Novel Use of Substituted 1,4-Dihydrobenz[*d*][1,3]oxazin-2-ones in the Synthesis of Important Aminomethyl *o*-Nitroanilines

Sham S. Nikam,* Po-Wai Yuen, Brian E. Kornberg, Brian Tobias, and Michael F. Rafferty

Department of Chemistry, Parke-Davis Pharmaceutical Division/Warner-Lambert Company, 2800 Plymouth Road, Ann Arbor, Michigan 48105

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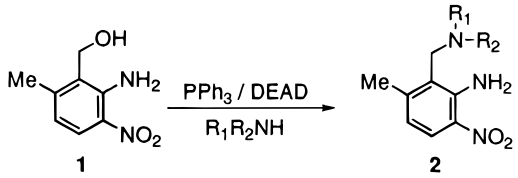
Introduction

Multifunctional *o*-nitroanilines are important intermediates in the synthesis of a variety of nitrogen heterocycles.[1] However, there are very few efficient methods to synthesize heteroalkyl side chains ortho to the amino group, which give the corresponding peri position substitution in the resultant nitrogen heterocycle. Earlier, we standardized a novel method for the synthesis of benzylamine derivatives **2** with an aminomethyl side chain ortho to the amino group of the *o*-nitroaniline derivative via a modified Mitsunobu reaction (Scheme 1)[2] starting from the substituted benzyl alcohol **1**. This synthesis had a few limitations with regard to the amines that could be used and moderate yield of the starting benzyl alcohol **1** from commercially available 6-methylanthranilic acid.[3] Our continued interest in a variety of aminomethyl-substituted *o*-nitroanilines and their tremendous utility in the synthesis of several nitrogen heterocycles prompted us to investigate other versatile and efficient methodologies for their synthesis. We would like to report here the synthesis of aminomethyl-substituted *o*-nitroanilines **9** starting from novel 6-bromo-5-methyl-8-nitro-1,4-dihydrobenzo[*d*][1,3]-oxazin-2-one (**6**).

Results and Discussion

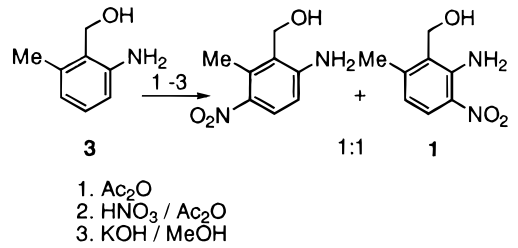
Synthesis of the benzyl alcohol **1** involved nitration of *o*-aminobenzyl alcohol **3** in acetic anhydride using concentrated nitric acid[3] (Scheme 2). The desired nitro derivative **1** was isolated in about 40% yield from a mixture of regioisomers. The moderate yields of this starting material and the need for a variety of substituted aminomethyl *o*-nitroanilines **2** led us to optimize the synthesis of this starting material (Scheme 3). Thus *o*-aminobenzyl alcohol **3** was cyclized to form the 5-methyl-1,4-dihydrobenz[*d*][1,3]oxazin-2-one (**4**) by treating **3** with phosgene in the presence of triethylamine in THF. The benz[*d*][1,3]oxazin-2-one derivative **4** was brominated using bromine in an acetic acid−TFA mixture to give the 6-bromo derivative **5**, which was subsequently nitrated using potassium nitrate in sulfuric acid to give the desired 6-bromo-5-methyl-8-nitro-1,4-dihydrobenz[*d*]-[1,3]oxazin-2-one (**6**) in excellent isolated yields. Bromination step to give 6-bromo derivative **5** was necessary as direct nitration of **4** gave a mixture of 6-nitro (**7**) and 8-nitro (**8**) regioisomers (∼4:6). Further, the bromine substituent can be penultimately removed, as required via catalytic hydrogenation. The structure of the regioisomer (**7**) was confirmed by ^{1}H NOE NMR studies (Scheme 3).

Scheme 1. Synthesis of Benzylamines (2) Using Benzyl Alcohols (1) under Mitsunobu Reaction Conditions



1 2

Scheme 2. Nitration of *o*-Aminobenzyl Alcohol



3 1:1 1

1. Ac_2O
2. HNO_3 / Ac_2O
3. KOH / MeOH

The benz[*d*][1,3]oxazin-2-one derivative **6** was directly treated with nucleophilic amines to give the corresponding aminoalkyl derivatives **9** (Table 1) in modest to good yields (Scheme 4). Thus, in a typical reaction 6-bromo-5-methyl-8-nitro-1,4-dihydrobenz[*d*][1,3]oxazin-2-one (**6**) was treated with various amines (>6 equiv), neat or in a high-boiling solvent such as dimethylformamide. The reaction mixture was heated to reflux or >140 °C for about 8 h. The products were isolated by crystallization or column chromatography. The various substituted aminomethyl *o*-nitroanilines synthesized are listed in Table 1. Unlike the Mitsunobu method,[2] which worked only with amines having pK_a > 9, the present method was found to be more general with respect to a variety of amines. For example, 2-(methylamino)ethanol, methylaminoacetaldehyde dimethyl acetal, and morpholine (Table 1, entries 1, 2, 9, respectively) gave the desired benzylamines in modest to good yields. These amines did not give the desired product on reaction with benzyl alcohol **1** under Mitsunobu conditions. In general, amines with pK_a > 8 gave the desired products, whereas weakly basic amines such as aniline did not give the desired product. The reaction also appears to be dependent on the steric bulk of the amines. Thus, dibenzylamine (Table 1, entry 6) and *N*-isopropylbenzylamine (Table 1, entry 5) gave the desired product in low yield, whereas the *N*-methylbenzylamine (Table 1, entry 3) and *N*-ethylbenzylamine (Table 1, entry 4) gave the product in good yield.

Initially, the mechanism proposed for this reaction was the nucleophilic ring opening of the cyclic carbamate via an S_N2 mechanism. However, on careful investigation and with our prior experience with the Mitsunobu reaction, we postulated that the reaction probably pro-

* Corresponding author. Phone (313)-996-7452. Fax: (313)-996-5165. E-mail: nikams@aa.wl.com.

(1) For reviews on chemistry of various nitrogen heterocycles from *o*-nitroanilines, see: Preston, P. N.; Smith, D. M.; Tennant, G. *Heterocycl. Compds.* **1981**, 40. Cheeseman, G. W. H.; Werstiuk, E. S. G. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Boulton, A. J., Eds.; Academic Press: New York, 1978; Vol. 22, pp 368−425. Cheeseman, G. W. H.; Cookson, R. F. In *Chemistry of Heterocyclic Compounds*; Weissburger, A., Taylor, E. C., Eds.; Academic Press: New York, 1977; pp 1−261.

(2) Nikam, S. S.; Kornberg, B. E.; Rafferty, M. F. *J. Org. Chem.* **1997**, *62,* 3754.

(3) Utaka, M.; Takatsu, M.; Takeda, A. *Bull. Chem. Soc. Jpn.* **1977**, *50,* 3276.

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Scheme 3. Synthesis of 6-Bromo-5-methyl-8-nitro-1,4-dihydrobenz[*d*][1,3]oxazin-2-one and Observed NOEs for Regioisomer 7

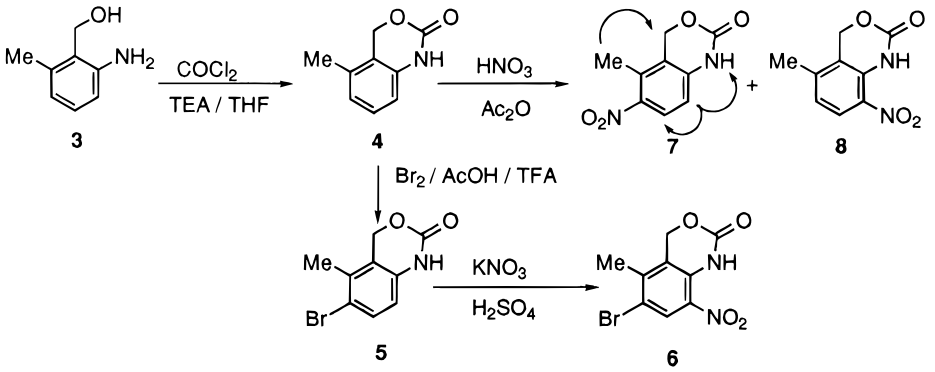
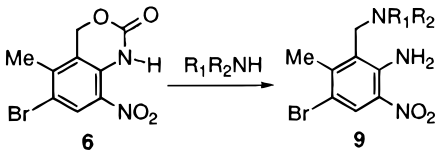


Table 1. Substituted Benzylamines 9 from Substituted 1,4-Dihydrobenz[*d*][1,3]oxazin-2-one (6)

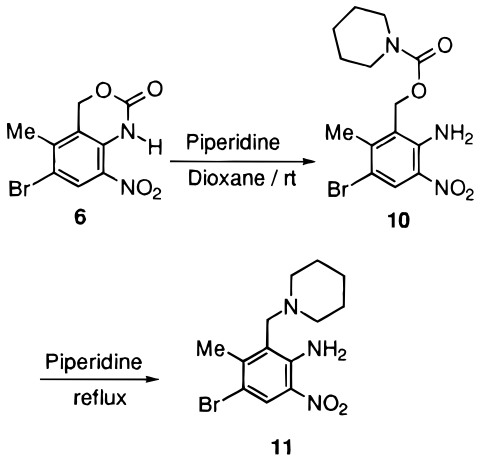
entry	$-NR_1R_2$	yield (%)[a]
1	2-(methylamino)ethanol	28
2	methylaminoacetaldehyde dimethyl acetal	78
3	*N*-methylbenzylamine	70
4	*N*-ethylbenzylamine	57
5	N-isopropylbenzylamine	12
6	dibenzylamine	11 (50)[b]
7	pyrrolidine	76
8	piperidine	67
9	morpholine	71
10	3-azaspiro[5.5]undecane	51
11	sarcosine ethyl ester	34

[a] Isolated yields. [b] Reaction of **10** with dibenzylamine.

Scheme 4

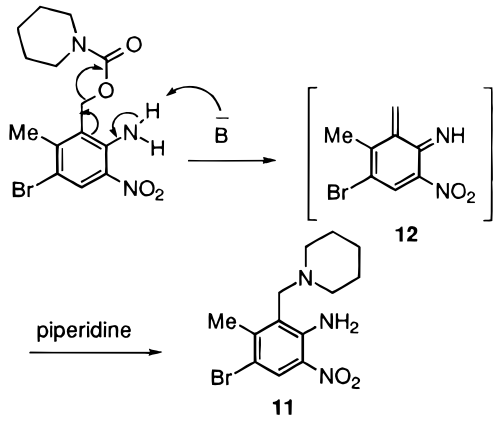


Scheme 5



ceeds via the azaquinodimethane intermediate **12** (Scheme 6). Thus, the reaction of benz[*d*][1,3]oxazin-2-one derivative **6** with piperidine was investigated at various temperatures. At rt, the product isolated was the corresponding acyclic piperidinyl carbamate **10** in very good yield (Scheme 5). This intermediate is then proposed to undergo base-induced elimination to form the azaquinodimethane intermediate **12** followed by conjugate addition of the amine to give the desired piperidinyl-substituted *o*-nitroaniline **11** (Scheme 6). In a separate experiment **10** was treated with excess piperidine at

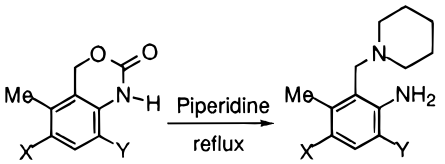
Scheme 6. Proposed Mechanism Involving Azaquinodimethane Intermediate



reflux to give **11**. Heating **10** in DMF to 130 °C in the absence of excess piperidine did not give **11**, indicating that excess amine is required to convert **10** to **11** and the process is not an intramolecular process. This result was important as the piperidinyl carbamate **10** could now be used to synthesize benzylamines which could not be synthesized in good yields directly by heating **6** with the amine. For example, treatment of **10** with an excess of dibenzylamine at 160 °C gave the corresponding dibenzylamino derivative (Table 1, entry 6) in 50% yield. These results also indicate that the yield-limiting step is the initial amine attack at the carbamate carbonyl group, which is dependent on the steric bulk and basicity of the amines as discussed earlier in this paper. Heating the benz[*d*][1,3]oxazin-2-one derivative **6** to reflux in DMF, 2,2,6,6-tetramethylpiperidine, or TEA gave back the starting material confirming that the temperature or basicity was not the only criterion for the generation of the azaquinodimethane intermediate and the overall success of the reaction.

The mechanism was further investigated by exploring the reactivity of other derivatives of **6** (Table 2) with piperidine at reflux. There was no reaction with the unsubstituted (Table 2, entry 1) or the 8-amino- (Table 2, entry 2) derivatives of **1**, whereas the 8-nitro- and 6,8-dibromo-1,4-dihydrobenz[*d*][1,3]oxazin-2-ones (Table 2, entries 5, 6) gave the desired product indicating the importance of the electron-withdrawing group ortho to the amine functionality, which is critical for the base-induced elimination to give the azaquinodimethane intermediate. The proximity of the electron-withdrawing group is also important for the success of the reaction. The benz[*d*][1,3]oxazin-2-one derivatives having a bromo

Table 2. Reactions of Piperidine Differentially Substituted Benz[*d*][1,3]oxazin-2-ones



entry	X	Y	yield (%)[a]
1	H	H	no rxn
2	H	NH_2	no rxn
3	Br	H	no rxn
4	NO_2	H	no rxn
5	H	NO_2	84
6	Br	Br	36
7	Br	NO_2	67[b]

[a] Isolated yields. [b] Entry 8 in Table 1.

or nitro moiety para to the carbamoyl NH (Table 2, entries 3, 4, respectively) did not give the desired benzylamine derivative on treatment of piperidine under reaction conditions mentioned above. These results can be attributed to the acidity of the amine group protons, with *o*-nitroaniline ($pK_a = -0.25$) being more acidic than *p*-nitroaniline ($pK_a = 1.05$) or *p*-bromoaniline ($pK_a = 3.89$).[4] The mechanism proposed is analogous to that postulated for the Mitsunobu method, but the present methodology is more broadly applicable to the preparation of highly functionalized 6-(aminomethyl)-*o*-nitroanilines. Generation of an azaquinodimethane or aza-*o*-xylylene intermediate via CO_2 extrusion under high temperatures or high-vacuum pyrolysis and trapping of this intermediate by a dienophile to give the adduct have been discussed earlier.[5,6] Our mechanism adds a new dimension to this area, in that the intermediate azaquinodimethane **12** can be generated under milder conditions from appropriately substituted and readily synthesizable benz[*d*][1,3]oxazin-2-ones.

Conclusion

A new methodology for the synthesis of substituted aminomethyl *o*-nitroanilines **9** via the novel intermediate 6-bromo-5-methyl-8-nitro-1,4-dihydrobenz[*d*][1,3]oxazin-2-one (**6**) has been developed. The probable generation of the azaquinodimethane intermediate **12** from 6-bromo-5-methyl-8-nitro-1,4-dihydrobenz[*d*][1,3]oxazin-2-one (**6**) under mild conditions is new and could have broad utility in organic synthesis especially in synthesizing substituted nitrogen heterocycles.

Experimental Section

Materials. All chemicals were purchased from Aldrich and used without additional purification. Phosgene solution in toluene (1.93 M) was purchased from Fluka AG. ^{1}H NMR spectra and ^{1}H NOE NMR studies were recorded at 400 MHz in $CDCl_3$ or DMSO-d_6. Chemical shifts are referenced to the residual proton signal for $CDCl_3$ (7.26 ppm) or DMSO-d_6 (2.49 ppm). The starting benzyl alcohol **1** was synthesized from 6-methylanthranilic acid as reported earlier.[3]

5-Methyl-1,4-dihydrobenz[*d*][1,3]oxazin-2-one (4). To a solution of (2-amino-6-methylphenyl)methanol (**3**) (478 g, 3.49 mol) and triethylamine (884 g, 8.75 mol) in THF (10 L) was added phosgene solution in toluene (1.93 M, 1.86 L, 3.6 mol) slowly over 1 h keeping the temperature below 10 °C. The reaction mixture was allowed to warm to rt and was stirred for 16 h. Cold water (150 mL) and aq NH_4OH (10%, 200 mL) were added under stirring followed by EtOAc (12 L). The EtOAc extracts were washed with water and brine and dried over $MgSO_4$. The product (buff solid) was crystallized from EtOAc: yield 536 g, 94%; mp 224−226 °C; ^{1}H NMR (DMSO-d_6) δ 2.19 (s, 3H), 5.31 (s, 2H), 6.66 (d, $J = 8.1$ Hz, 1H), 6.82 (d, $J = 8.1$ Hz, 1H), 7.1 (dd, $J = 7.8$ Hz, 1H), 8.82 (bs, 1H); MS (CI) *m*/*z* 163 (M + H). Anal. Calcd for $C_9H_9NO_2$: C, 66.25; H, 5.56; N, 8.61. Found: C, 66.34; H, 5.63; N, 8.61.

6-Bromo-5-methyl-1,4-dihydrobenz[*d*][1,3]oxazin-2-one (5). To a solution of 5-methyl-1,4-dihydrobenz[*d*][1,3]oxazin-2-one (**4**) (400 g, 2.45 mol) in glacial acetic acid (2.5 L) and TFA (1 L) was gradually added a solution of Br_2 (151 mL, 468 g, 2.93 mol) in TFA (500 mL) over 1 h at 5 °C under stirring. The reaction mixture was stirred for an additional 5 h and poured into ice−water (12 L). The yellow precipitate was filtered, washed with water until neutral, and dried: yield 558 g, 94%; mp 287−288 °C; ^{1}H NMR (DMSO-d_6) δ 2.18 (s, 3H), 5.31 (s, 2H), 6.6 (d, $J = 8.8$ Hz, 1H), 7.41 (d, $J = 8.8$ Hz, 1H), 10.16 (s, 1H); MS (CI) *m*/*z* 242, 243, 244 (M + H, M + 2H, M + 3H). Anal. Calcd for $C_9H_8BrNO_2$: C, 44.66; H, 3.33; N, 5.79. Found: C, 44.92; H, 3.28; N, 5.69.

6-Bromo-5-methyl-8-nitro-1,4-dihydrobenz[*d*][1,3]oxazin-2-one (6). To a cooled (5 °C) solution of 6-bromo-5-methyl-1,4-dihydrobenz[*d*][1,3]oxazin-2-one (**5**) (556 g, 2.3 mol) in concentrated H_2SO_4 (1200 mL) was added KNO_3 (242 g, 2.39 mol) portionwise keeping the temperature below 5 °C. Reaction mixture was allowed to warm to rt and stirred for 18 h. The viscous liquid was poured into ice−water (12 L) with stirring. The yellow precipitate was filtered, washed with water until neutral, and air-dried: yield 656 g, 99%; mp 187 °C; ^{1}H NMR (DMSO-d_6) δ 2.32 (s, 3H), 5.47 (s, 2H), 8.23 (s, 1H), 9.76 (bs, 1H); MS (CI) *m*/*z* 287, 289 (M + H, M + 2H). Anal. Calcd for $C_9H_7BrN_2O_4$: C, 37.66; H, 2.46; N, 9.76. Found: C, 37.44; H, 2.57; N, 9.56.

6-Nitro-5-methyl-1,4-dihydrobenz[*d*][1,3]oxazin-2-one (7) and 8-Nitro-5-methyl-1,4-dihydrobenz[*d*][1,3]oxazin-2-one (8). To a solution of 5-methyl-1,4-dihydrobenz[*d*][1,3]oxazin-2-one (**4**) (1.62 g, 10 mmol) in acetic anhydride (15 mL) was added concentrated HNO_3 (70%, 2 mL) at 15 °C under stirring. The reaction mixture was warmed to 40 °C for 3 h and poured into crushed ice. An off-white solid separated, which was filtered. The sticky solid was triturated with EtOAc (~250 mL) and filtered. A buff-colored solid was obtained (0.711 g, 34%) which was confirmed to be the 6-nitro-5-methyl-1,4-dihydrobenz[*d*]-[1,3]oxazin-2-one (**7**) by ^{1}H NMR and NOE studies: ^{1}H NMR (DMSO-d_6) δ 2.27 (s, 3H), 5.4 (s, 2H), 7.04 (d, $J = 8.7$ Hz, 1H), 7.95 (d, $J = 8.7$ Hz, 1H), 9.67 (s, 1H); MS (CI) *m*/*z* 209 (M + H). Anal. Calcd for $C_9H_8N_2O_4$: C, 51.93; H, 3.87; N, 13.46. Found: C, 52.12; H, 3.73; N, 13.28.

The mother liquor was partially evaporated to give yellow crystals of 8-nitro-5-methyl-1,4-dihydrobenz[*d*][1,3]oxazin-2-one (**8**): yield, 0.964 g, 46%; ^{1}H NMR (DMSO-d_6) δ 2.27 (s, 3H), 5.39 (s, 2H), 6.81 (d, $J = 8.7$ Hz, 1H), 7.85 (d, $J = 8.7$ Hz, 1H), 10.61 (s, 1H); MS (CI) *m*/*z* 209 (M + 1). Anal. Calcd for $C_9H_8N_2O_4$: C, 51.93; H, 3.87; N, 13.46. Found: C, 51.63; H, 3.84; N, 13.37.

8,6-Dibromo-5-methyl-1,4-dihydrobenz[*d*][1,3]oxazin-2-one (starting material for entry 6 in Table 2). To a solution of 5-methyl-1,4-dihydrobenz[*d*][1,3]oxazin-2-one (**4**; 9 g, 55.2 mmol) in acetic acid (40 mL) was added Br_2 (19.2 g, 120 mmol) dropwise (~15 min). The reaction mixture was stirred for 16 h and the reaction quenched with ice water. The yellow precipitate was washed with water till neutral and dried: yield 16.8 g, 95%; ^{1}H NMR (DMSO-d_6) δ 2.24 (s, 3H), 5.31 (s, 2H), 7.26 (bs, 1H), 7.65 (s, 1H); MS (CI) *m*/*z* 320, 322 (M + H, M + 3H). Anal. Calcd for $C_9H_7Br_2N_1O_2$: C, 33.68; H, 2.2; N, 4.36. Found: C, 33.9; H, 2.22; N, 4.36.

General Procedure for the Synthesis of Substituted Aminomethyl *o*-Nitroanilines (9) Starting from 6-Bromo-5-methyl-8-nitro-1,4-dihydrbenz[*d*][1,3]oxazin-2-one (6) (representative example with NR_1R_2 = piperidine as the amine). A stirred solution of 6-bromo-5-methyl-8-nitro-1,4-dihydrobenz[*d*][1,3]oxazin-2-one (**6**; 10 g, 35 mmol) in piperidine (50 mL) was heated to reflux for 8 h. The dark reaction mixture was cooled, and volatile material was evaporated on a rotary

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evaporator to give a viscous oil. The dark oil was triturated with ethyl acetate with warming to form a solution. On cooling the product (Table 1, entry 6) crystallized to give a yellow solid: yield 7.58 g, 67%; ^{1}H NMR ($CDCl_3$) δ 1.43−1.55 (m, 6H), 2.36−2.45 (m, 4H), 2.41 (s, 3H), 3.59 (s, 2H), 7.84 (bs, 2H), 8.27 (s, 1H); MS (CI) *m/z* 328 (M + H). Anal. Calcd for $C_{13}H_{18}BrN_3O_2$: C, 47.57; H, 5.53; N, 12.8. Found: C, 47.81; H, 5.44; N, 12.6.

Spectral and analytical data for the compounds (entry numbers) synthesized and listed in Table 1 are as follows.

Entry 1: ^{1}H NMR ($CDCl_3$) δ 2.26 (s, 3H), 2.43 (s, 3H), 2.61 (m, 2H), 3.74 (m, 4H), 7.58 (bs, 2H), 8.3 (s, 1H); MS (CI) *m/z* 319, 320 (M + H, M + 2H). Anal. Calcd for $C_{11}H_{16}BrN_3O_3$: C, 41.52; H, 5.07; N, 13.21. Found: C, 41.72; H, 4.9; N, 12.79.

Entry 2: ^{1}H NMR ($CDCl_3$) δ 2.2 (s, 3H), 2.42 (s, 3H), 3.33 (s, 6H), 3.67 (s, 2H), 4.54 (bs, 1H), 7.7 (bs, 2H), 8.29 (s, 1H); MS (CI) *m/z* 362, 363 (M + H, M + 2H). Anal. Calcd for $C_{13}H_{20}BrN_3O_4$: C, 43.11; H, 5.57; N, 11.60. Found: C, 42.85; H, 5.43; N, 11.31.

Entry 3: ^{1}H NMR ($CDCl_3$) δ 2.02 (s, 3H), 2.39 (s, 3H), 3.47 (s, 2H), 3.67 (s, 2H), 7.2−7.31 (m, 5H), 7.75 (bs, 2H), 8.09 (s, 1H); MS (CI) *m/z* 364, 365 (M + H, M + 2H). Anal. Calcd for $C_{16}H_{18}BrN_3O_2$: C, 52.76; H, 4.98; N, 11.54. Found: C, 52.22; H, 4.87; N, 11.11.

Entry 4: ^{1}H NMR ($CDCl_3$) δ 1.08 (t, J = 7.8 Hz, 3H), 2.43 (s, 3H), 3.47 (q, J = 7.33 Hz, 2H), 3.49 (s, 2H), 3.72 (s, 2H), 7.19−7.29 (m, 5H), 7.72 (bs, 2H), 8.26 (s, 1H); MS (CI) *m/z* 378, 380 (M + H, M + 2H). Anal. Calcd for $C_{17}H_{20}BrN_3O_2$: C, 53.98; H, 5.33; N, 11.1. Found: C, 54; H, 5.22; N, 11.08.

Entry 5: ^{1}H NMR ($CDCl_3$) δ 1.1 (d, 6H), 2.45 (s, 3H), 2.86 (septet, 1H), 3.73 (s, 2H), 7.2−7.31 (m, 5H), 7.63 (bs, 2H), 8.22 (s, 1H); MS (CI) *m/z* 308, 310 (M + H, M + 2H). Anal. Calcd for $C_{18}H_{22}BrN_3O_2$: C, 55.10; H, 5.61; N, 10.71. Found: C, 55.13; H, 5.58; N, 10.54.

Entry 6: ^{1}H NMR ($CDCl_3$) δ 2.46 (s, 3H), 3.49 (s, 4H), 3.68 (s, 2H), 7.2−7.41 (m, 2H), 8.24 (s, 1H); MS (CI) *m/z* 440, 442 (M + H, M + 2H). Anal. Calcd for $C_{22}H_{22}BrN_3O_2$: C, 60.01; H, 5.04; N, 9.54. Found: C, 60.35; H, 5.18; N, 9.28.

Entry 7: ^{1}H NMR ($CDCl_3$) δ 1.75 (m, 4H), 2.44 (s, 3H), 2.48 (m, 4H), 3.76 (bs, 2H), 7.83 (bs, 2H), 8.28 (s, 1H); MS (APCI) *m/z* 315, 316 (M + H, M + 2H). Anal. Calcd for $C_{12}H_{16}BrN_3O_2$: C, 45.87; H, 5.13; N, 13.37. Found: C, 45.88; H, 5.05; N, 13.27.

Entry 8: ^{1}H NMR ($CDCl_3$) δ 1.43−1.52 (m, 6H), 2.37−2.45 (m, 4H), 2.41 (s, 3H), 3.59 (s, 2H), 7.85 (bs, 2H), 8.27 (s, 1H); MS (CI) *m/z* 328, 329 (M + H, M + 2H). Anal. Calcd for $C_{13}H_{18}BrN_3O_2$: C, 47.57; H, 5.53; N, 12.8. Found: C, 47.81; H, 5.44; N, 12.6.

Entry 9: ^{1}H NMR ($CDCl_3$) δ 2.48 (s, 3H), 2.51 (bs, 4H), 3.71 (bs, 6H), 7.67 (bs, 2H), 8.34 (s, 1H); MS (CI) *m/z* 330, 331 (M + H, M + 2H). Anal. Calcd for $C_{12}H_{16}BrN_3O_3$: C, 43.65; H, 4.88; N, 12.73. Found: C, 43.31; H, 4.76; N, 12.42.

Entry 10: ^{1}H NMR ($CDCl_3$) δ 1.24 (bs, 4H), 1.3 (bs, 10H), 2.31 (bs, 4H), 2.36 (s, 3H), 3.59 (s, 2H), 7.79 (bs, 2H), 8.08 (s, 1H); MS (CI) *m/z* 397, 398 (M + H, M + 2H). Anal. Calcd for $C_{18}H_{26}BrN_3O_2$: C, 54.55; H, 6.61; N, 10.6. Found: C, 54.51; H, 6.54; N, 10.43.

Entry 11: ^{1}H NMR ($CDCl_3$) δ 1.26 (t, J = 7.1 Hz, 3H), 2.28 (s, 3H), 2.42 (s, 3H), 3.28 (s, 2H), 3.76 (s, 2H), 4.18 (q, J = 7, 7.1 Hz, 2H), 7.85 (bs, 2H), 8.31 (s, 1H); MS (CI) *m/z* 360, 362 (M + H, M + 3H). Anal. Calcd for $C_{13}H_{18}BrN_3O_4$: C, 43.35; H, 5.04; N, 11.67. Found: C, 44.36; H, 4.96; N, 11.16.

Reaction of Piperidine with 8-Nitro-5-methyl-1,4-dihydrobenz[*d*][1,3]oxazin-2-one (7) (Table 2, entry 5) and 8,6-Dibromo-5-methyl-1,4-dihydrobenz[*d*][1,3]oxazin-2-one (Table 2, entry 6). The reactions were carried as described above in the general procedure for the synthesis of substituted aminomethyl *o*-nitroanilines. Spectral and analytical data for the compounds are listed in Table 2.

3-Methyl-2-(piperidin-1-ylmethyl)-6-nitrophenylamine (entry 5): ^{1}H NMR ($CDCl_3$) δ 1.53 (bs, 2H), 1.54−1.58 (m, 4H), 2.31 (s, 3H), 2.39 (bs, 4H), 3.56 (s, 2H), 6.45 (d, J = 8.9 Hz, 1H), 7.87 (bs, 2H), 7.95 (d, J = 8.9 Hz, 1H); MS (CI) *m/z* 250 (M + H). Anal. Calcd for $C_{13}H_{19}N_3O_2$: C, 62.63; H, 7.68; N, 16.85. Found: C, 62.63; H, 7.73; N, 16.61.

4,6-Dibromo-3-methyl-2-(piperidin-1-ylmethyl)phenylamine (entry 6): ^{1}H NMR ($CDCl_3$) δ 1.42 (bs, 2H), 1.55−1.59 (m, 4H), 2.34 (s, 3H), 2.38 (bs, 4H), 3.85 (s, 2H), 5.42 (bs, 2H), 7.58 (s, 1H); MS (CI) *m/z* 360.8, 362.8, 364.8 (M, M + 2H, M + 4H). Anal. Calcd for $C_{13}H_{18}Br_2N_2$: C, 43.12; H, 5.01; N, 7.74. Found: C, 42.75; H, 4.85; N, 7.64.

Piperidine-1-carboxylic Acid 2-Amino-5-bromo-6-methyl-3-nitrobenzyl Ester (10). 6-Bromo-5-methyl-8-nitro-1,4-dihydrobenz[*d*][1,3]oxazin-2-one (**6**; 8.61 g, 30 mmol) was dissolved in THF (50 mL), and piperidine (6.65 g, 90 mmol) was added keeping the temperature below 25 °C. The reaction mixture was stirred for 8 h at rt, monitored by TLC (SiO_2, petroleum ether:EtOAc, 1:1), and filtered. A dark solid was obtained, which was dissolved in $CHCl_3$ (200 mL), washed with dilute HCl (5%), aq $NaHCO_3$, and water, and dried over $MgSO_4$. The solvent was evaporated to give a yellow residue, which was triturated with petroleum ether:EtOAc (7:3, 50 mL), filtered, and dried: yield 7.46 g, 67%; ^{1}H NMR ($CDCl_3$) δ 1.56 (m, 6H), 3.4 (m, 4H), 5.26 (s, 2H), 7.26 (bs, 2H), 8.38 (s, 1H); MS (CI) *m/z* 373, 374, 375 (M + H, M + 2H, M + 3H). Anal. Calcd for $C_{14}H_{18}BrN_3O_4$: C, 45.18; H, 4.87; N, 11.29. Found: C, 44.98; H, 4.64; N, 10.71.

Reaction of Piperidine-1-carboxylic Acid 2-Amino-5-bromo-6-methyl-3-nitrobenzyl Ester (10) with Amines. A solution of piperidine-1-carboxylic acid 2-amino-5-bromo-6-methyl-3-nitrobenzyl ester (**10**; 3.72 g, 10 mmol) was dissolved in dibenzylamine (7.88 g, 40 mmol). The solution was heated to 160 °C for 18 h. The reaction mixture was cooled and the dark oil triturated with methanol to give a yellow-brown crystalline solid. The solid was filtered, washed with methanol, and dried: yield 2.06 g, 50%. The product had identical ^{1}H NMR and TLC (SiO_2, petroleum ether:EtOAc, 1:1) to the product isolated from the reaction of **1** with dibenzylamine. (Table 1, entry 4). Similarly, the reaction of carbamate **10** with piperidine gave the corresponding product (Table 1, entry 6) in 86% yield.

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