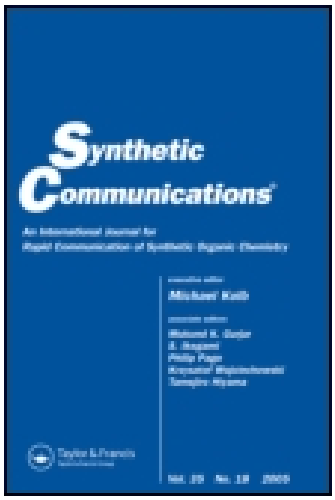

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A Novel Method for the Synthesis of 2(3*H*)-Benzimidazolones, 2(3*H*)-Benzoxazolone, and 2(3*H*)-Benzothiazolone via In Situ Generated Ortho Substituted Benzoic Acid Azides: Application of Ammonium Azide and Vilsmeier Complex for Acid Azide Generation

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ABSTRACT

An easy and generalized route to 2(3*H*)-benzimidazolones, 2(3*H*)-benzoxazolone and 2(3*H*)-benzothiazolone is attempted. A novel one-pot method for the in situ generation and cyclisation of *ortho* substituted benzoic acid azides is reported via the application of ammonium azide and Vilsmeier complex.

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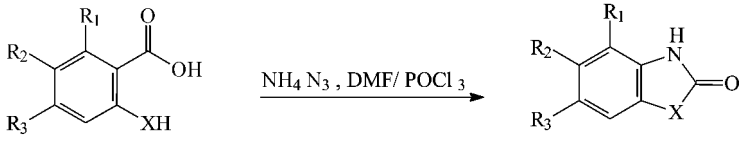
Key Words: Vilsmeier complex; Acid azide; Curtius rearrangement; 2(3*H*)-benzimidazolone; 2(3*H*)-benzoxazolone; 2(3*H*)-benzothiazolone.

Acyl azides serve as valuable synthetic intermediates in organic chemistry.[1] They undergo Curtius rearrangement[2] to isocyanates and thereby leading to a variety of products.[1] In our recent communication we have reported the synthesis of acyl azides using Vilsmeier complex starting from the respective acids in one-pot.[3] In continuation of our research interests on the synthesis of heterocyclic compounds[4] using the Vilsmeier complex, we aimed to synthesize these title compounds from in situ formed *ortho* substituted benzoic acid azides after Curtius rearrangement at room temperature (Sch. 1). Benzimidazole derivatives possess a variety of biological activities.[5] A large number of derivatives of benzimidazole found to show trypanosomicidal and spirocheticidal action and are active against diseases caused by protozoa.[6] Most of them are derivatives of 2(3*H*)-benzimidazolethione or 2(3*H*)-benzimidazolone.

Since the first report on the hypnotic properties of 2-benzoxazolinone[7a] a number of derivatives have been tested for various activities including anticonvulsant, antipyretic, analgesic, cardiotonic, antiulcer, antineoplastic or antibacterial, antimicrobial and antifungal effects.[7b] 2(3*H*)-benzothiazolone and its derivatives possess excellent biological activities.[8] There are several synthetic routes to 2(3*H*)-benzimidazolones,[9] 2(3*H*)-benzoxazolones[10] and 2(3*H*)-benzothiazolones.[11] But most of the synthetic routes[12] to 2(3*H*)-benzimidazolone involve *o*-phenylenediamine as the starting material, which is a suspected carcinogen and is costlier. And there is no generalized strategy available for the synthesis of these title compounds in one pot. Hence we aimed at a generalized procedure, which is simpler for the preparation of 2(3*H*)-benzimidazolones, 2(3*H*)-benzoxazolone and 2(3*H*)-benzothiazolone. The novelty in the synthesis of these heterocycles is achieved here not only through the in situ formation of acyl azides but also by the employment of



1 a - h where X = NH, O, S 2 a - h

Scheme 1. Synthesis of 2(3*H*)-benzimidazolones, 2(3*H*)-benzoxazolone and 2(3*H*)-benzothiazolone.

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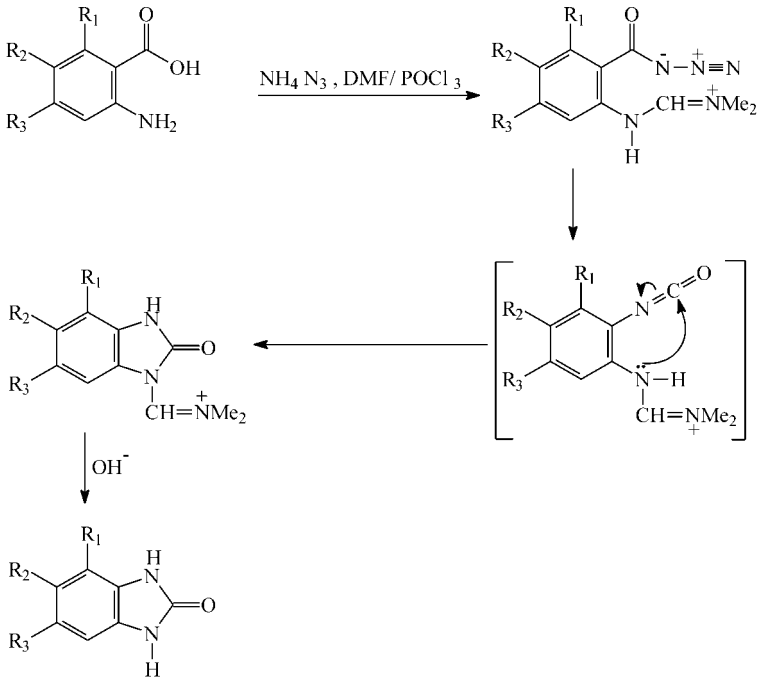
ammonium azide for the generation of acyl azides. Since efficient application of sodium azide in the introduction of azide moiety involves trituration and its storage under nitrogen atmosphere,[13] ammonium azide[14] was employed instead of sodium azide. And it was found that in situ formed ammonium azide is more reactive and more advantageous.[15] Hence ammonium azide was generated in situ under reaction conditions using powdered sodium azide, ammonium chloride and DMF. The acyl azides thus formed being highly reactive, undergo Curtius rearrangement leading to unstable isocyanates. The amino group of anthranilic acid and substituted anthranilic acids which is viable to the attack of the Vilsmeier reagent takes up one mole of the same and cyclises with the neighbouring isocyanate moiety to form 2(3*H*)-benzimidazolones upon careful hydrolysis with 1N NaOH. *N*-Formyl benzimidazolones are also formed upon hydrolysis with H_2O along with 2(3*H*)-benzimidazolones. This rationalises the reaction path (Sch. 2).

In the case of 4-nitroanthranilic acid the dimerised product (95% yield) was obtained even at room temperature.[16] Salicylic acid and thiosalicylic acid yield 2(3*H*)-benzoxazolone and 2(3*H*)-benzothiazolone respectively in



Scheme 2. Mechanism involved in the synthesis of 2(3*H*)-benzimidazolones.

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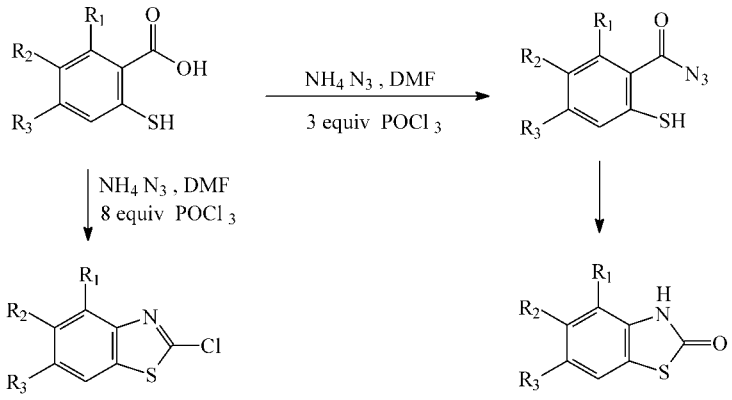
Table 1. Synthesis of 2(3*H*)-benzimidazolones, 2(3*H*)-benzoxazolone and 2(3*H*)-benzothiazolone.

Entry	X	R_1	R_2	R_3	% Yield[a]	Time (hrs)	Mp (°C)[b]
2a	NH	H	H	H	80	8	>300[17a]
2b	NH	Cl	H	H	88	8	>300
2c	NH	H	Cl	H	70	8	324–328[18]
2d	NH	H	H	Cl	15	10	324–328[18]
2e	NH	H	NO_2	H	75	8	308[19]
2f	NH	H	H	NO_2	dimerised product[16]	6	>250
2g	O	H	H	H	82	8	137[17b]
2h	S	H	H	H	70	8	138[17c]

[a]Isolated yields after column chromatography.
[b]All the products were characterised by ^1H and ^{13}C NMR, mass spectral and elemental analysis data.

good yields upon treatment with ammonium azide and three equivalents of DMF-$POCl_3$ complex (Table 1).

Excess $POCl_3$ (Sch. 3) replaces –OH group with –Cl yielding 94% of 2-chlorobenzothiazole. Stirring the reaction mixture at room temperature for about 6–10 h effected both rearrangement and cyclization. The versatility of our method involves a novel in situ generation and cyclisation of the *ortho* substituted benzoic acid azide obtained from the action of Vilsmeier complex, *ortho* substituted benzoic acid and in situ generated ammonium azide.



Scheme 3. Synthesis of 2(3*H*)-benzothiazolone and 2-chlorobenzothiazole.

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In summary a convenient one-pot conversion of *ortho* substituted benzoic acids into benzimidazolones, benzoxazolone and benzothiazolone at room temperature is reported.

EXPERIMENTAL

All the reagents were distilled prior to use from an appropriate drying agent. Infrared spectra were recorded as KBr pellets for all the samples except for 2-chlorobenzothiazole, which is a liquid and was recorded as a film on a Perkin Elmer FT-IR instrument. Nuclear Magnetic Resonance spectra recorded on a Jeol Spectrometer, at 500 MHz (PMR) and at 125 MHz (^{13}C NMR). Mass spectra were obtained on Perkin Elmer Mass Spectrometer.

General Procedure for the in situ Generation and Cyclization of the *ortho* Substituted Benzoic Acid Azide

To a stirred solution of the substituted benzoic acid (0.686 g, 5 mmol) and sodium azide (0.358 g, 5.5 mmol, 1.1 equiv.) in 20 ml dry DMF, ammonium chloride (0.03 g, 10 mol%) was added upon cooling to 0°C. Then $POCl_3$ (1.4 mL, 3 equiv.) was added drop wise to the solution. After the addition was over the reaction mixture was allowed to attain room temperature gradually. The solution after stirring for 8 h was neutralised with 1 N NaOH and extracted with chloroform. The solvent was then evaporated off under reduced pressure and the crude material was purified by column chromatography on silica gel (s.d.fine, 100–200 mesh, hexane/ethyl acetate, 5 : 1) to afford the pure product, which was characterised by ^{1}H NMR, ^{13}C NMR, mass spectral and elemental analysis data.

Spectral analysis of 4-chloro-2(3*H*)-benzimidazolone (Compound 2b). IR (KBr) 3119 1745, 1665 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d, ppm): δ 11.14 (s, 1H), 10.9 (s, 1H), 6.99–6.97 (dd, $J = 1.145$, 8.018 Hz, 1H), 6.95–6.92 (t, $J = 7.447$, 8.018 Hz, 1H), 6.90–6.89 (dd, $J = 1.145$, 7.447 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d, ppm): δ 155.57, 131.46, 127.96, 122.17, 120.83, 113.35, 170.89; EI MS 168 (M +), 140, 105, 78. Anal. calcd for $C_7H_5ClN_2O$: C, 49.87; H, 2.99; N, 16.62. Found: C, 49.77; H, 3.02; N, 16.78.

5-Chloro-2(3*H*)-benzimidazolone (Compound 2c). IR (KBr) 3174, 1752 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d, ppm): δ 11.45 (s, 1H), 11.29 (s, 1H), 7.820–7.816 (d, $J = 2.291$ Hz, 1H), 7.702–7.681 (dd, $J = 2.291$, 8.588 Hz, 1H), 7.20–7.18 (d, $J = 8.593$ Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d, ppm): δ 154.03, 131.87, 131.43, 130.97, 128.40, 118.96, 114.89; EI

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MS 168 (M +), 140, 105, 78. Anal. calcd for $C_7H_5ClN_2O$: C, 49.87; H, 2.99; N, 16.62. Found: C, 50.02; H, 3.06; N, 16.54.

5-Nitro-2(3*H*)-benzimidazolone (Compound 2e). IR (KBr) 3188, 1758 cm^{-1}; ^1H NMR (400 MHz, DMSO-d, ppm): δ 11.40 (s, 1H), 11.17 (s, 1H), 7.94–7.91 (dd, $J = 2.17$, 8.68 Hz, 1H), 7.81–7.80 (d, $J = 2.11$ Hz, 1H), 7.13–7.11 (d, $J = 8.68$ Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d, ppm): δ 155.97, 141.47, 135.07, 129.13, 118.06, 108.58, 104.35; EI MS 179 (M +), 178, 148, 133, 105, 78. Anal. calcd for $C_7H_5N_3O_3$: C, 46.92; H, 2.81; N, 23.46. Found: C,46.87; H, 2.85; N, 23.55.

4-Nitro-2-[7-nitro-3,4-dihydro-4-oxo-3-quinazolinyl]-*N*,*N*-dimethylbenzamide (Compound 2f). IR (KBr) 1691, 1637 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, ppm): δ 8.72–8.71 (d, $J = 2.291$ Hz, 1H), 8.49–8.47 (m, 3H), 8.42–8.40 (d, $J = 8.593$ Hz, 1H), 8.34–8.32 (dd, $J = 2.291$, 8.588 Hz, 1H), 7.92–7.90 (d, $J = 8.593$ Hz, 1H), 2.90 (s, 3H), 2,82 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 165.76, 159.76, 152.06, 149.54, 148.65, 148.54, 141.84, 135.87, 129.42, 129.29, 126.45, 125.69, 125.21, 123.06, 121.95, 39.21, 34.98; EI MS 383, 182, 164, 146, 117, 101, 91, 75. Anal. calcd for $C_{17}H_{13}N_5O_6$: C, 53.27; H, 3.42; N, 18.27. Found: C, 53.19; H, 3.43; N, 18.34.

2-Chlorobenzothiazole. IR (KBr) 3070, 1710, 1483, 1009 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, ppm): δ 7.94–7.93 (d, $J = 8.588$ Hz, 1H), 7.76–7.74 (d, $J = 8.018$ Hz, 1H), 7.48–7.45 (t, $J = 8.$ 593, 8.018 Hz, 1H), 7.41–7.37 (t, $J = 8.593$, 8.018 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 153.40, 151.09, 136.19, 126.81, 125.88, 123.00, 121.21; EI MS 169 (M +), 134, 108, 82, 69.

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