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Synthesis of substituted 4-(3-alkyl-1,2,4-oxadiazol-5-ylmethyl)-3,4-dihydro-2*H*-1,4-benzoxazines and 4-(1*H*-benzimidazol-2-ylmethyl)-3,4-dihydro-2*H*-1,4-benzoxazines

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Abstract—Substituted 2*H*-1,4-benzoxazines were synthesized from substituted 2-amino phenols and 1,2-dibromoethane using K_2CO_3 in good to excellent yields. The cyclized products were further reacted with alkyl bromides to obtain the desired N-substituted 3,4-dihydro-2*H*-1,4-benzoxazines.

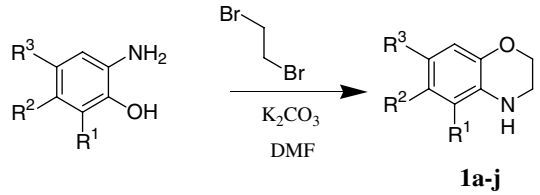
The 1,4-benzoxazine[1] structure is an integral part of several naturally occurring substances. For example, various glycosides of the 2-hydroxy-2*H*-1,4-benzoxazine skeletons have been found to occur in gramineous plants such as maize, wheat, rye, and rice, and have been suggested to act as plant resistance factors against microbial diseases and insects.[2] The 1,4-benzoxazine moiety is also found in various antibiotics such as C-1027.[3]

Various benzoxazine derivatives have been shown to have interesting pharmacological properties. Thus, nazasetran hydrochloride (Y-25130), *N*-(1-azabicyclo[2.2.2]oct-3-yl)-6-chloro-3,4-dihydro-4-methyl-3-oxo-2*H*-1,4-benzoxazine-8-carboxamide hydrochloride, a highly potent 5-HT3 receptor antagonist, has been reported as an antirheumatic agent and as a cure for severe nausea and vomiting induced by chemotherapy in cancer patients.[4] Several 3,4-dihydro-2*H*-1,4-benzoxazine derivatives have been reported to be potassium channel openers (PCOs) in vascular smooth muscle.[5] Benzoxazino-rifamycin KRM-1648 has been shown to have in vitro and in vivo activities against *Mycobacterium tuberculosis*.[6] Recently, a number of methotrexate derivatives incorporating the benzoxazine moiety have been synthesized which were found to be potent and safe candidates as antirheumatic agents[7] Benzoxazine derivatives have also been used as intermediates for the synthesis of other heterocyclic structures of biological importance.[8,9]

Several methods for the synthesis of 1,4-benzoxazine derivatives have been reported.[10–13] However, most of the methods reported targeted the synthesis of specific benzoxazines and lacked generality. Moreover, some of the routes involved reduction of 4*H*-benzoxazin-3-ones which requires costly reagents and has to be performed carefully. We report here a simple and general

Table 1. Preparation of substituted 3,4-dihydro-2*H*-1,4-benzoxazines

Product (**1**)	R^1	R^2	R^3
a	H	H	H
b	CH_3	H	H
c	H	CH_3	H
d	H	H	CH_3
e	H	Cl	H
f	H	OCH_3	H
g	H	F	H
h	H	CF_3	H
i	H	$CH_2OC_2H_5$	H
j	H	CH_2OH	H



1a-j

Scheme 1.

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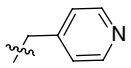
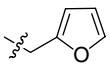
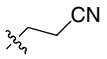
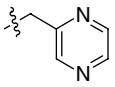
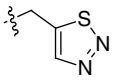
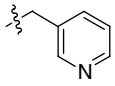
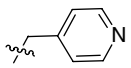
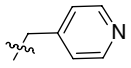
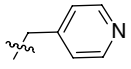
Table 2. Preparation of N-substituted 3,4-dihydro-2*H*-1,4-benzoxazines

Entry	Product (**2a–l**)[a]	Product (**3a–l**)	Product (**4a–l**)	Product (**5a–l**)	Yields (%)
a	$R^1 = H$, $R^2 = H$, $R^3 = H$, $R^4 = Et$	$R^1 = H$, $R^2 = H$, $R^3 = H$, $R^5 =$ 	$R^1 = H$, $R^2 = H$, $R^3 = H$, $R^6 = Me$	$R^1 = H$, $R^2 = H$, $R^3 = H$, $R^7 = H$, $R^8 = H$, $R^9 = H$	**2a** = 83 **3a** = 81 **4a** = 52 **5a** = 61
b	$R^1 = H$, $R^2 = H$, $R^3 = H$, $R^4 = Me$	$R^1 = H$, $R^2 = H$, $R^3 = H$, $R^5 =$ 	$R^1 = H$, $R^2 = H$, $R^3 = H$, $R^6 = Et$	$R^1 = H$, $R^2 = H$, $R^3 = H$, $R^7 = H$, $R^8 = F$, $R^9 = H$	**2b** = 80 **3b** = 71 **4b** = 50 **5b** = 64
c	$R^1 = H$, $R^2 = H$, $R^3 = H$, $R^4 =$ 	$R^1 = H$, $R^2 = H$, $R^3 = H$, $R^5 =$ 	$R^1 = H$, $R^2 = H$, $R^3 = H$, $R^6 = Ph$	$R^1 = H$, $R^2 = H$, $R^3 = H$, $R^7 = H$, $R^8 = Me$, $R^9 = H$	**2c** = 81 **3c** = 75 **4c** = 48 **5c** = 62
d	$R^1 = H$, $R^2 = H$, $R^3 = H$, $R^4 =$ 	$R^1 = H$, $R^2 = H$, $R^3 = H$, $R^5 = CH_2COOBn$	$R^1 = Me$, $R^2 = H$, $R^3 = H$, $R^6 = Ph$	$R^1 = Me$, $R^2 = H$, $R^3 = H$, $R^7 = Me$, $R^8 = Me$, $R^9 = H$	**2d** = 68 **3d** = 78 **4d** = 49 **5d** = 63
e	$R^1 = H$, $R^2 = H$, $R^3 = H$, $R^4 = CH_2Ph$	$R^1 = H$, $R^2 = H$, $R^3 = H$, $R^5 = C_3H_7$	$R^1 = H$, $R^2 = H$, $R^3 = Me$, $R^6 = Me$	$R^1 = H$, $R^2 = H$, $R^3 = H$, $R^7 = H$, $R^8 = Cl$, $R^9 = Cl$	**2e** = 78 **3e** = 74 **4e** = 51 **5e** = 56
f	$R^1 = H$, $R^2 = H$, $R^3 = H$, $R^4 =$ 	$R^1 = H$, $R^2 = H$, $R^3 = H$, $R^5 =$ 	$R^1 = H$, $R^2 = H$, $R^3 = H$, $R^6 = Et$	$R^1 = H$, $R^2 = H$, $R^3 = H$, $R^7 = Me$, $R^8 = Me$, $R^9 = H$	**2f** = 71 **3f** = 69 **4f** = 53 **5f** = 62
g	$R^1 = Me$, $R^2 = H$, $R^3 = H$, $R^4 = Et$	$R^1 = Me$, $R^2 = H$, $R^3 = H$, $R^5 =$ 	$R^1 = H$, $R^2 = Me$, $R^3 = H$, $R^6 = Et$	$R^1 = H$, $R^2 = H$, $R^3 = Me$, $R^7 = H$, $R^8 = Cl$, $R^9 = Cl$	**2g** = 89 **3g** = 72 **4g** = 49 **5g** = 57
h	$R^1 = H$, $R^2 = Me$, $R^3 = H$, $R^4 = Et$	$R^1 = H$, $R^2 = Me$, $R^3 = H$, $R^5 =$ 	$R^1 = H$, $R^2 = H$, $R^3 = Me$, $R^6 = Me$	$R^1 = H$, $R^2 = Me$, $R^3 = H$, $R^7 = H$, $R^8 = Cl$, $R^9 = Cl$	**2h** = 82 **3h** = 71 **4h** = 47 **5h** = 59
i	$R^1 = H$, $R^2 = H$, $R^3 = Me$, $R^4 = Et$	$R^1 = H$, $R^2 = H$, $R^3 = Me$, $R^5 =$ 	$R^1 = H$, $R^2 = H$, $R^3 = Me$, $R^6 = Et$	$R^1 = H$, $R^2 = H$, $R^3 = Me$, $R^7 = H$, $R^8 = Cl$, $R^9 = Cl$	**2i** = 80 **3i** = 70 **4i** = 46 **5i** = 58
j	$R^1 = Me$, $R_2 = H$, $R^3 = H$, $R_4 = Me$	$R^1 = Me$, $R^2 = H$, $R^3 = H$, $R^5 =$ 	$R^1 = H$, $R^2 = H$, $R^3 = Me$, $R^6 = Ph$	$R^1 = Me$, $R^2 = H$, $R^3 = H$, $R^7 = H$, $R^8 = F$, $R^9 = H$	**2j** = 81 **3j** = 65 **4j** = 40 **5j** = 60
k	$R^1 = H$, $R^2 = Me$, $R^3 = H$, $R^4 = Me$	$R^1 = H$, $R^2 = Me$, $R^3 = H$, $R^5 =$ 	$R^1 = H$, $R^2 = Me$, $R^3 = H$, $R^6 = Me$	$R^1 = H$, $R^2 = H$, $R^3 = Me$, $R^7 = H$, $R^8 = H$, $R^9 = H$	**2k** = 82 **3k** = 62 **4k** = 51 **5k** = 65
l	$R^1 = H$, $R^2 = H$, $R^3 = Me$, $R^4 = Me$	$R^1 = H$, $R^2 = H$, $R^3 = Me$, $R^5 =$ 	$R^1 = H$, $R^2 = H$, $R^3 = Me$, $R^6 = Me$	$R^1 = H$, $R^2 = H$, $R^3 = Me$, $R^7 = H$, $R^8 = H$, $R^9 = H$	**2l** = 83 **3l** = 60 **4l** = 52 **5l** = 61

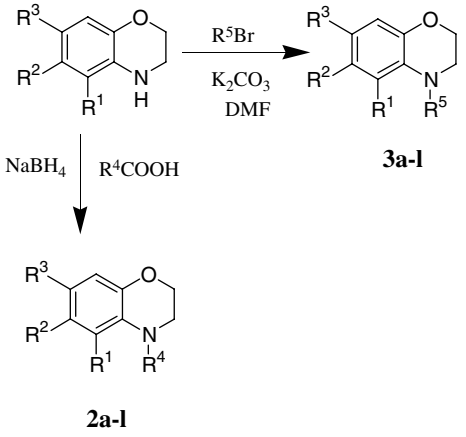
[a] Acids were dissolved in THF.

route for the synthesis of various 3,4-dihydro-2*H*-1,4-benzoxazines and N-substituted derivatives.

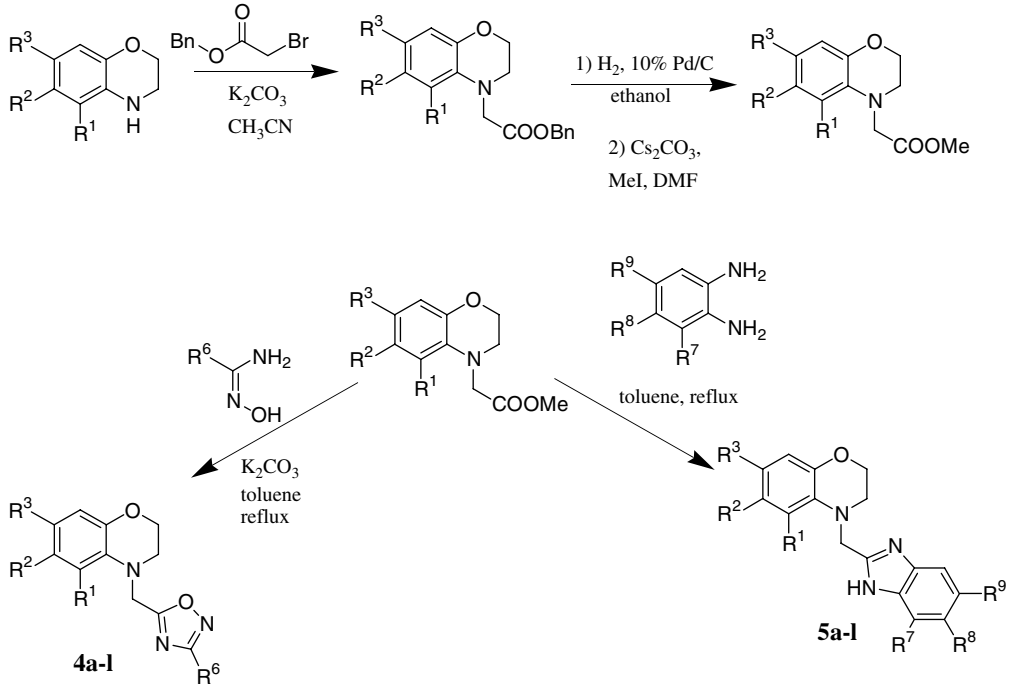
The reaction of 2-aminophenol (45 mmol) with 1,2-dibromoethane (1.2 equiv) in the presence of K_2CO_3 (3 equiv) in dry DMF at 125 °C proceeded smoothly and provided an 82% yield of **1a**.[14] Other solvents such as acetone and DCM were found to be far less effective. The presence of dry K_2CO_3 is crucial for a high yield of the product as it neutralizes the byproduct, that is, HBr. Increasing the amount of DMF resulted in a lower yield. This process was generalized to synthesize various substituted 3,4-dihydro-2*H*-1,4-benzoxazines as shown in Table 1. The time taken for the completion of the reaction was between 12 and 16 h; the amount of K_2CO_3 used ranged from 3 to 4 equiv depending upon the nature of the substituent. The 2-aminophenols with alkyl substituents were found to require less K_2CO_3 as compared to those with halogen substituents (Scheme 1).

This method was extended to the synthesis of various N-substituted 3,4-dihydro-2*H*-1,4-benzoxazines following the routes shown in Scheme 2. Most of the substitution reactions proceeded readily with high yields. The reduction route was found to be highly exothermic and required cooling. The reaction was found to proceed cleanly with about 68–89% yield of the product. These processes provided versatile routes for the synthesis of various N-substituted 3,4-dihydro-2*H*-1,4-benzoxazines as shown in Table 2. In the reductive aminations, a solvent was required only in the reactions involving benzoic acid, substituted furan-2-carboxylic acid, pyrazine-2-carboxylic acid and thiadiazole-5-carboxylic acid; however, the quantity of the solvent used was minimal.[15,16] This reductive route was followed for those alkyl bromides which did not undergo substitution reactions.

The investigation was further extended to the synthesis of substituted 4-(3-alkyl-1,2,4-oxadiazol-5-ylmethyl)-3,4-dihydro-2*H*-1,4-benzoxazines and 4-(1*H*-benzimidazol-2-ylmethyl)-3,4-dihydro-2*H*-1,4-benzoxazines as shown in Scheme 3 utilising (2,3-dihydro-2*H*-1,4-benzoxazin-4-yl)acetic acid methyl ester. N-Alkylation using benzyl bromoacetate was followed by de-benzylation to yield the corresponding acid. The acid was then converted into the methyl ester using MeI in the presence of Cs_2CO_3, since normal esterification did not yield any product. The methyl ester served as a good precursor for the synthesis of thiazole, imidazole and benzimidazole rings attached to the benzoxazine moiety. For compounds (**4a**–**j**), the methyl ester derivatives were refluxed in toluene with amidoximes in the presence of K_2CO_3 to give the desired products in 40–53% yields. For the synthesis of (**5a**–**j**), substituted *ortho*-phenylenediamines were



Scheme 2.



Scheme 3.

refluxed in toluene with the methyl ester in 56–65% yields; a catalytic amount of I_2 enhanced the rate and increased the overall yields of these reactions.

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14. *Synthesis of 3,4-dihydro-2H-1,4-benzoxazines* **1**. To a suspension of 2-aminophenol (46 mmol) and potassium carbonate (229 mmol) in dry DMF (40 ml), 1,2-dibromoethane (69 mmol) was added. The mixture was heated at 125 °C for 15 h. After cooling, the mixture was treated with crushed ice and then extracted with ethyl acetate. The organic extracts were dried over Na_2SO_4 and evaporated. The residue was purified by chromatography on a silica gel column using ethyl acetate and hexane (1:10) as the eluent. Compound **1a** was reddish oil (73% yield) IR (film) ν cm^{-1} 3385 (NH). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm 3.25 (d, 2H, $J = 2.7$ Hz), 4.07 (t, 2H, $J = 8.6$ Hz), 5.69 (s, 1H), 6.46–6.65 (m, 4H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) 60.2 (NCH_2), 73.1 (OCH_2), 112.8, 116.8, 117.3, 119.5, 140.1, 130.2. MS (CI) $m/z = 136.21$. Calcd for C_8H_9NO: C, 71.09; H, 6.71; N, 10.36; found: C, 72.12; H, 6.69; N, 10.31.
15. *Synthesis of N-alkylated 3,4-dihydro-2H-1,4-benzoxazines* **2** *by reduction*: To a solution of the acid (7 mmol) and 3,4-dihydro-2*H*-1,4-benzoxazines (7 mmol), $NaBH_4$ (73 mmol) was added slowly at 0 °C. The reaction was highly exothermic and care was taken to maintain the temperature around 0–5 °C. The reaction was stirred for 2–3 h. On completion, the mixture was neutralized using NaOH and extracted with ethyl acetate. The organic layer was dried and evaporated. The residue was chromatographed on silica gel column using ethyl acetate and hexane as eluents to obtain the desired product in high yield. Compound **2a** was a reddish oil, IR (film) showed the absence of NH stretching.^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 1.18 (t, 3H, $J = 14.2$ Hz), 3.30 (q, 2H, $J = 8.7$ Hz), 3.34 (t, 2H, $J = 14.1$ Hz), 4.24–4.26 (t, 2H, $J = 8.8$ Hz), 6.6–6.84 (m, 4H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz); δ ppm 14.5, 49.5, 59.1, 72.3, 112.9, 116.9, 117.1, 122.1, 130.1, 143.6. MS (CI) $m/z = 164.1$. Calcd for $C_{10}H_{13}NO$ is C, 73.59; H, 8.03; N, 8.58; found: C, 73.12; H, 8.09; N, 8.6.
16. *Synthesis of N-alkylated 3,4-dihydro-2H-1,4-benzoxazines* **3** *by alkylation*: Amine **1** (6 mmol) and dry K_2CO_3 (15 mmol) were dissolved in dry DMF (15 ml), then an alkyl halide (8.6 mmol) was added. The reaction mixture was stirred at room temperature overnight. After completion of the reaction (TLC monitoring), crushed ice was added and the product was extracted using ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified over silica gel eluting with ethyl acetate and hexane (1:20) to obtain the product. Compound **3a** was a reddish oil, IR (film) showed the absence of NH stretching. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 0.98 (d, 6H, $J = 6.6$ Hz), 1.62–1.67 (m, 1H), 1.77–1.82 (m, 2H), 3.46 (t, 2H, $J = 14.1$ Hz), 4.26 (t, 2H, $J = 8.1$ Hz), 6.5–6.84 (m, 4H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 20.3, 28.1, 59.1, 65.8, 72.3, 112.9, 116.9, 117.1, 122.1, 130.1, 143.6; MS (CI) $m/z = 190.13$. Calcd for $C_{12}H_{17}NO$ is C, 75.35; H, 8.96; N, 7.32; found: C, 75.12; H, 9.01; N, 7.31.