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CONDENSATION OF THIOAMIDES WITH 2-AMINOTHIOPHENOLS : A VERSATILE SYNTHESIS OF BENZOTHIAZOLES.

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Abstract: Thioamides condense with 2-aminothiophenols under convenient and mild conditions to provide a variety of simple and functionalized benzothiazoles in fair to good yields.

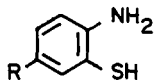
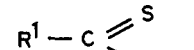
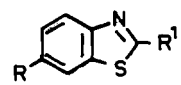
The Condensation of 2-aminothiophenols (2-ATP) with carboxylic acids[1,2] and their derivatives such as esters[1], acid chlorides[1,3], acid anhydrides[1], nitriles[1], and an N-ethoxy carbonyl thioamides[4] constitute one of the most widely used methods for the preparation of benzothiazoles. However this method suffers from the requirement of strong acids (H_2SO_4, PPA or P_2O_5-CH_3SO_3H), elevated temperatures (upto 250°C) and prolonged reaction time, conditions which could prove deleterious when sensitive functionality may be involved.

Recently, for a project pertaining to benzothiazolophane syntheses, several 2,6-functionalized benzothiazoles were needed in quantity. However, procedures based on condensation of appropriately functionalized 2-ATP with carboxylic acids or acid chlorides either failed completely or provided disappointingly low yields of functionalized benzothiazoles[5].

We have now found that thioamides can serve as excellent acid equivalents in condensation with 2-ATP, to provide under acid catalysis, a variety of benzothiazoles in fair to good yields. Our results of condensation using simple as well as functionalized thioamides bearing ether, olephinic linkage, ester and nitrile groups with a few 2-ATP are shown in the Table.

Although NMP and acetic acid could be used as the reaction solvents, we preferred ethylene glycol in terms of high substrate solubility and easy product isolation. All reaction were carried out using 10mmol of 2-ATP and 11 mmol of thioamides in ethylene glycol (except for the Entry 14 in which case NMP was used) containing slightly more than 1 equivalent of HCl. In general, reactions are clean and in several cases, benzothiazoles directly precipitate out during the reaction or upon dilution in good purity.

Table[6] : Condensation of thioamides with 2 - ATP[a].

Entry	2 - ATP 	Thioamides. 	Benzothiazoles 	Yields %
1	R = H (1)	R^1 = Me (6)	R = H; R^1 = Me (13)[b]	70
2	(1)	R^1 = Ph (7)	R = H; R^1 = Ph (14)[b]	85
3	(1)	$R^1 = CH_2OPh$ (8)	R = H; $R^1 = CH_2OPh$ (15)[b]	65
4	(1)	$R^1 = CH_2O\overset{O}{\overset{\|}{C}}Ph$ (9)	R = H; $R^1 = CH_2O\overset{O}{\overset{\|}{C}}Ph$ (16)	60
5	(1)	$R^1 = CH_2CN$ (10)	R = H; $R^1 = CH_2CN$ (17)[b]	75
6	R = Me (2)	(6)	R = R^1 = Me (18)[b]	75
7	(2)	(8)	R = Me; $R^1 = CH_2OPh$ (19)	70
8	(2)	(9)	R = Me; $R^1 = CH_2O\overset{O}{\overset{\|}{C}}Ph$ (20)	75
9	R = Cl (3)	(6)	R = Cl; R^1 = Me (21)[b]	80
10	(3)	$R^1 = \overset{O}{\overset{\|}{C}}Ph$ (11)	R = Cl; $R^1 = \overset{O}{\overset{\|}{C}}Ph$ (22)[b]	50
11	(3)	$R^1 = CH_2\overset{O}{\overset{\|}{C}}OEt$ (12)	R = Cl; $R^1 = CH_2\overset{O}{\overset{\|}{C}}OEt$ (23)	75
12	R = COOH (4)	(6)	R = COOH; R^1 = Me (24)[b]	90
13	(4)	(8)	R = COOH; $R^1 = CH_2OPh$ (25)	85
14	R = COOMe (5)	(6)	R = COOMe; R^1 = Me (26)[b,c]	70

(a) All reactions conducted on steam bath (7 - 10 hrs) using 10 mmol of 2 - ATP and 11 mmol of thioamides in ethylene glycol containing 1 ml conc. HCl or mentioned otherwise. (b) Known products characterized by m.p. comprisons and spectral data, (c) Reaction in NMP (100° C, 6 hrs) containing 1 ml conc. HCl.

As can be seen from the Table, the reactions are widely applicable and in spite of the presence of potentially reactive acid, ester or nitrile functions, the reaction occurs selectively with the thioamide moiety only. Thus for the first time, thioamide methodology allows for the direct preparation of 2-cyanomethyl[7] and 2-phenoxymethyl benzothiazoles[8] (products 17 and 15, respectively), which have been previously reported via circuitous routes only. Moreover, certain functionalized benzothiazoles (products 19 and 20) which could not be prepared satisfactorily via corresponding acids or esters[5], are now readily accessible using appropriate thioamides in good yields.

Since substituted benzothiazoles are of interest as agrochemicals[9] and pharmaceuticals[10,11] and as masked carbonyl equivalents[12] in synthetic organic chemistry, the present procedure, being simple, mild and tolerant of sensitive functionalities, appears superior compared to other available conditions for the preparation of benzothiazoles.

EXPERIMENTAL :

The general procedure is illustrated with 2-methyl-6-chloro benzothiazole (21) :- To a solution of ethylene glycol (15 ml) containing 1ml of conc. HCl,

was added 5-chloro-2-aminothiophenol[13] (1.595gm, 10mmol) and thioacetamide (0.825gm, 11mmol). The reaction mixture was heated on steam bath under nitrogen atmosphere, the gas outlet being connected to an aqueous KOH trap to absorb H_2S gas. After 7 hrs of heating, the reaction mixture was diluted with cold water. The precipitated solid was filtered, air dried and crystallized from aqueous alcohol to give 2-methyl-6-chloro benzothiazole (Amount 1.46gm, yield 80%) M.P. 84-85°C, Lit[14] m.p. 85-87°C.

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(5) For instance, condensation of phenoxy acetic acid or its ethyl ester with 5-methyl-2-aminothiophenol under a variety of acids (H_2SO_4, PPA or P_2O_5 - CH_3SO_3H) gave none of the expected 2-phenoxymethyl-6-methyl benzothiazole(Product 19), where as with phenoxy acetyl chloride in NMP solvent, only 15% yield of this compound was obtained after chromatographic seperation. Also, 2-benzoxymethyl-6-methyl benzothiazole (Product 20) was not accessible by attempted reaction of benzoxy acetic acid or its ethyl ester with 5-methyl-2-aminothiophenol.

(6) Substrates, 2-aminothiophenols and thioamides are all known compounds and were prepared by literature methods. In cases where benzothiazole products are new, mp, ir and ^{1}H-nmr spectral data are given below :

Product 16 : m.p. 76-78°C (from Petroleum ether 60-80°C); ir (KBr) 1740, 1600, 1530, 1450, 1350, 1260, 1190 and 870cm^{-1}; nmr ($CDCl_3$), δ 5.65(2H,S) 7.2-8.2 (9H,m).

Product 19 : m.p. 106-108°C (from petroleum ether-ethyl acetate); ir (KBr) 1600, 1530, 1440, 1360, 1250, 1170, 1060, 820cm^{-1}; nmr ($CDCl_3$), δ 2.50(3H,S), 5.45(2H,S), 6.8-7.8(8H,m).

Product 20 : m.p. 77-78°C (from Petroleum ether 60-80°C); ir (KBr) 1720, 1600, 1450, 1350, 1270, 1110, 810cm^{-1}; nmr ($CDCl_3$), δ 2.95(3H,S), 5.60(2H,S), 7.0-8.0(8H,m).

Product 23 : m.p. 110-112°C (from alcohol); ir (KBr) 1730, 1590, 1510, 1440, 1360, 1240, 1190, 820, 765cm^{-1}; nmr($CDCl_3$) δ 1.2(3H,t,J=7Hz), 4.25(2H,q,J = 7Hz), 4.0 (2H,S), 7.2-8.2(3H,m).

Product 25 : m.p. 215-217°C (from aq.alcohol); ir (KBR) 3000, 1720, 1600, 1520, 1500, 1370, 1330, 1250, 1200, 1070, 900cm^{-1}; nmr($CDCl_3$-DMSO) δ 3.8(1H,bs), 5.4(2H,s), 7.0-8.0(8H,m).

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