REGIOSPECIFIC SYNTHESIS OF N-1 AND N-2 SUBSTITUTED PYRIMIDINONES EMPLOYING A NOVEL 1,3-OXAZINE PREPARATION

Harvey I. Skulnick and Wendell Wierenga

Cancer and Viral Diseases Research
The Upjohn Company
Kalamazoo, MI 49001, USA

Abstract - Reaction of ethyl benzoylacetate with methylthiopseudourea resulted in expulsion of methylmercaptan to afford 2-amino-6-phenyl-4H-1,3-oxazin-4-one in good yield. This novel oxazine synthesis was exploited to secure N-1 and N-2 substituted pyrimidinones regiospecifically.

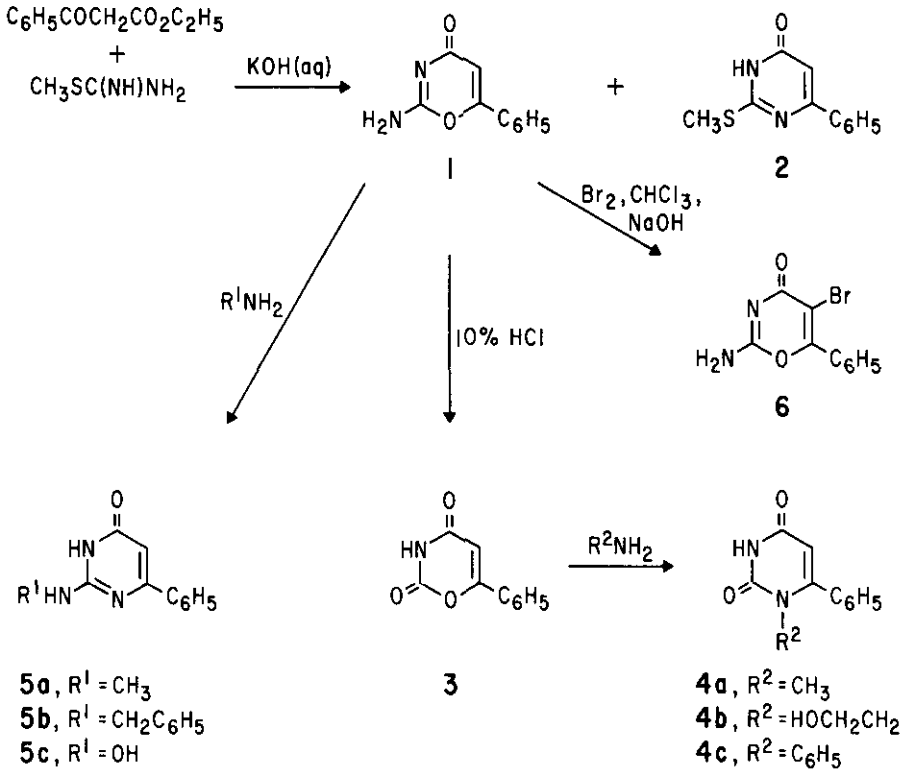
We uncovered several years ago the interesting antiviral and interferon-inducing properties of 2-amino-5-bromo-6-phenyl-4(3H)-pyrimidinone (ABPP) and several analogs.[1,2] In exploring the SAR with these biologic activities[3-5] as well as antiinflammatory activity[6] we had need of an efficient route to N-1 and N-2 substituted analogs. Since direct condensation procedures involving β-ketoesters with substituted guanidines afford mixtures of N-2 and N-3 products (substituted ureas gave N-3 products), we explored the use of 1,3-oxazines[7] as intermediates to the desired pyrimidinones.

The early work of Lacey demonstrated that 1,3-oxazines could be derived from diketene and cyanamides or substituted ureas.[8] Obviously this approach is limited by diketene as the starting material. Improvements on this procedure have been reported by Takahashi, et al.[9] and Perronnet, et al.[10] In 1976 Shaw, et al.[11], reported that the reaction of β-ketoesters with N,N-dialkylurea yielded 1,3-oxazines. Unfortunately the yield of the 6-phenyl analog was less than 10%. Also 6-substituted 1,3-oxazines were described recently as being derived from 6-chloro-1,3-oxazine-2,4-diones[12] which in turn were prepared from alkyl isocyanates and malonyl dichloride.[13] Applicability to 6-phenyl analogs was not described and would likely be difficult.

We have found that the condensation of ethyl benzoylacetate with methylthiopseudourea under controlled alkaline conditions affords 2-amino-6-phenyl-4H-1,3-oxazin-4-one(1) in 60% yield (Scheme 1). The expected product, 2, is produced in the reaction in increasing amounts as a function of reaction time. The longer the reaction proceeds the more 2 is formed at the expense of 1 (80% yield of 2 at 48 h). Both are readily separable with an ethanolic trituration (2 being reasonably soluble). We speculate the 2 is not formed directly, but results from the reaction of 1 with the methylmercaptide produced in the initial production of 1. This course of events is unusual since condensations of β-ketoesters with ambident nucleophiles normally involves initial reaction with

the ketone rather than the less electrophilic ester carbonyl required by the production of 1.

Scheme I



The structure of 1 was confirmed by spectral means and comparison to literature data.[11] In addition the 2-amino-1,3-oxazine was readily converted[11] to the known 1,3-oxazine-1,4-dione, 3. This transformation provided the desired entry to the antiinflammatory N-1 substituted 6-phenylpyrimidine-2,4-diones, 4, by heating 3 with the appropriate alkylamine. In the case of arylamines the intermediate, ring opened aryl urea does not reclose under the reaction conditions but requires a second step involving acid catalyzed cyclization.

Condensation of 1 with substituted amines yielded exclusively N-2-substituted pyrimidinones, 5. The structures were assigned based on ^{1}H and ^{13}C couplings secured from their respective NMR spectra (off resonance analysis of fully coupled ^{13}C-NMR spectrum). We have previously demonstrated the conversion of pyrimidinones to their corresponding 5-bromo analogs[1,3] (the 5-hydrogen compounds were inactive). The 2-amino-1,3-oxazine could likewise be converted to 5-bromo analog with bromine in aqueous base and chloroform.

Thus we have uncovered an efficient, regioselective approach to N-1 and N-2 substituted 6-phenylpyrimidinones by exploiting a novel, one-step preparation of 2-amino-6-phenyl-1,3-oxazin-2-one in good yield.

EXPERIMENTAL

2-Amino-6-phenyl-1,3-oxazin-4-one (1). To 9.45 g (0.034 mol) of methylthiopseudourea·H_2SO_4 was added 40 ml of water and 8.0 g (0.142 mol) of potassium hydroxide. With vigorous stirring, 12.0 g (0.0625 mol) of ethyl benzoylacetate (Aldrich) was added and the heterogeneous mixture allowed to stir at ambient temperature for 18 h. The resulting solids were filtered and washed very well with water followed by ether and dried at 60°C in a vacuum oven to yield 7.20 g (62.3%) of 1. Recrystallization from 95% EtOH:DMF afforded mp 244-246°C (lit.[11], 242-244°C). Calc'd for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.28; N, 14.89; Found: C, 63.45, H, 4.45, N 15.02; MS: Calc'd: 188.0568, Found: 188.0586. ^{1}H-NMR (d_6DMSO): 8.08-7.81 (m, 2H); 7.71-7.50 (m, 3H); 6.53 (s, 1H).

Small amounts of 2-methylthio-6-phenylpyrimidin-4-one (2) can be detected in the supernatant of the initial filtration. It can be isolated by concentrating the soln and purified by silica gel chromatography (mp 240-242°C, decomp.). Anal. Calcd for $C_{11}H_{10}N_2OS$: C, 60.52; H, 4.61; N, 12.83; S, 14.69. Found: C, 60.75; H, 4.73; N, 13.17; S, 14.23. ^{1}H-NMR (d_6-DMSO): 8.16 and 7.58 (m, 5H), 6.73 (s, 1H), 2.61 (s, 3H).

2-Amino-5-bromo-6-phenyl-1,3-oxazin-4-one (6). To 1.88 g (10 mmol) of 2-amino-6-phenyl-4H-1,3-oxazine (1) was added 11.0 ml of a 1 N NaOH and 100 ml of water. The mixture was heated to reflux to dissolve all the solids cooled to 50°C and added, with stirring, a solution of 550 µl of Br_2 in 100 ml of $CHCl_3$. Additional 1 N NaOH was added to keep aqueous neutral; continued to stir at ambient temperature for 24 h. The resulting solids were filtered, washed well with water and dried to yield 215 mg of 1. The filtrate was evaporated to dryness and chromatographed over 50 g of silica gel using 1:2 acetone:cyclohexane as eluant to yield 1.72 g of 6 (R_f=0.35 in 1:1 acetone:cyclohexane, 0.4 in 10% MeOH:$CHCl_3$). Anal. Calcd for $C_{10}H_7BrN_2O_2$: C, 44.96; H, 2.65, N, 10.49, Found: C, 45.23; H, 2.70; N, 10.46.

2-(N-Methylamino)-6-phenyl-4-pyrimidinone (5a). To 4.0 g (21.2 mmol) of 1 was added a sat'd soln of methylamine in methanol (150 ml). The reaction solution was allowed to stir at ambient temperature for 72 h and evaporated to dryness. The residue was triturated with 50 ml of hot methanol, allowed to cool, filtered and the filtrate evaporated to dryness to yield 3.0 g of crude product. Chromatography on 150 g of silica gel (dry) using 1:1 acetone:cyclohexane as eluant gave 600 mg (R_f=0.6) of 5a. This material was identical to that obtained previously.[6]

2-Benzylamino-6-phenyl-4-pyrimidinone (5b). To 376 mg (2 mmol) of 1 was added 5.0 ml of DMF and 2.2 ml of benzylamine. The reaction mixture was allowed to stir at 50°C for 3 h after which time the solvents were evaporated under vacuum and the resulting white solid triturated with cold 95% ethanol. The solids were filtered, washed well with 95% ethanol followed by ethyl ether and dried to yield 213 mg (38.4%) of crude 5a. Recrystallization from 8 ml of 95% ethanol gave 161 mg (29%) of 5a. Anal. Calcd for $C_{17}H_{15}N_3O$: C, 73.62; H, 5.45; N, 15.15. Found: C, 72.99; H, 5.44;

N, 15.62. ^{1}H-NMR (d_6-DMSO): 8.08-7.86 (m, 2H), 7.5-7.28 (m, 8H), 6.16 (s, 1H), 4.66-4.53 (m, 2H).

2-Hydroxyamino-5-phenyl-4-pyrimidinone (5c). To 207 mg (3 mmol) of hydroxylamine·HCl was added 10.0 ml of methanol and, when dissolution was complete, 0.47 ml (~162 mg~3 mmol) of a 25% CH_3ONa/CH_3OH soln. The soln was allowed to stir at ambient temperature while 188 mg (1 mmol) of 1 was added. After stirring for 18 h, the soln was evaporated to dryness, the residual solid triturated with water and filtered to yield 50 mg of 5c. This material had similar composition to the 1-N-hydroxy isomer previously prepared[5] except the ^{1}H-NMR and MS spectra were not identical. Therefore, the only alternative structure is the expected N-2-isomer. ^{1}H-NMR (d_6-DMSO): 9.16 (s, 1H), 7.83 and 7.35 (m, 5H), 6.05 (s, 1H). GC-MS: 2'-10% SE-30, 120-250°C at 15°/min, R.T.=5.3 min M^+ 347 (10%, bis-TMS), 332 (M^+-15, 70%) from BSTFA/py/70°C/2 min. This material was identical to the product of ethyl benzoylacetate with o-benzylhydroxyguanidine followed by hyrogenative debenzylation.

6-Phenyl-2H-3,4-dihydro-1,3-oxazine-2,4-dione (3). To 230 mg (1.22 mmol) of 1 was added 8 ml of a 10% aq. HCl. The reaction mixture was heated, with stirring, at reflux for 30 min. The reaction mixture was allowed to cool to room temperature and filtered. The solids were washed well with water and dried at 60°C in vacuum oven for 18 h (230 mg 100%). Recrystallization from 95% EtOH gave mp >210°C (decomp.). Anal. Calcd for $C_{10}H_7NO_3$: C, 63.49; H, 3.72; N, 7.40. Found: C, 63.41; H, 3.78; N, 7.32. ^{1}H-NMR (d_6DMSO): 7.95-7.78 (m, 2H), 7.60-7.43 (m, 3H), 6.65 (s, 1H).

1-Methyl-6-phenyluracil (4a). To 189 mg (1 mmol) of 3 was added 10 ml of a 40% aq. methylamine. The reaction mixture was allowed to heat at reflux for 18 h and cooled to room temperature. The soln was filtered, washed well with water, and dried at 60° under vacuum to yield 146 mg (72%) (mp 183-185°C).[14] Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.18; H, 4.98; N, 13.79. ^{1}H-NMR (d_6-DMSO: 7.55 (s), 5.45 (s, 1H), 3.03 (s, 3H).

1-(2-Hydroxyethyl)-6-phenyluracil (4b). To 1.89 g (10 mmol) of 3 was added 10.0 ml of 3-amino-1-propanol and 10.0 ml of H_2O. The reaction was heated at 100°C for 18 h, cooled, and evaporated to dryness under high vacuum. The thick solution was held under high vacuum at 80°C for 3 h; ethanol and 20.0 g of silica gel were added. The slurry was evaporated to a white powder and this powder was placed on top of 75 g of dry silica gel. The column was eluted with 1:1 acetone:cyclohexane (R_f of desired material 0.2 in 1:1 acetone:cyclohexane) to yield, after recrystallization from acetone:hexane 1.05 g (42.6%) (mp 153-154°C). Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.72; N, 11.37. Found: C, 63.24; H, 5.86; N, 11.49. ^{1}H-NMR ($CDCl_3$): 7.45 (m, 5H), 5.85 (s, OH/NH), 5.6 (s, 1H), 3.9-3.2 (m, 4H), 2-1.4 (m, 2H).

1,6-Diphenyluracil (4c). To 189 mg (1 mmol) of 3 was added 5 ml of ethanol and 3.0 ml of aniline. The reaction mixture was heated at reflux at 4 h, cooled, filtered, and the solids washed well with ethanol followed by ethyl ether to yield 170 mg after drying. Recrystallization from H_2O:DMF gave

78 mg (27%) of N-phenyl[-N'-1-(3-phenyl)-1,3-diketone] urea, mp 205-206°C. Anal. Calcd for $C_{16}H_{14}N_2O_3$: C, 68.07; H, 4.99; N, 9.92. Found: C, 67.80; H, 4.96; N, 9.89; MS: Calcd 282.1004, Found 282.1001. ^{1}H-NMR (d_6-DMSO), 8.05-7.0 (m, 10H), 3.36 (s, 2H); ^{13}C-NMR (d_6-DMSO) 197.95, 174.06, 154.56 (C=O).

To 2.20 g (7.80 mM) of this intermediate was added ~25 g of polyphosphoric acid. The slurry was placed in an oil bath at 110-120°C and allowed to stir at 120°C for 3 h. The reaction slurry was removed from the oil bath, cooled to room temperature, 100 ml of ice-H_2O added to the gummy residue, and the resulting solids were broken up with a glass rod. The solids were filtered and washed well with H_2O to yield 1.80 g (88%) after drying. Recrystallization from absolute ethanol, using Darco for decoloration yielded 1.35 g (66%) (mp 269-270°C).[14] Anal. Calcd for $C_{16}H_{12}N_2O_2$: C, 7271; H, 4.58; N, 10.60. Found: C, 72.40; H, 4.79; N, 10.59. MS: Calcd 264.0899, Found: 264.0894. ^{1}H-NMR (d_6-DMSO): 7.26 (s, 10H), 5.66 (s, 1H).

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Received, 8th March, 1985