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An Aerobic Oxidative Coupling Approach for the Synthesis of N-substituted 2-aminobenzothiazole Derivatives using Iron Catalyst

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ABSTRACT

A facile and convenient method was developed for the formation of novel N substituted 2-aminobenzothiazoles via an iron-catalysed condensation of 2-aminobenzothizole with different amines. This method is applicable for a wide range of aliphatic, aromatic and heterocyclic amines furnishing moderate yields of the corresponding products and thus rendering the methodology as a highly eco-friendly, inexpensive alternative to the existing methods.

Keywords: 2-Aminobenzothiazole, N-substituted, synthesis, aerobic oxidative coupling, Iron catalyst.

INTRODUCTION

Substituted benzothiazoles exhibits various biological and therapeutical activities[1,2] Aminobenzothiazoles are synthesised by employing various catalysts: cobalt was used by Zhu[3,4], palladium by Vera[5], copper by Saha[6] and Khatun[7], nano copper oxide[8, 9]. Other methods of synthesising aminobenzothiazoles is by Herz method[10], solid phase synthesis[11], using benzyltrimethylammonium tribromide[12] or sodium dichloroiodate[13], starting from o-nitroaniline[14] or in water[15]. Apart from synthesis, following biological activities were reported: Aurora-A kinase inhibitor[16], calcium channel blockers[17], anti-cancer[18,19,] herbicidal activity[20], mitochondrial apoptotic inducers[21], neuronal nitric oxide synthase inhibitor[22], anti-inflammatory[23,24], antimalarials[25], antimicrobial[26, 27].

Oxidative coupling reactions with amines are reported in literature. Zhou *et al*[28, 29] used boron-dipyrromethene (BODIPY) under mild condition, Yu *et al*[30] used oxone and trifluoroacetic acid in PEG-400 for the green method. Also, various metals are used for these conversions: gold[31], gold nanoparticle[32], copper[33], silica supported vanadium[34], ruthenium[35] and cobalt[36].

Synthesis of N-substituted amines reported in literature does not use iron as catalyst. In view of these reports and literature, attempt was made to synthesize novel N-substituted aminobenzothiazole derivatives using iron as catalyst via oxidative coupling route.

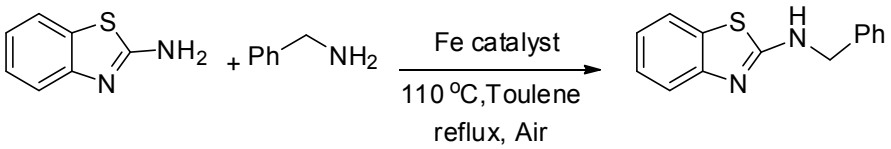
RESULTS AND DISCUSSION

Different iron compounds ($FeCl_3$, $FeCl_2$, $FeCl_2.2H_2O$, $FeSO_4.7H_2O$, $Fe(OAc)_2$ and $FeBr_2$) were used for the optimisation. The reactions (scheme-1) were carried out with 10% mol of the catalyst and found that $FeBr_2$ results in 63% yield. Therefore, concentration of the catalyst was further reduced to 5% and 2%. This resulted in 64 and 29% yields respectively. Also the effect of the inert medium was evaluated by using N_2 and Ar environment and that resulted in 6 and 3% yields respectively. Hence the concentration of $FeBr_2$ was optimised at 5% mol.

While optimising the concentration of the catalyst, the reactants were used 1.5 equivalents of aminobenzothiazole and 1 equivalent of benzylamine. After finalising the concentration of the catalyst, the reactants concentrations were changed to 1 and 2 equivalents respectively and the yield obtained was only 48%.

It has been found that $FeBr_2$ gave better yields amongst all other iron catalysts used. To optimise the conditions, different concentrations were used and 5% mol found to be the optimum concentration without the usage of inert conditions (Table-1). To substantiate our proposed mechanism (scheme - 3), we have carried out the reactions in inert conditions. During the process, oxygen starved environment has yielded very low product.

Under these optimised conditions, various N-substituted 2-aminobenzothiazoles (3 a - e) were synthesised from their corresponding amine (2 a – e) and 2-amino benzothiazole (1) (scheme – 2). These newly synthesised compounds were characterised by IR, NMR and MS. In order to cross check applicability for different amines, aromatic,



Scheme 1: Reaction scheme for the optimisation of the reaction conditions

Table 1: Optimisation Parameters For The Synthesis Of N-Substituted Aminobenzothiazoles

Entry	Catalyst (% mol)	Environment, (%mol of 2 amino benzothiazole : %mol of Benzylamine)	Isolated yield (%)
1	FeCl3 (2% mol)	Air, (1.5:1)	Traces
2	FeCl2 (10% mol)	Air, (1.5:1)	Traces
3	FeCl2.2H2O (10% mol)	Air, (1.5:1)	Not recovered
4	FeSO4.7H2O (10% mol)	Air, (1.5:1)	Not recovered
5	Fe(OAc)2 (10% mol)	Air, (1.5:1)	Not recovered
6	FeBr2 (10% mol)	Air, (1.5:1)	63
7	FeBr2 (5% mol)	Air, (1.5:1)	64
8	FeBr2 (2% mol)	Air, (1.5:1)	29
9	FeBr2 (10% mol)	N2, (1.5:1)	6
10	FeBr2 (10% mol)	Ar, (1.5:1)	3
11	FeBr2 (10% mol)	Air, (2:1)	48
12	No catalyst	Air, (1.5:1)	Not recovered

aliphatic and heterocyclic substrates were employed and produced moderate yields.

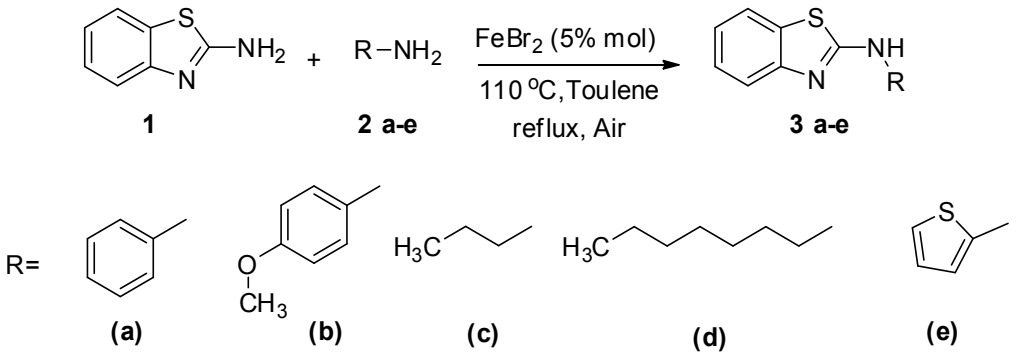
Here we are reporting the iron as catalyst via oxidative coupling approach for the synthesis of novel N-substituted aminobenzothiazole derivatives (3 a – e).

General procedure

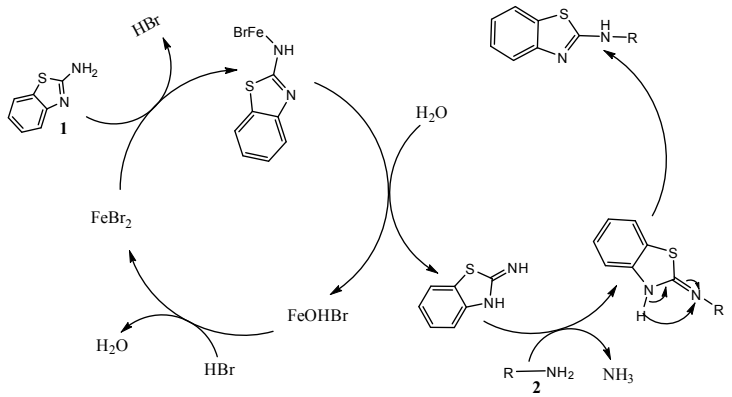
Iron catalyst was added to a two-necked, round-bottom flask containing the 2-aminobenzothiazole and an amine at room temperature. The resulting reaction mixture was heated at 110ºC for 24 h. The progress of the reaction was monitored by TLC. After 24 hours, the reaction mixture was directly purified using column chromatography.

N-benzylbenzo[d]thiazol-2-amine (3a): The title compound was synthesised as per the general method using benzyl amine. Yield: 64%. Mp: 244-246ºC.^{1}H NMR (400 MHz, DMSO-d_6): δ 8.52 (s, 1H, NH), 7.68 – 7.00 (m, 9H, aromatic), 4.60 (s, 2H, CH_2). ^{13}C NMR (75 MHz, DMSO -d_6): δ 166.6, 158.8, 152.9, 131.2, 130.8, 129.3, 125.9, 121.4, 118.5, 48.7. Mol Wt: 240.32, m/z: 240.09. Anal. Calcd for $C_{14}H_{12}N_2S$: C, 69.97; H, 5.03; N, 11.66; S, 13.34. Found: C, 70.05; H, 5.29; N, 11.80; S, 12.85.

N-(4-methoxybenzyl)benzo[d]thiazol-2-amine (3b): The title compound was synthesised as per the general method using 4-methoxybenzyl amine.Yield: 67%. Mp: 296-298ºC. ^{1}H NMR (400 MHz, DMSO -d_6): δ 8.43 (s, 1H, NH), 7.67- 6.89 (m, 8H, aromatic), 4.51 (s, 2H, CH_2), 3.73 (s, 3H, OCH_3).^{13}C NMR (75 MHz, DMSO -d_6): δ 166.6, 158.8, 152.9, 131.2, 130.8, 129.3, 125.9, 121.4, 118.5, 114.2, 55.5, 47.2. Mol Wt: 270.35, m/z: 270.21**.** Anal. Calcd for $C_{15}H_{14}N_2OS$: C, 66.64; H, 5.22; N, 10.36; S, 11.86. Found: C, 66.91; H, 5.34; N, 10.41; S, 11.46.



Scheme 2:



Scheme 3: Possible mechanism

N-butylbenzo[d]thiazol-2-amine (3c): The title compound was synthesised as per the general method using n-butyl amine.Yield: 72%. Mp: 199-201ºC. ^{1}H NMR (400 MHz, DMSO - d_6): δ 8.06 (s, 1H, NH), 7.96 - 7.08 (m, 4H, aromatic), 3.56 – 3.48 (t, 2H, $NHCH_2$), 1.52 to 1.33 (m, 4H, CH_2-CH_2), 0.91 (t, 3H, CH_3). ^{13}C NMR (75 MHz, DMSO -d_6): δ 166.6, 153.4, 130.8, 125.8, 121.4, 121.2, 118.4, 47.7, 40.5, 39.7, 39.4. Mol Wt: 206.31, m/z = 206.10. Anal. Calcd for $C_{11}H_{14}N_2S$: C, 64.04; H, 6.84; N, 13.58; S, 15.54. Found C, 64.24; H, 6.99 N, 13.67; S, 15.08.

N-octylbenzo[d]thiazol-2-amine (3d): The title compound was synthesised as per the general method using n-octyl amine.Yield: 75%. Mp: 233-235ºC. ^{1}H NMR (400 MHz, DMSO - d_6): δ 7.99 (s, 1H, NH), 7.65 -6.97 (m, 4H, benzothiozol), 3.36 – 3.31 (t, 2H, $NHCH_2$), 1.61 - 1.26 (m, 12H, CH_2), 0.87 – 0.84 (t, 3H, CH_3). ^{13}C NMR (75 MHz, DMSO - d_6): δ 166.6, 153.2, 130.7, 125.9, 121.2, 121.2, 118.3, 47.7, 40.8, 40.5, 40.0, 39.7, 39.4, 39.2. Mol Wt: 262.41, m/z = 262.01. Anal. Calcd for $C_{15}H_{22}N_2S$: C, 68.66; H, 8.45; N, 10.68; S, 12.22. Found: C, 68.87; H, 8.57; N, 10.93; S, 11.63.

N-(thiophen-2-ylmethyl)benzo[d]thiazol-2-amine (3e): The title compound was synthesised as per the general method using 2-(Aminomethyl) thiophene.Yield: 59%. Mp: 199-201ºC. ^{1}H NMR (400 MHz, DMSO - d_6): δ 8.22 (s, 1H, NH), 7.51 – 6.98 (m, 7H, aromatic), 4.48 (s, 2H, CH_2). ^{13}C NMR (75 MHz, DMSO - d_6): δ 166.6, 158.6, 152.8, 141.2, 131.4, 130.8, 129.3, 126.6, 125.9, 121.4, 118.5, 51.7. Mol Wt: 246.35, m/z = 246.09. Anal. Calcd for $C_{12}H_{10}N_2S_2$: C, 58.51; H, 4.09; N, 11.37; S, 26.03. Found: C, 58.67; H, 4.21; N, 11.42; S, 25.69.

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