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A novel route for the synthesis of highly congested aryl-tethered 2-aminobenzylamines through ring transformation of 2-pyranones

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Abstract—An innovative and efficient synthesis of highly congested 2-amino-3-aminomethyl-5-methylsulfanyl/*sec*-aminobiphenyl-4-carbonitriles **4** has been delineated through base catalyzed ring transformation of 6-aryl-4-methylsulfanyl/*sec*-amino-2*H*-pyran-2-one-3-carbonitriles **1** with Boc-protected 1,3-diamino-2-propanone **2**, followed by TFA catalyzed hydrolysis of the intermediate [3-*tert*-butoxycarbonylaminomethyl-4-cyano-5-methylsulfanyl/*sec*-aminobiphenyl-2-yl]carbamic acid *tert*-butyl ester **3** in moderate yields as the TFA salts.

The presence of amino groups makes molecules highly versatile for generating molecular diversity through C–N bond formation. Amines are very good ligands for the synthesis of metal chelates. Additionally, amines are useful building blocks for the construction of various natural products and are important precursors for the synthesis of polyamides, polyimides pharmaceuticals[1] and agrochemicals.[1] They are intermediates for the synthesis of quinazolines[2,3] (**I**, **II**), diazepines[4] (**III**) and hardening agents for resins (Fig. 1).[5]

2-Aminobenzylamines are usually prepared[6] by the reaction of 2-nitrobenzyl chloride, 2-nitrobenzaldehyde, 2-aminobenzophenone, 2-aminoacetophenones and 2-aminopropiophenones with ammonia followed by sodium borohydride reduction or catalytic hydrogenation. Catalytic reduction of an anthranilonitrile over Pd/C or lithium aluminum hydride[7] reduction or hydrogenation of 2-nitrophenylcarbonitrile[8] over Pt in acetic anhydride have also been used to prepare 2-aminobenzylamine. Other approaches include lithium borohydride reduction[9] of 2-aminobenzamide and hydrogenation of 2-aminobenzaldehyde oxime or 2-nitrobenzylamine over Raney nickel in ethanol followed by refluxing with Zn dust, ammonium acetate and aqueous ammonia in ethanol.[3,10] These procedures are summarized in Figure 2.

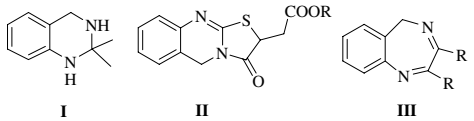

Figure 1. Pharmacologically active drugs derived from 2-aminobenzylamines.

Herein, we report an efficient new approach to the synthesis of highly congested aryl-tethered 2-aminobenzylamines through base catalyzed ring transformation of

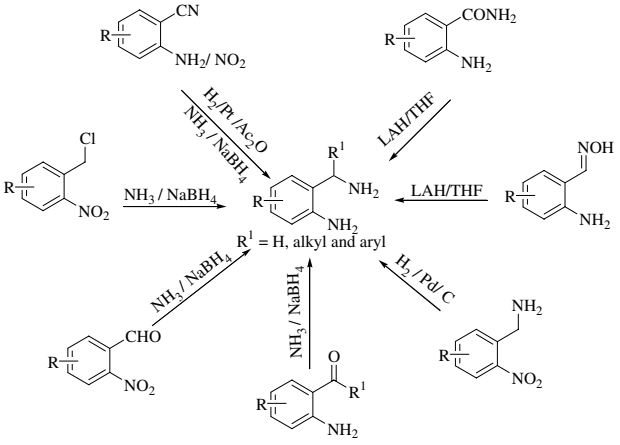

Figure 2. General routes for the preparation of 2-aminobenzylamines.

Keywords: 2-Aminobenzylamine; Ring transformation; 2*H*-Pyran-2-one.
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2*H*-pyran-2-ones **1** with 1,3-di(Boc-amino)-2-propanone **2**, obtained[11] from the reaction of 1,3-diamino-2-propanone with di-*tert*-butyldicarbonate. The various 6-aryl-4-methylsulfanyl-2*H*-pyran-2-one-3-carbonitriles **1a–d** used as precursors were prepared from the reaction of aryl methyl ketones and methyl 2-cyano-3,3-dimethylthioacrylate.[12] Amination[13] of **1a–d** with a *sec*-amine in boiling ethanol led to 6-aryl-4-*sec*-amino-2*H*-pyran-2-one-3-carbonitriles **1e–j**.

Doubly Boc-protected 1,3-diamino-2-propanone was used as a nucleophile to achieve our objective to introduce an amino and an aminomethyl group directly to the aryl ring without the use of any catalyst. The reason for using an amino-protected ketone was mainly to avoid the side reactions due to free amino functionalities as well as to reduce the influence of the +I effect on the carbanion generated for the ring transformation.

Our approach to synthesize diamines **4** is based on ring transformation of 6-aryl-3-cyano-4-methylsulfanyl-2*H*-pyran-2-ones (**1a–d**) and 6-aryl-3-cyano-4-*sec*-amino-2*H*-pyran-2-ones (**1e–j**) with 1,3-di(Boc-amino)-2-propanone **2** to give **3a–d** and **3e–j**, with subsequent acid hydrolysis affording diamines **4** as trifluoroacetate salts in moderate yields (Table 1).

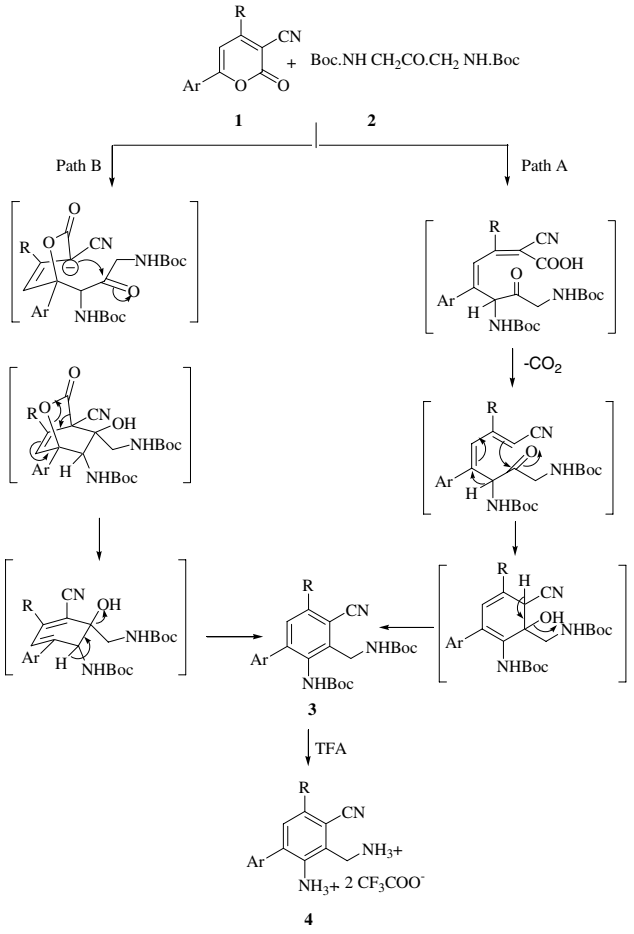
We assume that during ring transformation, a carbanion generated from **2** attacks at C-6 of the pyran ring with ring closure and concomitant loss of carbon dioxide and water to yield **3** as shown in Scheme 1 (Path A).

Alternatively, the reaction might involve an inverse electron demand Diels–Alder type cycloaddition with ketone **2**, and subsequent removal of carbon dioxide to yield **3** (Path B). Since the reaction takes place at room temperature under very mild conditions, we believe Path B is less likely. All the synthesized compounds were characterized by spectroscopic data and elemental analyses.[14]

This methodology provides a simple and general route to the synthesis of highly congested 2-aminobenzylamines with diverse functionalities such as *sec*-amino, methylsulfanyl, cyano and aryl groups.

Table 1. A list of synthesized compounds **1**, **3**, **4**

1, 3, 4	Ar	R	Yield (%)	
			3	4
a	4-BrC_6H_4	SCH_3	62	95
b	4-$BocNHC_6H_4$	SCH_3	55	—
c	4-$MeOC_6H_4$	SCH_3	64	96
d	2-Naphthyl	SCH_3	57	—
e	2-Naphthyl	Piperidin-1-yl	59	—
f	2-Naphthyl	4-Methylpiperidin-1-yl	61	—
g	2-Naphthyl	Morpholin-1-yl	58	—
h	2-Naphthyl	4-Phenylpiperazin-1-yl	56	97
i	4-BrC_6H_4	4-Phenylpiperazin-1-yl	53	—
j	2-Naphthyl	Dimethylamino	60	—



Scheme 1. A plausible mechanism for the formation of **4**.

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14. *General procedure for the synthesis of [3-(tert-butoxycarbonylaminomethyl)-4-cyano-5-methylsulfanyl-biphenyl-2-yl]-carbamic acid tert-butyl ester* (**3a**–**d**): A mixture of 6-(4-bromophenyl)-4-methylsulfanyl-2-oxo-2*H*-pyran-3-carbonitrile **1a** (321 mg, 1.0 mmol) and **2** (288 mg, 1.0 mmol) was stirred for 4 h in a suspension of powdered K_2CO_3 (207 mg, 1.5 mmol) in DMF (5 mL). The progress of the reaction was monitored by TLC in a mixture of hexane–ethyl acetate (7:3). The reaction mixture was poured into ice cold water and neutralized with 10% HCl. The solid precipitate formed was filtered, washed with water and purified by silica gel chromatography eluting with hexane–ethyl acetate (9:1). Compound **3a**: White solid; mp 182–183 °C; IR(KBr) ν 3329 (NH), 2221 (CN), 1697 cm^{-1} (CO); MS (FAB): m/z 548 (M^++1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.25 (s, 9H, Boc), 1.44 (s, 9H, Boc), 2.44 (s, 3H, SCH_3), 4.70 (s, 2H, CH_2), 5.53 (br s, 1H, NH), 7.16 (s, 1H, ArH), 7.28 (d, $J = 7.8$ Hz, 2H, ArH), 7.55 (d, $J = 7.8$ Hz, 2H, ArH), 8.19 (br s, 1H, NH); Anal. Calcd for $C_{25}H_{30}BrN_3O_4S$: C, 54.74; H, 5.51; N, 7.66. Found: C, 54.66; H, 5.56; N, 7.59. Compound **3b**: White solid; mp 185–186 °C; IR(KBr) ν 3334 (NH), 2220 (CN), 1725 cm^{-1} (CO); MS (FAB): m/z 585 (M^++1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.46 (s, 9H, Boc), 1.54 (s, 9H, Boc), 1.56 (s, 9H, Boc), 2.46 (s, 3H, SCH_3), 4.72 (s, 2H, CH_2), 5.01 (br s, 1H, NH), 7.14 (s, 1H, ArH), 7.30 (d, $J = 8.4$ Hz, 2H, ArH), 7.52 (d, $J = 8.4$ Hz, 2H, ArH), 8.19 (br s, 1H, NH); Anal. Calcd for $C_{30}H_{40}N_4O_6S$: C, 61.62; H, 6.90; N, 9.58. Found: C, 61.58; H, 6.82; N, 9.60. Compound **3c**: White solid; mp 135–136 °C; IR(KBr) ν 3338 (NH), 2219 (CN), 1716 cm^{-1} (CO); MS (FAB): m/z 500 (M^++1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.46 (s, 9H, Boc), 1.60 (s, 9H, Boc), 2.47 (s, 3H, SCH_3), 3.87 (s, 3H, OCH_3), 4.76 (s, 2H, CH_2), 5.90 (br s, 1H, NH), 6.99 (s, 1H, ArH), 7.03 (d, $J = 8.4$ Hz, 2H, ArH), 7.29 (d, $J = 8.4$ Hz, 2H, ArH), 8.20 (br s, 1H, NH); Anal. Calcd for $C_{26}H_{33}N_3O_5S$: C, 62.50; H, 6.66; N, 8.41. Found: C, 62.58; H, 6.80; N, 9.50. Compound **3d**: White solid; mp 159–160 °C; IR(KBr) ν 3339 (NH), 2220 (CN), 1711 cm^{-1} (CO); MS (FAB): m/z 520 (M^++1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.25 (s, 9H, Boc), 1.46 (s, 9H, Boc), 2.57 (s,3H, SCH_3), 4.45 (s, 2H, CH_2), 5.56 (br s, 1H, NH), 7.31 (s, 1H, ArH), 7.49–7.52 (m, 3H, ArH), 7.84–7.90 (m, 4H, ArH), 8.20 (br s, 1H, NH); Anal. Calcd for $C_{29}H_{33}N_3O_4S$: C, 67.03; H, 6.40; N, 8.09. Found: C, 67.08; H, 6.48; N, 8.29.

Synthesis of [3-(tert-butoxycarbonylaminomethyl)-4-cyano-5-sec-aminobiphenyl-2-yl]carbamic acid tert-butyl ester (**3e**–**j**): These were prepared by stirring a mixture of **1** (1.0 mmol) and **2** (288 mg, 1.0 mmol) for 4 h in a suspension of powdered K_2CO_3 (207 mg, 1.5 mmol) in DMF (5 mL). The reaction was worked up and purified as described earlier. Compound **3e**: White solid; mp 161–163 °C; IR(KBr) ν 3304 (NH), 2220 (CN), 1716 cm^{-1} (CO); MS (FAB): m/z 557 (M^++1); ^{1}H NMR (CD_3OD, 300 MHz) δ 1.17 (s, 9H, Boc), 1.45 (s, 9H, Boc), 1.62–1.64 (m, 2H, CH_2, piperidinyl), 1.78–1.80 (m, 4H, CH_2, piperidinyl), 3.19–3.21 (m, 4H, CH_2, piperidinyl), 4.41 (s, 2H, CH_2), 5.02 (br s, 1H, NH), 7.11 (s, 1H, ArH), 7.45–7.52 (m, 3H, ArH), 7.86–7.91 (m, 4H, ArH), 8.22 (br s, 1H, NH); Anal. Calcd for $C_{33}H_{40}N_4O_4$: C, 71.20; H, 7.24; N, 10.06. Found: C, 71.28; H, 7.32; N, 10.24. Compound **3f**: White solid; mp 113–115 °C; IR(KBr) ν 3340 (NH), 2217 (CN), 1695 cm^{-1} (CO); MS (FAB): m/z 571 (M^++1); ^{1}H NMR (CD_3OD, 300 MHz) δ 0.90 (d, $J = 6.0$ Hz, 3H, CH_3), 1.33–135 (m, 1H, CH, piperidinyl), 1.37 (s, 9H, Boc), 1.45 (s, 9H, Boc), 1.62–1.64 (m, 2H, CH_2, piperidinyl), 1.65–1.69 (m, 2H, CH_2, piperidinyl), 2.67–2.74 (m, 2H, CH_2, piperidinyl), 3.44–3.48 (m, 2H, CH_2, piperidinyl), 4.51 (s, 2H, CH_2), 5.02 (br s, 1H, NH), 7.00 (s, 1H, ArH), 7.35–7.41 (m, 3H, ArH), 7.76–7.80 (m, 4H, ArH), 8.22 (br s, 1H, NH); Anal. Calcd for $C_{34}H_{42}N_4O_4$: C, 71.55; H, 7.42; N, 9.82. Found: C, 71.41; H, 7.32; N, 9.76. Compound **3g**: White solid; mp 127–128 °C; IR(KBr) ν 3337 (NH), 2218 (CN), 1714 cm^{-1} (CO); MS (FAB): m/z 559 (M^++1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.16 (s, 9H, Boc), 1.46 (s, 9H, Boc), 3.01–3.12 (m, 4H, CH_2, morpholinyl), 3.89–3.92 (m, 4H, CH_2, morpholinyl), 4.44 (s, 2H, CH_2), 5.56 (br s, 1H, NH), 7.03 (s, 1H, ArH), 7.48–7.52 (m, 3H, ArH), 7.83–7.89 (m, 4H, ArH), 8.20 (br s, 1H, NH); Anal. Calcd for $C_{32}H_{38}N_4O_5$: C, 68.80; H, 6.86; N, 10.03. Found: C, 68.64; H, 6.80; N, 10.23. Compound **3h**: White solid; mp 183–185 °C; IR(KBr) ν 3341 (NH), 2218 (CN), 1697 cm^{-1} (CO); MS (FAB): m/z 634 (M^++1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.11 (s, 9H, Boc), 1.46 (s, 9H, Boc), 3.40 (s, 8H, CH_2, piperazinyl), 4.46 (s, 2H, CH_2), 5.56 (br s, 1H, NH), 6.87–6.92 (m, 1H, ArH), 6.97–6.99 (m, 2H, ArH), 7.09 (s, 1H, ArH), 7.29–7.32 (m, 2H, ArH), 7.49–7.52 (m, 3H, ArH), 7.84–7.90 (m, 4H, ArH), 8.20 (br s, 1H, NH); Anal. Calcd for $C_{38}H_{43}N_5O_4$: C, 72.01; H, 6.84; N, 11.05. Found: C, 71.84; H, 6.72; N, 11.16. Compound **3i**: White solid; mp 179–180 °C; IR(KBr) ν 3329 (NH), 2218 (CN), 1697 cm^{-1} (CO); MS (FAB): m/z 662 (M^++1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.25 (s, 9H, Boc), 1.46 (s, 9H, Boc), 3.38 (s, 8H, CH_2, piperazinyl), 4.42 (s, 2H, CH_2), 5.53 (br s, 1H, NH), 6.80–6.99 (m, 4H, ArH), 7.26–7.32 (m, 4H, ArH), 7.54 (d, $J = 8.10$ Hz 2H, ArH), 7.99 (br s, 1H, NH); Anal. Calcd for $C_{34}H_{40}BrN_5O_4$: C, 61.63; H, 6.08; N, 10.57. Found: C, 61.46; H, 6.12, N; 10.38. Compound **3j**: White solid; mp 109–110 °C; IR(KBr) ν 3363 (NH), 2218 (CN), 1698 cm^{-1} (CO); MS (FAB): m/z 517 (M^++1); ^{1}H NMR (CD_3OD, 300 MHz) δ 1.16 (s, 9H, Boc), 1.45 (s, 9H, Boc), 3.04 (s, 6H, NCH_3), 4.41 (s, 2H, CH_2), 5.56 (br s, 1H, NH), 7.05 (s,1H, ArH), 7.46–7.52 (m, 3H, ArH), 7.86–7.90 (m, 4H, ArH), 8.20 (br s, 1H, NH); Anal. Calcd for $C_{30}H_{36}N_4O_4$: C, 69.74; H, 7.02; N, 10.84. Found: C, 69.63; H, 7.18; N, 10.72.

Synthesis of 2-amino-3-aminomethyl-5-methylsulfanyl/sec-aminobiphenyl-4-carbonitriles (**4a**, **4c**, **4h**): Compound **4a** was obtained by stirring **3a** (100 mg) in a solution of 20% TFA in DCM at room temperature for 2 h. After completion of the reaction, TFA was removed under reduced pressure and the residue washed with dichloromethane leaving a TFA salt. Similarly **4c** and **4h** were prepared from **3c** and **3h,** respectively. Compound **4a**: White solid; mp >250 °C; IR(KBr) ν 3362 (NH), 2221 (CN), 1676 cm^{-1} (CO); MS (FAB): m/z 348 (M^++1); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.40 (s, 3H, SCH_3), 4.20 (s, 2H, CH_2), 6.88 (s, 1H, ArH), 7.04 (d, $J = 8.4$ Hz, 2H,

ArH), 7.40 (d, $J = 8.4$ Hz, 2H, ArH); Anal. Calcd for $C_{19}H_{16}BrF_6N_3O_4S$: C, 39.60; H, 2.80; N, 7.29. Found: C, 39.73; H, 2.94; N, 7.48. Compound **4c**: White solid; mp >250 °C; IR(KBr) ν 3362 (NH), 2219 (CN), 1776 cm^{-1} (CO); MS (FAB): m/z 300(M^++1); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.38 (s, 3H, SCH_3), 3.81 (s, 3H, OCH_3), 4.21 (s, 2H, CH_2), 6.86 (s, 1H, ArH), 7.06 (d, $J = 8.4$ Hz, 2H, ArH), 7.41 (d, $J = 8.4$ Hz, 2H, ArH); Anal. Calcd for $C_{20}H_{19}F_6N_3O_5S$: C, 45.54; H, 3.63; N, 7.97. Found: C, 45.62; H, 3.76; N, 7.86. Compound **4h**: White solid; mp >250 °C; IR(KBr) ν 3364 (NH), 2219 (CN), 1697 cm^{-1} (CO); MS (FAB): m/z 434 (M^++1); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.07 (s, 8H, CH_2, piperazinyl), 4.2 (s, 2H, CH_2), 6.76–6.81 (m, 1H, ArH), 6.97–7.00 (m, 2H, ArH), 7.11 (s, 1H, ArH), 7.20–7.25 (m, 2H, ArH), 7.56–7.62 (m, 3H, ArH), 7.96–8.05 (m, 4H, ArH).