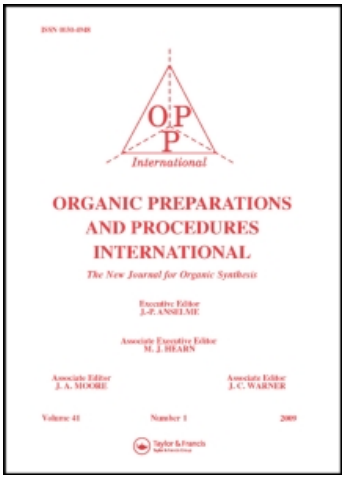

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A RAPID AND EFFICIENT SYNTHESIS OF 2H-1,4-BENZOXAZINE-3(4H)-THIONES AND 2H-1,4-BENZOTHIAZINE-3(4H)-THIONES

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A RAPID AND EFFICIENT SYNTHESIS OF 2H-1,4-BENZOXAZINE-3(4H)-THIONES AND 2H-1,4-BENZOTHIAZINE-3(4H)-THIONES+

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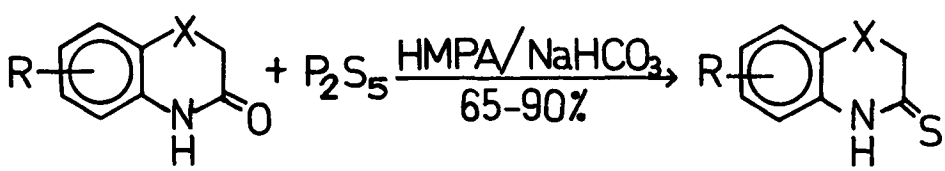
Some 2H-1,4-benzoxazine- and benzothiazine-3(4H)-thiones were needed in substantial quantities for the preparation of imidazo(2,1-c)(1,4)benzoxazine and benzothiazine derivatives of medicinal interest. Previous syntheses[1-5] of some of these thiolactams (IIIa-j) involving the treatment of the corresponding lactams (Ia-j) with P_2S_5 in solvents such as xylene, pyridine, acetonitrile, CH_2Cl_2 etc. suffer from disadvantages such as long reaction times (24-72 hrs), formation of difficultly purifiable mixtures of products and variable and



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often poor yields. Although Lawesson's reagent[6,7] was found to be generally satisfactory for the thionation of lactams like Ia-j which do not carry an additional carbamoyl function, neither this method nor the other thionation procedures[1-5] were found to be suitable for the selective thionation of the

lactams (Ik-n) to give the desired thiolactams (IIIk-n). In most of these cases, the required products were found to be generally contaminated with substantial quantities of the unwanted dithioxo derivatives (IIIk & l, R = $NHCSCH_3$; IIIm & n, R = $NHCSC_6H_5$, X = O) resulting from the concomitant thionation of the other carbamoyl group which required tedious purification procedures for the isolation of the desired products. Recently Smolders *et al.*[8] reported the preparation of some 9-acridonethiones by treatment of the corresponding 9-oxo analogues with P_2S_5 in hexamethylphosphoric triamide (HMPA). When applied to the preparation of some of the title compounds, this method gave the desired products of relatively low purity in 50-60% yields.

We now report that the use of $NaHCO_3$ as a basic additive in Smolders' procedure results in both rapid and selective thionation of the lactam carbonyl function to give the desired thiolactams (IIIa-n) in excellent yields (65-90%). The physical data of some of these thiolactams (IIIa-j) are reported in the Table.

A mixture of P_2S_5 and $NaHCO_3$ readily dissolves in HMPA with the evolution of CO_2. The resulting solubilized and presumably more reactive thionation agent could be expected to attack preferentially the comparatively more reactive[9] lactam carbonyl group of Ik-n thus perhaps explaining the facile and selective thionation.

The mild reaction conditions (heating the components in HMPA at 80° for 0.5-1 hr), the easy work-up, the selective thionation of only the lactam carbonyl function in lactams

carrying other carbamoyl groups, the high yields and purity of the products make the present synthesis a rapid and efficient general method for the preparation of a variety of benzoxazine and benzothiazine-3-thiones.

TABLE. Physical Data of Thiolactams IIIa-j

Compd. No.	X	R	Yield[a] (%)	mp.[b] (°C)	lit. mp. (°C)
IIIa	O	H	90	120	119-120[6]
IIIb	O	6-Cl	85	195-196	195-196[6]
IIIc	O	6-Me	87	204-206	204-206[5]
IIId	O	6-NO_2	80	204-206	204-206[5]
IIIe	O	7-NO_2	82	202-204	201-203[10]
IIIf	S	H	90	128	128-129[6]
IIIg	S	7-Cl	88	206-208	206-208[6]
IIIh	S	7-Br	86	207-209	206-208[5]
IIIi	O	6-$NHCOOCH_3$	80	202	202[5]
IIIj	O	7-$NHCO_2CH_3$	78	248	248[5]

a) Isolated yields starting from compounds I. TLC showed absence of any other products. b) mps. are determined by means of a capillary and are uncorrected.

EXPERIMENTAL SECTION

Melting points were determined in glass capillaries on a Gallenkamp melting point apparatus and are uncorrected. Elemental analyses were performed using a Hosli microcombustion apparatus MK 101. Mass spectra were recorded on a Varian MAT CH 7A mass spectrometer. IR spectra were taken on a Perkin-Elmer 577 spectrophotometer and the NMR spectra were recorded on a Varian A-90 (EM-390) spectrometer. The starting lactams I were prepared following the methods reported earlier.[11-14]

CAUTION: As HMPA is known to be a potent animal carcinogen and is also suspected to be a human carcinogen; contact with skin and exposure to its vapour must be scrupulously avoided and all operations must be performed in an efficient hood.

General Procedure .- The appropriate lactam (I, 0.1 mol) was

added to a solution of P_2S_5 (II, 26.64 gm, 0.12 mol) and $NaHCO_3$ (25.2 gm, 0.3 mol) in HMPA (100 ml) and the resulting solution was stirred at 80° for 0.5 to 1 hr. It was then cooled to room temperature and added to ice cold water (2000 ml) when the required product separated as a solid. It was filtered, washed with water and recrystallised from either aqueous ethanol (IIIa-j) or acetone/pet.ether (IIIk-n) to give the corresponding thiolactam III.

6-Acetamido-2H-1,4-benzoxazine-3(4H)-thione (IIIk, X = O, R = 6-$NHCOCH_3$), 70% yield, mp. 142-144°; IR (nujol): 3340 (NH), 1670 cm^{-1} (CONH); NMR (DMSO-d_6): δ 2.1 (s, 3H, CH_3), 4.83 (s, 2H, CH_2), 6.7-7.6 (m, 3H, ArH), 10.13 (bs, CONH, exchangeable with D_2O), 12.8 (bh, 1H, CSNH, exchangeable with D_2O); MS:m/e 222(M^+), 179 $(M-CH_3CO)^+$, 43 (CH_3CO).

Anal. Calcd. for $C_{10}H_{10}N_2O_2S$: C, 54.05; H, 4.50; N, 12.64
Found : C, 54.29; H, 4.66; N, 12.76

7-Acetamido-2H-1,4-benzoxazine-3(4H)-thione (IIIl, X = O, R = 7-$NHCOCH_3$), 65% yield, mp. 148-150°; IR (nujol): 3280 (NH), 1675 cm^{-1} (CONH); NMR (DMSO-d_6): δ 2.0 (s, 3H, CH_3), 4.72 (s, 2H, CH_2), 7.0-7.3 (m, 2H, ArH), 7.4 (s, 1H, ArH), 10.0 (bs, 1H, CONH, exchangeable with D_2O), 12.6 (h, 1H, CSNH, exchangeable with D_2O); MS: m/e 222 (M^+), 179 $(M-CH_3CO)^+$, 43 (CH_3CO).

Anal. Calcd. for $C_{10}H_{10}N_2O_2S$: C, 54.05; H, 4.50; N, 12.64
Found : C, 53.93; H, 4.61; N, 12.52

6-Benzamido-2H-1,4-benzoxazine-3(4H)-thione (IIIm, X = O, R = 6-$NHCOC_6H_5$), 75% yield, mp. 223-225°; IR (nujol): 3300 (NH),

1650 cm^{-1} (CONH); NMR (DMSO-d_6) : δ 4.8 (S, 2H, CH_2), 7.0-8.1 (m, 8H, ArH), 10.3 (bs, 1H, CONH, exchangeable with D_2O), 12.8 (bs, 1H, CSNH, exchangeable with D_2O); MS: m/e 284 (M^+), 105 (C_6H_5CO).

Anal. Calcd. for $C_{15}H_{12}N_2O_2S$: C, 63.30; H, 4.20; N, 9.80
Found : C, 63.52; H, 4.38; N, 9.62

7-Benzamido-2H-1,4-benzoxazine-3(4H)-thione (IIIn, X = O, R = 7-$NHCOC_6H_5$), 72% yield, mp. 205°; IR (nujol) : 3340 (NH), 1660 cm^{-1} (CONH); NMR (DMSO-d_6) : δ 4.72 (s, 2H, CH_2), 7.1-8.2 (m, 8H, ArH), 10.25 (bs, 1H, CONH, exchangeable with D_2O), 12.68 (h, 1H, CSNH, exchangeable with D_2O); MS: m/e 284 (M^+), 105 (C_6H_5 CO).

Anal. Calcd. for $C_{15}H_{12}N_2O_2S$: C, 63.30; H, 4.20; N, 9.80
Found : C, 63.15; H, 4.36; N, 10.02.

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