivity of $BiBr_3$ was studied in other polar solvents like CH_3CN, $CHCl_3$, THF, and DMF that gives rise to lower yield (10–38%) with longer reaction time (6–10 h). Among the bismuth salts studied, $Bi(OTf)_3$ and $BiCl_3$ demonstrate the moderate yield of *N*-protected α-amino nitriles (35 and 42%) while $Bi(NO_3)_3\cdot 5H_2O$ fails to give the product. Accordingly 5 mol % of $BiBr_3$ can be the optimum amount in 3 h reaction time (entry 11, Table 1).

Various aliphatic and aromatic aldehydes were used for the synthesis of *N*-benzyloxycarbonylamino phenyl *p*-tolylsulfones that in turn react with TMSCN to give the *N*-protected α-amino nitriles (Table 2). The α-amido *p*-tolylsulfone, **1** containing unsubstituted benzene ring is able to give 90% yield (entry 1). *N*-benzyloxycarbonylamino phenyl *p*-tolylsulfones containing electron-donating MeO- and Me- groups on *p*-, *m*-, and *o*- position of phenyl ring provide quite good yield of the products (entry 3–9). Beside α-amido *p*-tolylsulfones, α-amido phenylsulfones also show similar

Table 1
Cyanation of *N*-benzyloxycarbonylamino phenyl *p*-tolylsulfone with TMSCN[a]



1 **2** **3**

Cbz: benzyloxycarbonyl

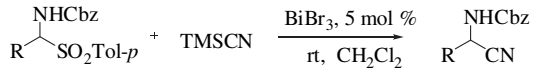
Entry	Catalyst	Mol %	Solvent	Reaction time (h)	Yield[b] (%)
1	Nafion-SAC-13	30 mg	CH_2Cl_2	10	NR
2	Nafion-NR-50	30 mg	CH_2Cl_2	10	NR
3	$BiBr_3$	10	CH_2Cl_2	3	90
4	$B(C_6F_5)_3$	10	CH_2Cl_2	6	30
5	Montmorillonite K-10	30 mg	CH_2Cl_2	10	NR
6	PMA	10	CH_2Cl_2	10	NR
7	$BiBr_3$	10	CH_3CN	5	38
8	$BiBr_3$	10	THF	6	43
9	$BiBr_3$	10	$CHCl_3$	10	30
10	$BiBr_3$	10	DMF	10	10
11	$BiBr_3$	5	CH_2Cl_2	3	90
12	$BiBr_3$	3	CH_2Cl_2	8	64
13	$Bi(OTf)_3$	5	CH_2Cl_2	5	35
14	$BiCl_3$	5	CH_2Cl_2	5	42
15	$Bi(NO_3)_3\cdot 5H_2O$	5	CH_2Cl_2	5	NR
16	$FeCl_3$	5	CH_2Cl_2	3	48
17	$FeBr_3$	5	CH_2Cl_2	3	33
18	$RhI_3\cdot H_2O$	5	CH_2Cl_2	8	NR
19	$TlCl_3\cdot 4H_2O$	5	CH_2Cl_2	8	17

[a] Reagent and conditions: 1 mmol of *N*-benzyloxycarbonylamino phenyl *p*-tolylsulfone, 1 mmol of TMSCN, and 5 mol % of $BiBr_3$ were employed at rt.
[b] Isolated yield of the products.

reactivity toward cyanation reaction and produce the corresponding product in good yield (entries 2 and 6). When electron-withdrawing groups are located in the phenyl ring of R in 4 (entries 8–15), the yield shows somewhat lower than in case of *para*-substituted electron-donating ones (entries 1–7). Comparing the yield of entry 4 and entry 15, the lower yield of entry 15 (67%) may be due to electron-withdrawing power of bromine atom. *ortho*-Me displays 88% yield in entry 4 that can be considered to hardly exhibit the steric hindrance. Van der Waals radius of CH_3 and Br are 200 pm and 185 pm, respectively.[16] The electron-withdrawing power is exemplified with *p*-NO_2– and *p*-CN– that show no reactivity at all toward the Strecker reaction even after 8 h reaction time (entries 16 and 17).

α-Amido *p*-tolylsulfones derived from acid-sensitive heterocyclic 2-thiophenaldehyde and 2-pyridinecarboxyladehyde undergo smoothly for the formation of the products (entries 18 and 19). Similarly the sulfone containing naphthalene ring is also able to provide the amino nitrile with good yield (entry 20). α-Amido *p*-tolylsulfones prepared from aliphatic aldehydes is moderately reactive toward the cyanation reaction under present condition (entries 21–22). Cyclic aliphatic groups containing sulfone have shown somewhat lower yield of products relative to aromatics. Besides TMSCN, the catalytic system is also effectively utilized for the cyanation of α-amido *p*-tolylsulfones with bulky silyl cyanide, such as *tert*-butyldimethylsilyl cyanide (TBSCN). The reaction of α-amido *p*-tolylsulfones with TBSCN gives 62% of the yield within 12 h reaction time. The lower yield with longer reaction time may be due to the steric effects of TBSCN. The *N*-Boc-protected α-amido *p*-tolylsulfones is also underwent the cyanation with TMSCN under the present reaction condition (Scheme 3). α-Amido *p*-tolylsulfones with *N*-Boc-protection (79 and 67%) shows lower yield relative to Cbz-protected α-amido *p*-tolylsulfones (90 and 80%) toward the cyanation reaction. Similar type of reaction has been reported with indium chloride as the catalyst that indicates similar result with the present one.[8]

Table 2
$BiBr_3$ catalyzed cyanation of α-amido *p*-tolylsulfones with TMSCN[a]



4 **2** **5**

Cbz: benzyloxycarbonyl

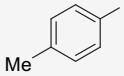
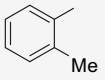
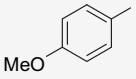
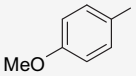
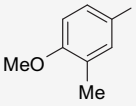
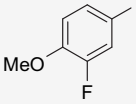
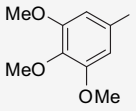
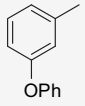
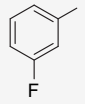
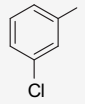
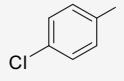
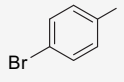
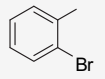
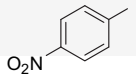
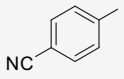
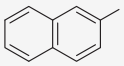
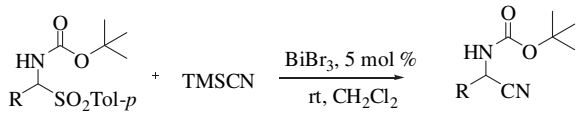
Entry	R in **4**	**5**	Time (h)	Yield[b] (%)
1		**5a**	3	90
2		**5b**	3	90[c]
3		**5c**	3	88
4		**5d**	3	88
5		**5e**	3	90
6		**5f**	3	90[c]
7		**5g**	3	90
8		**5h**	3	81
9		**5i**	3	90
10		**5j**	3	84
11		**5k**	3	82
12		**5l**	5	78
13		**5m**	3	85
14		**5n**	4	80
15		**5o**	3	67
16		**5p**	8	NR

Table 2 (*continued*)

Entry	R in **4**	**5**	Time (h)	Yield[b] (%)
17		**5q**	8	NR
18		**5r**	4	77
19		**5s**	4	80
20		**5t**	3	91
21		**5u**	8	65
22		**5v**	9	62

[a] Reagent and conditions: 1 mmol of α-amido *p*-tolylsulfones, 1 mmol of TMSCN, and 5 mol % of $BiBr_3$ were employed at rt.
[b] Isolated yield of products.
[c] Instead of $-SO_2-Tol-p$, $-SO_2-Ph$ was used.



6 **2** **7**

6a: Benzene — 7a: 3 h, 79%
6b: 2-Pyridine — 7b: 3 h, 67 %

Scheme 3. Cyanation of *N*-Boc-protected α-amido *p*-tolylsulfones with TMSCN.

3. Summary

A very simple and novel method has been developed for the synthesis of *N*-protected α-amino nitriles from α-amino *p*-tolylsulfones via the formation of *N*-acyliminium ions. The various types of α-amido *p*-tolylsulfones derived from aromatic and aliphatic aldehydes react with TMSCN to give the *N*-protected α-amino nitriles in considerably good yield. In addition to TMSCN this catalytic protocol is applicable for bulky silyl cyanide (TBSCN) as cyanide source. The major advantage of the method is the lowest catalyst quantity required among other reported works.

4. Experimental section

4.1. General

In all cases the ^1H NMR (200 MHz) spectra were recorded with Varian Gemini 4000 spectrometer. Chemical shifts are reported in parts per million in $CDCl_3$ with tetramethylsilane as an internal standard. ^{13}C NMR data were collected on a Varian Gemini 2000 spectrometer (50 MHz).

4.2. General procedure for the synthesis of *N*-protected α-amino nitriles

To a mixture of α-amido *p*-tolylsulfones (1 mmol) and $BiBr_3$ (5 mol %), TMSCN (1.0 mmol) was added at rt. The completion of the reaction was monitored with TLC. After the completion of reaction, the reaction mixture was concentrated and the viscous mass was subject to silica gel flash column chromatography to obtain the pure compound.

All products were characterized by ^1H and ^{13}C NMR data that are consistent with literature values.[7b,8,17] HRMS–FAB, melting point and IR values for new products are given below.

*4.2.1. Compound (**5a**).* ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.42–7.33 (m, 10H), 5.79 (d, J=8.2 Hz, 1H), 5.20 (d, J=6.2 Hz, 1H), 5.14 (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 47.0, 68.4, 118.0, 127.4, 128.7, 129.0, 129.1, 130.0, 130.1, 130.3, 133.5, 136.0, 155.6.

*4.2.2. Compound (**5c**).* ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.42–7.34 (m, 5H), 7.25 (d, J=7.2 Hz, 2H), 7.20 (d, J=7.6 Hz, 2H), 5.70 (d, J=8.0 Hz, 2H), 5.30 (d, J=8.0 Hz, 1H), 5.10 (s, 2H), 2.35 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 21.6, 46.8, 68.3, 118.1, 127.3, 128.7, 129.0, 129.1, 130.4, 136.0, 140.1, 155.6.

*4.2.3. Compound (**5d**).* White solid; mp 108–109 °C; IR (KBr): 3311, 3032, 2235, 1602, 1275, 738 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.62 (d, J=8.2 Hz, 1H), 7.31–7.42 (m, 8H), 5.75 (d, J=8.0 Hz, 1H), 5.35 (d, J=8.0 Hz, 1H), 5.12 (s, 2H), 2.32 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 18.0, 44.8, 68.0, 118.0, 127.0, 127.5, 128.2, 128.4, 128.6, 130.0, 131.0, 131.4, 136.0, 136.2, 155.0; HRMS–FAB: $[MH]^+$ calcd for $C_{17}H_{17}O_2N_2$: 281.1290, found: 281.1292.

*4.2.4. Compound (**5e**).* White solid; mp 116–117 °C; IR (KBr): 3296, 3016, 2235, 1686, 1316, 1030, 823 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38–7.36 (m, 5H), 7.30 (d, J=7.6 Hz, 2H), 6.90 (d, J=7.6 Hz, 2H), 5.74 (d, J=8.0 Hz, 1H), 5.52 (d, J=8.0 Hz, 1H) 3.80 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 46.0, 55.4, 67.8, 114.6, 117.6, 128.3, 128.4, 128.5, 128.6, 135.5, 156.4, 160.4; HRMS–FAB: $[MH]^+$ calcd for $C_{17}H_{17}O_3N_2$: 297.1239, found: 297.1237.

*4.2.5. Compound (**5g**).* White solid; mp 132–133 °C; IR (KBr): 3417, 3332, 2233, 1952, 1690, 1071, 735 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.44–7.34 (m, 5H), 7.28 (d, J=7.2 Hz, 1H), 6.80 (d, J=8.0 Hz, 1H), 7.20 (s, 1H), 5.70 (d, J=8.0 Hz, 1H), 5.20 (s, 1H), 5.34 (d, J=8.0 Hz, 1H), 5.1 (s, 2H), 3.82 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 16.7, 46.72, 56.00, 110.7, 118.3, 126.2, 128.5, 128.8, 129.1, 129.7, 159.2; GC–MS: m/z: 310 [M^+], 219, 175, 160, 148, 107, 91, 79.

*4.2.6. Compound (**5h**).* White solid; mp 118–119 °C; IR (KBr): 3332, 3032, 2254, 2042, 1693, 745 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.45 (s, 1H), 7.35–7.25 (m, 4H), 7.19 (d, J=7.6 Hz, 2H), 6.97 (t, J=7.6 Hz, 1H), 5.76 (d, J=8.0 Hz, 1H), 5.43 (d, J=8.0 Hz, 1H), 5.61 (s, 2H), 3.89 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 46.2, 56.8, 68.5, 114.23, 114.2, 115.2, 115.6, 117.7, 123.5, 123.6, 126.2, 126.3, 128.8, 129.0, 129.1, 135.9, 150.4, 155.6; HRMS–FAB: $[MH]^+$ calcd for $C_{17}H_{16}O_3N_2F$: 315.1145, found: 315.1143.

*4.2.7. Compound (**5i**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.34–7.32 (m, 5H), 6.61 (s, 2H), 6.12 (d, J=8.0 Hz, 1H), 5.72 (d, J=8.0 Hz, 1H), 5.16 (s, 2H), 3.79 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 46.7,56.1, 60.8, 66.8, 103.9, 117.6, 128.0, 128.2, 128.5, 128.6, 136.1, 138.4, 153.3, 156.9.

*4.2.8. Compound (**5j**).* White solid; mp 71–72 °C; IR (KBr): 3432, 3283, 2251, 1693, 1247, 785 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38–7.27 (m, 8H), 7.20–6.98 (m, 4H), 6.95 (d, J=7.6 Hz, 2H), 5.7 (d, J=8.0 Hz, 1H), 5.4 (d, J=8.0 Hz, 1H), 5.1 (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 46.0, 67.8, 117.0, 117.1, 119.1, 121.1, 123.8, 128.1, 128.3, 128.4, 129.8, 130.5, 134.8, 135.2, 156.0; HRMS–FAB: $[MH]^+$ calcd for $C_{22}H_{19}O_3N_2$: 359.1396, found: 359.1396.

*4.2.9. Compound (**5k**).* White solid; mp 103–104 °C; IR (KBr): 3343, 2919, 3032, 2246, 1679, 1266, 951 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.40–7.04 (m, 8H), 5.84 (d, J=8.0 Hz, 1H), 5.67 (d, J=8.0 Hz, 1H), 5.14 (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 45.2, 67.3, 113.2, 113.6, 115.7, 116.1, 16.2, 121.8, 127.5, 127.8, 127.9, 130.2, 134.5, 156; HRMS–FAB: $[MH]^+$ calcd for $C_{16}H_{14}O_2N_2F$: 285.1039, found: 285.1040.

*4.2.10. Compound (**5l**).* White solid; mp 98–99 °C; IR (KBr): 3291, 3032, 2746, 2244, 1691, 1290, 708 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.38 (d, J=8.8 Hz, 2H), 7.31–7.23 (m, 7H), 5.78 (d, J=7.8 Hz, 1H), 5.09 (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 45.8, 68.0, 116.8, 125.0, 127.0, 128.1, 128.5, 129.6, 130.5, 135.0, 135.1, 155.0; HRMS–FAB: $[MH]^+$ calcd for $C_{16}H_{14}O_2N_2Cl$: 301.0744, found: 301.0746.

*4.2.11. Compound (**5m**).* White solid; mp 108–109 °C; IR (KBr): 3319, 3032, 2733, 2246, 1693, 1515, 874 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36 (d, J=8.4 Hz, 2H), 7.32–7.29 (m, 5H), 6.91 (d, J=8.4 Hz, 2H), 5.80 (d, J=8.0 Hz, 1H), 5.65 (d, J=8.0 Hz, 1H), 5.14 (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 46.0, 68.0, 117.0, 128.3, 128.6, 128.5, 129.5, 131.5, 135.8, 156.2; HRMS–FAB: $[MH]^+$ calcd for $C_{16}H_{14}O_2N_2Cl$: 301.0744, found: 301.0743.

*4.2.12. Compound (**5n**).* White solid; mp 135–136 °C; IR (KBr): 3280, 2246, 1693, 1528, 1075, 760 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.54 (d, J=8 Hz, 2H), 7.44–7.37 (m, 5H), 7.29 (d, J=6.6 Hz, 2H), 5.80 (d, J=8.0 Hz, 1H), 5.65 (d, J=8.0 Hz, 1H), 5.14 (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 46.0, 68.6, 117.5, 124.4, 129.0, 129.1, 129.2, 132.7, 133.1, 135.8, 155.5; HRMS–FAB: $[MH]^+$ calcd for $C_{16}H_{14}O_2N_2Br$: 345.0239, found: 345.0239.

*4.2.13. Compound (**5o**).* White solid; mp 126–127 °C; IR (KBr): 3322, 2737, 2256, 1682, 1236, 745 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.65–7.59 (m, 2H), 7.39–7.31 (m, 7H), 6.03 (d, J=8.2 Hz, 1H), 5.80 (d, J=8.0 Hz, 1H), 5.65 (d, J=8.0 Hz, 1H), 5.13 (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 46.0, 68.0, 117.0, 128.2, 128.6, 129.6, 131.4, 132.2, 133.8, 135.8, 156.5; HRMS–FAB: $[MH]^+$ calcd for $C_{16}H_{14}O_2N_2Br$: 345.0239, found: 345.0239.

*4.2.14. Compound (**5r**).* Brown solid; mp 127–128 °C; IR (KBr): 3273, 2924, 2242, 1689, 1282, 960 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.30 (d, J=4.0 Hz, 1H), 7.20 (d, J=4.2 Hz, 1H), 7.19–7.16 (m, 5H), 6.94 (dd, J=5.1, 4.4 Hz, 1H), 5.95 (s, 1H), 5.4 (s, 1H), 5.10 (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 45.2, 68.6, 117.9, 127.8, 128.2, 128.9, 129.2, 136.0, 156.2; HRMS–FAB: $[MH]^+$ calcd for $C_{14}H_{14}O_2NS$: 273.0698, found: 273.0698.

*4.2.15. Compound (**5s**).* Yellow oil; IR (KBr): 3436, 3274, 2246, 1703, 1236, 1660, 1048, 708 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.60 (s, 1H), 7.82 (t, J=7.7 Hz, 2H), 7.45 (d, J=5.8 Hz, 1H), 7.38–7.32 (m, 5H), 6.18 (d, J=8.0 Hz, 1H), 5.7 (d, J=8.0 Hz, 1H), 5.12 (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 47.5, 66.8, 118.1, 122.5, 124.8, 138.1, 150.3, 125.0; GC–MS: m/z: 267 [M^+], 233, 178, 160, 131, 107, 56.

*4.2.16. Compound (**5t**).* ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.94–7.82 (m, 5H), 7.62–7.32 (m, 7H), 5.92 (d, J=8.0 Hz, 1H), 5.55 (d, J=8.0 Hz, 1H), 5.15 (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 46.1, 67.4, 117.0, 123.3, 125.8, 126.5, 126.7, 127.2, 127.7, 128.0, 128.1, 129.0, 129.6, 132.4, 132.8, 134.9, 154.5.

*4.2.17. Compound (**5u**).* White solid; mp 89–90 °C; IR (KBr): 3286, 3032, 2237, 1692, 1249, 745 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.34–7.31 (m, 5H), 5.52 (s, 2H), 5.12 (d, J=8.0 Hz, 1H), 4.49 (t, J=7.8 Hz, 1H), 1.86–1.78 (m, 4H), 1.70–1.67 (m, 1H), 1.26–1.06 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 25.2, 25.3, 25.6, 28.4, 28.7, 40.5, 48.1, 67.5, 117.8, 128.1, 128.3, 128.5, 135.5, 155.3; HRMS–FAB: $[MH]^+$ calcd for $C_{17}H_{21}O_2N_2$: 273.1603, found: 273.1602.

*4.2.18. Compound (**5v**).* White solid; mp 78–79 °C; IR (KBr): 3280, 2904, 2246, 1686, 1251, 1048, 688 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.37–7.32 (m, 5H), 5.71–5.68 (m, 1H), 5.64–5.31 (m, 1H), 5.39–5.33 (m, 1H), 5.12 (s, 1H), 4.55 (d, J=7.8 Hz, 1H), 2.18–2.04 (m, 3H), 1.94–1.75 (m, 3H), 1.51–1.39 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 24.3, 27.4, 37.0, 47.5, 67.8, 117.8, 124.4, 127.1, 128.2, 128.6, 135.2,

155.2; HRMS–FAB: $[MH]^+$ calcd for $C_{17}H_{19}O_2N$: 271.1447, found: 271.1445.

*4.2.19. Compound (**7a**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.49–7.39 (m, 5H), 5.77 (d, J=8 Hz, 1H), 5.27 (s, 1H), 1.47 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 28.2, 46.0, 81.5, 117.80, 124.85, 126.9, 129.3, 129.4, 129.6, 133.5.

*4.2.20. Compound (**7b**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.62 (s, 1H), 7.72 (t, J=7.7 Hz, 2H), 7.41 (d, J=5.8 Hz, 1H), 6.12 (d, J=8.0 Hz, 1H), 5.70 (d, J=8.0 Hz, 1H), 1.28 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 28.2, 47.0, 81.4, 117.5, 121.8, 122.0, 124.3, 127.8, 137.0, 37.7, 149.8, 150.2, 153.7; HRMS–FAB: $[MH]^+$ calcd for $C_{12}H_{16}O_2N_3$: 234.1243, found: 134.1242.

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