Available online at www.scholarsresearchlibrary.com

Scholars Research Library

Archives of Applied Science Research, 2010, 2 (1) 80-85
(http://scholarsresearchlibrary.com/archive.html)

ISSN 0975-508X
CODEN (USA) AASRC9

Synthesis of New N_1-Substituted Benzotriazoles as Anthelmintic Agents

S. S. Pawar[*1], P. L. Gorde[1], R. B. Kakde[2]

[1]*Department of Chemistry, Sanjivani College of Pharmaceutical Education and Research, At- Sahajanandanagar, Ahmednagar (M.S.), India*
[2] *Department of Chemistry, Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur, India*

Abstract

Benzotriazole (2), synthesized by conventional method on treatment with ethylene chloride and potassium carbonate yielded N_1-(chloro methyl) benzotriazole (3). The derivatives were synthesized by condensation of N_1-(chloro methyl) benzotriazole with substituted hydroxy compounds and amines. The structures were established on the basis of spectral data. All compounds were screened for anthelmintic activity and were found to exhibit significant activity.

Key words: Benzotriazole, Anathematic activity, Albendazole, *Pheretima posthuma*, N_1-(chloro methyl) benzotriazole

---

Introduction

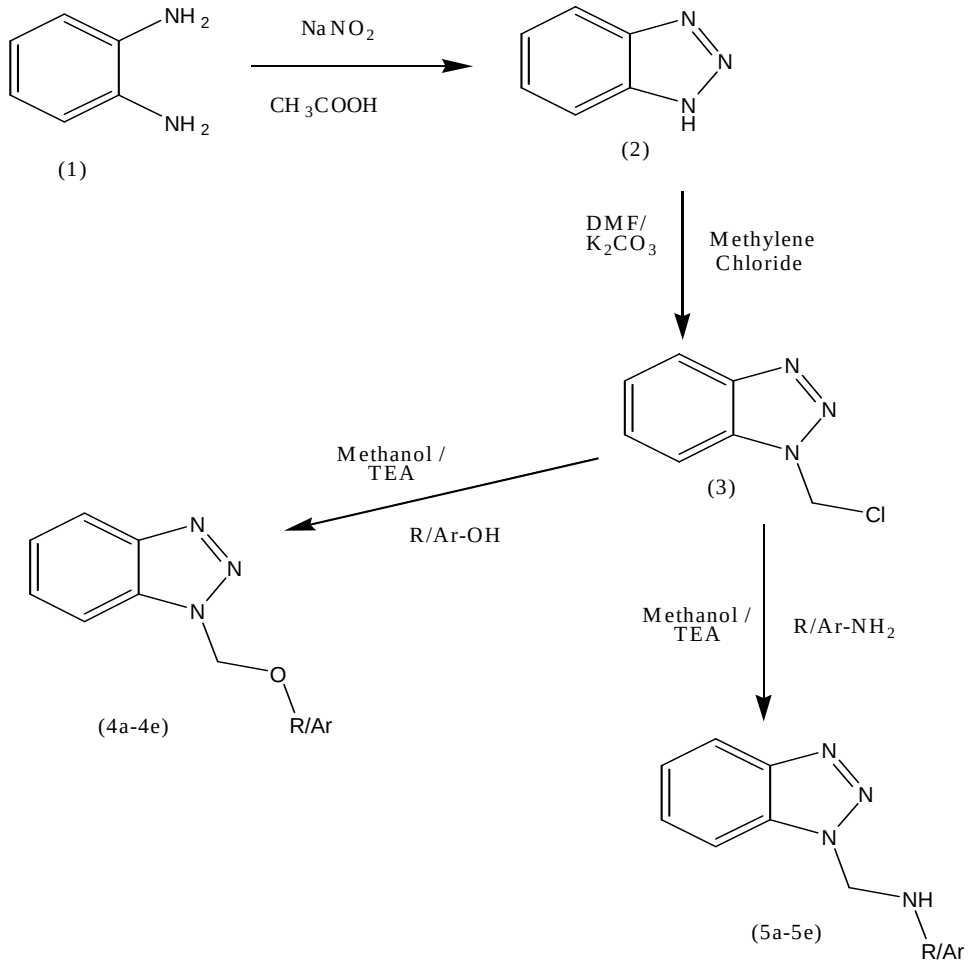
Azoles have played a crucial part in the history of heterocyclic chemistry and also been used extensively as important synthons in organic synthesis. Owing to the versatile chemotherapeutical activities of azoles, a significant research activity has been directed towards this class. Synthesis and activity of benzotriazole derivatives as antiprotozoal agents [1] (inhibitors of *Acanthamoeba castellanii*) have been reported in the literature. Benzotriazole acts as a precursor in many organic syntheses [2, 3] and has proven to be fertile source of medicinal agents such as antimicrobial [4], anticonvulsant, anti-inflammatory [5], anti-tumour [6] etc. Several derivatives of benzotriazole are reported as agonists of peroxisome proliferator activated receptors [7]. Synthesis and biological activity of 1H-benzotriazole analogues as inhibitors of the NT pase / helicase and some related Flavivirade has been extensively investigated [8]. Also Benzotriazole is a parent material to produce UV-absorbers. Benzotriazole and its derivatives are versatile intermediates involved in the production of Corrosion Inhibitors, Anti-fading agent for metals, Antiseptic and Anticoagulant agent, Anti-fog for photograph, Anti-freeze Agent, Photoconductor, Copying systems, pesticide products and other specialty chemicals.

Materials and Methods

Experimental

The melting points of all the synthesized compounds were determined in open capillary tubes and are uncorrected. Purity of all the compounds was checked by TLC on precoated 0.1mm silica gel plates. The IR spectra in KBr (cm^{-}) were taken on FTIR-8400S (SHIMADZU) spectrometer at the Dept. of analysis, Sanjivani College of pharmaceutical education and research, Kopargaon. ^{1}H NMR spectra were recorded on a Brooker 300MHz NMR spectrophotometer using $CDCl_3$ as solvent and TMS as internal standard (chemical shifts in δ ppm).

Synthetic Scheme



Synthesis of Benzotriazole:

OPD (10.8 gm, 0.1 mol) was dissolved in a mixture of 12 gm (11.5 ml, 0.2 mol) of glacial acetic acid and 30 ml water content in a 250 ml beaker. The clear solution was cooled to 15˚C and stirred magnetically and then added a solution of 7.5 gm (0.11 mol) of $NaNO_2$ in 15 ml water in one portion. The reaction mixture becomes warm within 2-3 minutes and reaches a temp of about 85˚C and begins to cool while the color changes from deep red to pale brown continue stirring for 15 minutes, by which time the temp will have dropped to 35-40˚C and then thoroughly chilled in an ice water bath for 30 minutes. Pale brown solid was separated and washed with 30 ml portion of ice cold water.

Synthesis of N_1-(chloro methyl) benzotriazole: -

Benzotriazole (2g, 0.02mol) and dichloro methane (8.4ml, 0.1mol) were dissolved in 20 ml of DMF and K_2CO_3 (3.9g, 0.02mol) was added and the contents were refluxed for 6 hours. The solid residue was collected by adding ice cold water in to reaction mixture.

General procedure for synthesis of the derivatives of the N_1-(chloro methyl) Benzotriazole

In RBF N_1-(chloro methyl) benzotriazole (2g, 0.02mol), benzyl amine (10.7g, 0.1mol) and K_2CO_3 (3.9g, 0.02mol) were dissolved in 20ml DMF. The contents were refluxed for 6 hr. A solid residue was obtained by adding ice cold water into reaction mixture. The residue was filtered and dried.

General Structure of Derivatives: -

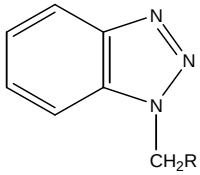


Table 1: Physical data and anthelmintic activity of compounds 4a-4e, 5a-5e

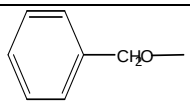
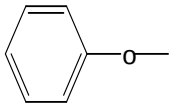
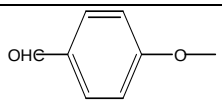
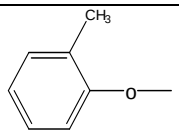
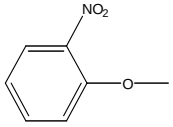
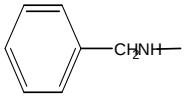
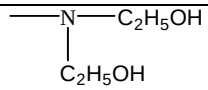
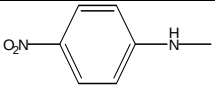
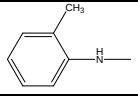
Sr. No.	R	Yield (g)	m.p. (^{0}C)	R_f value
4a		0.25	124-26	0.61
4b		0.16	120-21	0.40
4c		0.11	129-30	0.46
4d		0.11	145-46	0.24
4e		0.10	142-43	0.37
5a		0.25	100-02	0.66
5b	CH_3-$(CH_2)_3$-NH-	0.32	127-29	0.70
5c		0.07	140-41	0.81
5d		0.15	115-17	0.26
5e		0.15	124-25	0.63

Table 2: Data representing spectral characterization of synthesized derivatives

Comp.	^{1}H NMR ($CDCl_3$) (δ, ppm)	IR (KBr, cm^{-1})
4a	7.32-7.90 (5H, aromatic), 3.62 (benzyl CH_2), 6.04 (N- CH_2)	2941, 1460;
4b	7.32-7.50 (5H, aromatic), 6.36 (N- CH_2), 7.80 (H-5, H-6), 8.03 (H-7, H-4).	2941, 1460;
4c	7.20-7.31 (4H, aromatic), 6.31 (N- CH_2), 7.44 (H-5, H-6), 8.06 (H-7, H-4).	2960, 1480, 1710
4d	2.38 (-CH_3), 7.20-7.27 (4H, aromatic), 6.24 (N- CH_2), 7.60 (H-5, H-6), 8.04 (H-7, H-4).	2951, 1465
4e	8.09-8.31 (4H, p-NO_2 C_6H_4), 6.32 (N- CH_2), 7.42 (H-5, H-6)	2961, 1455, 1540
5a	7.32-7.60 (5H, aromatic), 6.92 (NH), 6.04 (N- CH_2) 7.89 (H-5, H-6), 8.03 (H-7, H-4).	3318 2945, 1460
5b	6.15 (NH-C$\underline{H}_2$), 6.24 (N- C$\underline{H}_2$), 2.56 (-CH_3), 7.60 (H-5, H-6), 8.04 (H-7, H-4).	2945, 1460
5c	3.65 (-$C_2\underline{H}_4$OH), 0.9 (-OH), 6.24 (N-CH_2)	1330, 2895, 1455
5d	10.24 (-N$\underline{H}$), 6.24 (N- CH_2), 7.56 (H-5, H-6) 8.09-8.31 (4H, p-NO_2 C_6H_4)	3320, 2961, 1455, 1560
5e	2.38 (-CH_3), 7.17-7.29 (4H, aromatic), 6.81 (NH), 6.24 (N-CH_2), 7.61 (H-5, H-6), 8.1H-7, H-4).	3325, 2857, 1465, 1290

Anthelmintic activity [9-12]

Animals

Indian adult earthworms (*Pheretima posthuma*) collected from moist soil and washed with normal saline to remove all faecal matter were used for the anthelmintic study. The earthworms of 3-5cm in length and 0.1-0.2 cm in width were used for all the experimental protocol due to their anatomical and physiological resemblance with the intestinal roundworm parasites of human beings [9].

Drugs and chemicals:

Albendazole (Pfizer Ltd., Bangalore), Saline water (Nurilife, Ahmedabad).

Preparation of suspensions

The suspensions of the synthesized derivatives were freshly prepared before starting the experiment. The appropriately weighed quantity was suspended in saline water to prepare the concentrations of 5mg/ml, 10mg/ml and 15mg/ml. Albendazole suspension was used as a reference standard.

Anthelmintic activity [10]

Twelve groups, of six earthworms each were released into 10 ml of desired formulations as follows; vehicles (normal saline), Albendazole (5 mg/ml), or the test suspensions (5 mg/ ml, each) in normal saline.

In the second set of experiment, twenty three groups of six earthworms were released in to 10 ml of desired formulations as follows; vehicle (normal saline), albendazole (10 mg/ml, 15mg/ml), or the test suspensions (10 mg/ ml, 15mg/ml each) in normal saline. Observations were made for the time taken to paralysis and death of individual worms. Time for paralysis was noted when no movement of any sort could be observed except when the worms were shaken vigorously. Time for death of worms were recorded after ascertaining that the worms

neither moved when shaken vigorously nor when dipped in warm water (50 °C).Death was concluded when the worms lost their motility followed with fading away of their body colors. The results are shown in Table 3.

Table 3: In *vitro* anthelmintic activity of synthesized benzotriazole derivatives

Treatment	Concentration (mg/ml)	Time taken for the paralysis (min)	Time taken for the death (min)
4a	**5**	4.57 ± 0.346	7.59 ± 0.346
	10	3.59 ± 0.256	5.49 ± 0.256
	15	2.15± 0.120	4.56 ± 0.120
4b	**5**	5.28 ± 0.180	9.12 ± 0.280
	10	4.34 ± 0.306	7.58 ± 0.206
	15	3.56 ± 0.220	5.36 ± 0.320
4c	**5**	5.58 ± 0.338	8.59 ± 0.238
	10	4.18 ± 0.186	6.18 ± 0.115
	15	3.59± 0.164	4.49± 0.186
4d	**5**	6.57 ± 0.280	12.34 ± 0.271
	10	5.48 ± 0.352	9.36 ± 0.231
	15	3.59± 0.086	5.36± 0.361
4e	**5**	6.49 ± 0.320	12.46 ± 0.320
	10	4.59 ± 0.231	8.36 ± 0.231
	15	3.12± 0.361	6.23 ± 0.361
5a	**5**	8.12 ± 0.320	12.23 ± 0.281
	10	5.29 ± 0.231	8.59 ± 0.112
	15	4.52± 0.361	6.53 ± 0.213
5b	**5**	7.18 ± 0.120	13.46 ± 0.152
	10	4.36 ± 0.331	9.36 ± 0.207
	15	3.59± 0.161	5.23 ± 0.208
5c	**5**	7.47 ± 0.280	11.36 ± 0.170
	10	5.58 ± 0.206	7.35 ± 0.276
	15	4.12 ± 0.200	6.38 ± 0.338
5d	**5**	3.59 ± 0.210	6.59 ± 0.298
	10	2.46 ± 0.332	4.36 ± 0.286
	15	1.56 ± 0.098	3.26 ± 0.326
5e	**5**	7.35 ± 0.206	11.35 ± 0.346
	10	5.26 ± 0.335	9.26 ± 0.178
	15	4.38± 0.095	6.38± 0.241
Albendazole	**5**	3.28 ± 0.280	4.56 ± 0.338
	10	2.03 ± 0.206	3.10 ± 0.206
	15	1.12± 0.200	1.59 ± 0.256

Results are expressed as Mean ± SEM. Control worms were alive up to 24 hrs of observation**.**

Results and Discussion

It is evident from the experimental data that the N^1alkyl/Arylaminomethylene benzotriazoles and N^1alkoxy/Aryloxymethylene Benzotriazoles showed significant anthelmintic activity at 5, 10 and 15 mg/ml. Results were comparable with the standard drug, Albendazole at same concentration. Table 3 reveals that N^1 – (p-nitrophenyl) aminomethylenebenzotriazole and N^1 –benzyloxymethylenebenzotriazole showed the best anthelmintic activity. These required the least time for causing paralysis and death of the earthworms. From the results it can be concluded that the N^1alkoxy/Aryloxymethylene Benzotriazoles are having good anthelmintic activity than the N^1alkyl/Aryl aminomethylene Benzotriazole derivatives.

Form the above evidence; it is clear that these derivatives can be used to discover bioactive synthetic products that may serve as leads for the development of new pharmaceuticals that address hither to unmet therapeutic needs. It is hoped that this study would lead to the establishment of some compounds that could be used to formulate new and more potent anthelmintic drugs of synthetic origin.

References

[1] K Kopanska; A Najda; J Zebrowska; L Chomicz; J Piekarezyk; P Myjak; M Bretner. *Bioorg Med Chem*, **2004**, 12, 2617.
[2] M Purohit; SK Srivastava. *Indian J Pharmaceutical Sciences*, **1992**, 54, 1, 25.
[3] M.Krasavin; DG Pershin; D Larkin; D Kravchenko. *Synthetic Communication*, **2005**, 35, 2587.
[4] F Al-omran; RM Mohareb; AA El-Khair. *J Heterocyclic Chem*, **2002**, 39, 5, 877.
[5] KM Dawood; H Abdel-Gawad; EA Rageb; M Ellithey; HA Mohammed. *Bioorg Med Chem*, **2006**, 14, 11, 3672.
[6] YA Al-Soud; NA Al-Masoudi; AR Ferwanah. *Bioorg Med Chem*, **2003**, 11, 8, 1701.
[7] A Sparatore; C Godia; E Perrino; S Romeo; B Stales; JC Fruchart; M Crestani. *Chemistry and Biodiversity*, **2006**, 3, 385.
[8] M Bretner; A Baier; K Kopanska; A Najda; A Schoof; M Reinholz; A Lipniacki; A Piasek; T Kulikowski; P Borowski. *Antivir Chem Chemother*, **2005**, 16, 315.
[9] Z Vigar. *Atlas of Medical Parasitology*, P. G. Publishing House, Singapur, , **1984**, 216-217
[10] VD Tambe; AS Girme; SA Nirmal; RS Bhambar.; PB Ghogare.; RD Bhalke; RS Jadhav. *Ind J Nat Prod*, **2006**, 22, 3, 27.
[11] KN Gaind; RD Budhiraja. *Ind. J. Pharm.*, **1967**, 29, 6, 185.
[12] S Sarkar; TY Pasha; B Shivkumar; R Chimkode. *Indian J of Heterocyclic Chem*, **2008**, 18, 95-96.