Heterocyclic Compounds. VIII. Synthesis of 3- and 2,3-Substituted Thienopyrimidones (1)

M. S. Manhas and S. G. Amin

Department of Chemistry and Chemical Engineering,
Stevens Institute of Technology, Hoboken, New Jersey 07030

Received October 11, 1976

The synthesis of a number of substituted thienopyrimidones and quinazolones has been described.

J. Heterocyclic Chem., **14**, 161 (1977).

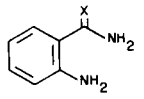
Dimethyl formamide (DMF) has been employed extensively in synthetic organic chemistry as a useful reagent (2). In formylation reactions it is often used in conjunction with thionyl chloride (3) or phosphorus oxychloride (4). In a few reactions, the formylation of aromatic amins has been achieved with DMF under basic condition (5). Zoltewicz (6) cyclized *o*-aminonitriles with DMF under acid-catalyzed conditions and an intermediate formyl derivative was postulated in this reaction. We wish to report a facile synthesis of thienopyrimidones in which DMF plays a key role. This reaction does not appear to have been studied previously.

The aminoamides (**1-4**) and the thioamide (**5**) on refluxing with an excess of DMF provide the corresponding pyrimidones (**6-10**). The yield in the case of furanopyrimidone (**9**) was extremely low (5-7%). It was also noticed that the yields of the pyrimidones were better and the work up of the reaction mixture was simpler when these cyclization reactions with the amino amides were carried out using 1.5 mole equivalent of DMF in ethanolic solution containing trace amounts of hydrochloric acid as a catalyst. The yield of **9** was consistently low under both of these reaction conditions.

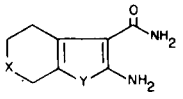
3-Substituted quinazolones have been synthesized through the intermediacy of isatoic anhydride (7), acylanthranil (8) or anthranilic acid (9). The reaction of *o*-aminoesters with substituted amides also results in the formation of this category of compounds (10). We have found that the aminoester (**11**) (11), can be converted in good yield to the formyl derivative (**12**) on refluxing with DMF under acidic conditions. Heating the formyl compound (**12**) with an appropriate amine affords 3-substituted thienopyrimidones (**13**).

In a parallel reaction, *o*-nitrobenzoic acid on treatment with *p*-anisidine and diethoxyphosphoryl chloride in the presence of triethylamine resulted in the nitroamide (**14**) (12). The reduction of **14** under catalytic conditions to the amino derivative (**15**) followed by DMF cyclization gave the quinazolone (**16**) (13).

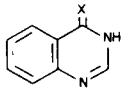
In an earlier communication (14) we had reported the synthesis of 2-methyl-3-aryl-thienopyrimidones of the general structure (**18**). These compounds were prepared by the reaction of an acylanthranil analog (**17**) with arylamines. This synthesis of the thienopyrimidones was not



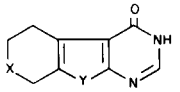
1 X = O
5 X = S



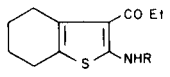
2 X = CH_2, Y = S
3 X = CH_2, Y = O
4 X = NCOPh, Y = S



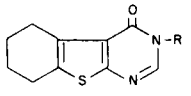
6 X = O
7 X = S



8 X = CH_2, Y = S
9 X = CH_2, Y = O
10 X = NCOPh, Y = S



11 R = H
12 R = CHO
19 R = $COCH_3$



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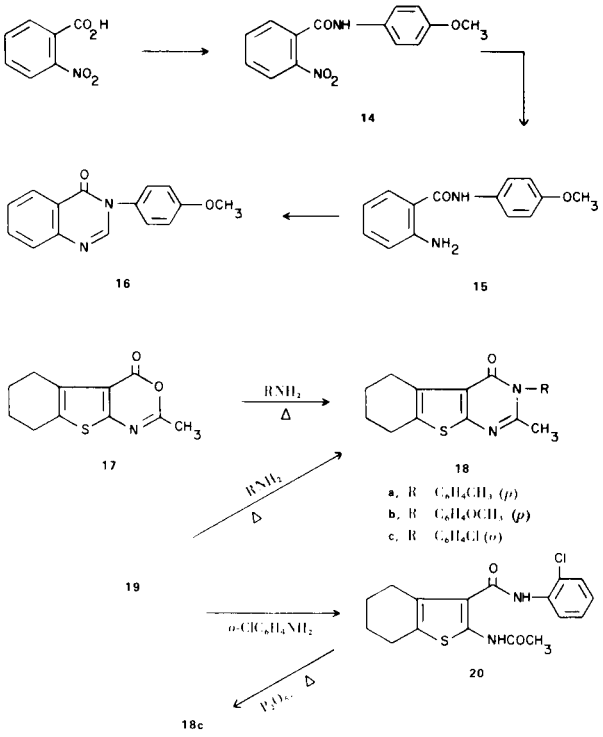
a, R = C_6H_5
b, R = $C_6H_4CH_3$ (*p*)
c, R = $C_6H_4CH_3$ (*o*)
d, R = $C_6H_4OCH_3$ (*m*)
e, R = $C_{10}H_7$ (β)
f, R = $-(CH_2)_2C_6H_5$

a very clean reaction and an extensive charring was observed. We have found that this class of compounds (**18**), which are of a potential biological interest, can be easily prepared from an arylamine and the acetamido compound (**19**) (15). In the case of *o*-chloroaniline, however, the main product was the diamide (**20**) which could be cyclized to the 2-3-disubstituted thienoperimidone (**18c**) in a very poor yield by refluxing it with phosphorus pentoxide in xylene.



Acknowledgment.

The authors wish to thank Miss S. Shah for technical assistance, Stevens Institute of Technology for research facilities and Dr. A. K. Bose for valuable suggestions.

EXPERIMENTAL

Melting points were determined in open capillary tubes using "Mel-Temp" apparatus and are uncorrected. Infrared spectra were obtained with a Perkin Elmer infracord. Nmr spectra were recorded on a Varian A-60A spectrometer operating at 60 MHz using trimethylsilane as an internal standard with chemical shifts expressed in ppm downfield from TMS. Mass spectra were obtained with a Perkin-Elmer RMU-7 mass spectrometer. Elemental analyses were performed by A. Bernhardt, Max-Planck Institute, Mulheim, West Germany and Central Drugs Research Institute, Lucknow, India.

2-Amino-3-carboxamido-4,5-tetramethylenethiophene (**2**) and 2-Amino-3-carbethoxy-4,5-tetramethylenethiophene (**11**).

These two compounds were prepared by the method of Gewald and coworkers (11).

Using the same reaction conditions, the amino amide (**4**) was obtained in 65% yield from *N*-benzoyl-4-piperidone, m.p. 239°.

Anal. Calcd. for $C_{15}H_{15}N_3O_2S$: C, 59.79; H, 5.02; N, 13.95. Found: C, 59.21; H, 5.50; N, 13.75.

2-Amino-3-carboxamido-4,5-tetramethylenefuran (**3**).

This compound was prepared by the method described in the literature (19).

2-Acetamido-3-carbethoxy-4,5-tetramethylenethiophene (**19**).

Acetyl chloride (0.89 g., 0.01 mole) in dry methylene chloride (30 ml.) was added dropwise to a stirred solution of the amino-ester (**12**) (2.2 g., 0.01 mole), triethylamine (1.0 g., 0.01 mole) in methylene chloride under a nitrogen atmosphere. After stirring overnight at room temperature the reaction product was washed with water and dried (magnesium sulfate). Removal of the solvent under reduced pressure gave 2.4 g. (89%), m.p. 165° (15).

General Procedure for the Cyclization of *o*-Aminoamide with DMF.

A mixture of the anthranilamide (**1**) (1.36 g., 0.01 mole) and DMF (2.2 g., 0.03 mole) in 30 ml. of ethanol containing a few drops of concentrated hydrochloric acid was refluxed for 4 hours. On cooling the quinazoline (**6**), which separated out as a white solid, was filtered to give 1 g. (70%) of pure material, m.p. 215-216° (16).

The quinazolones **7** (17), **8** (18), **9** (18), **10** (18) and **16** (13) were similarly prepared from **5**, **2**, **3**, **4**, and **15**, respectively.

Formylation of 2-Amino-3-carbethoxy-4,5-tetramethylenethiophene.

2-Amino-3-carbethoxy-4,5-tetramethylenethiophene (**11**) (5.5 g., 0.02 mole) was dissolved in 50 ml. of ethanol containing 2.2 g. of DMF and a few drops of hydrochloric acid. The solution was refluxed for 5 hours. Excess of ethanol was removed under reduced pressure. The crude product (**12**) was recrystallized from methylene chloride-hexane, m.p. 130° (65%); ir (nujol): 1680, 1660 cm^{-1}; nmr (deuteriochloroform): δ 1.3 (t, 3H, J = 7 Hz), 1.6-1.85 (b, 4H), 2.4-2.8 (b, 4H), 4.2 (q, 2H, J = 7 Hz), 6.0 (b, 1H), 9.8 (b, 1H). The crude formyl compound (**12**) was found to be of reasonable purity and was used as such for further reactions.

o-Nitro-*N*-(*p*-methoxyphenyl)benzamide (**14**).

A solution containing 10.0 mmoles of the *o*-nitrobenzoic acid, 10.0 mmoles of diethylphosphorochloridate in 100 ml. of dichloromethane was stirred at room temperature under nitrogen atmosphere for 20 minutes. To this solution was added dropwise a solution of *p*-anisidine (1.2 g., 10 mmoles) and triethylamine (2.0 g., 20 mmoles) in 100 ml. of dichloromethane over a period of 1 hour. The stirring was continued overnight. The reaction mixture was then washed with water and dried (magnesium sulfate). Removal of the solvent followed by recrystallization from dichloromethane-hexane gave the pure amide, m.p. 130° (80%); ir: 1680, 3300 cm^{-1}.

Anal. Calcd. for $C_{14}H_{12}N_2O_4$: C, 61.76; H, 4.44; N, 10.29. Found: C, 61.30; H, 4.36; N, 10.26.

General Procedure for the Reaction Between the *N*-Formyl-*o*-amino Ester (**12**) and an Amine.

An equimolar mixture of the *N*-formyl-*o*-aminoester (**12**) and aniline was heated in an oil bath at 175-180° for 5 hours. On cooling a jelly-like mass was formed. It was dissolved in methylene chloride and chromatographed over Florisil using dichloromethane

Table I

Spectral and Analytical Data

Compound	R	R′	M.p.	Yield	Formula	Analysis C	Analysis H	Analysis N	Spectral Data
13a	H	C_6H_5	150	60	$C_{16}H_{14}N_2OS$	67.99 (68.08)	5.08 (5.00)	9.80 (9.92)	ir: 1680 cm^{-1}; nmr (deuteriochloroform): δ 1.8-2.0 (b, 4H), 2.7-3.0 (b, 4H), 7.45 (S, 5H), 7.95 (S, 1H).
13b	H	$C_6H_4CH_3$ (*p*)	156-157	65	$C_{17}H_{16}N_2OS$	68.91 (69.01)	5.44 (5.32)	9.45 (9.40)	ir: 1680 cm^{-1}; nmr (deuteriochloroform): δ 1.7-1.9 (b, 4H), 2.6-3.1 (b, 4H), 2.38 (S, 3H), 7.25 (S, 4H), 7.9 (S, 1H).
13c	H	$C_6H_4CH_3$ (*o*)	133-134	30	$C_{17}H_{16}N_2OS$	68.96 (68.55)	5.44 (5.33)	9.45 (9.37)	ir: 1665 cm^{-1}; nmr (deuteriochloroform): δ 1.7-1.9 (b, 4H), 2.2 (S, 3H), 2.8-3.1 (b, 4H), 7.3-7.5 (m, 4H), 7.9 (S, 1H).
13d	H	$C_6H_4OCH_3$ (*m*)	180	55	$C_{17}H_{16}N_2O_2S$	65.38 (64.88)	5.16 (5.15)	8.97 (8.83)	ir: 1675 cm^{-1}; nmr (deuteriochloroform): δ 1.7-1.95 (b, 4H), 2.8-3.1 (b, 4H), 3.82 (S, 3H), 6.9-7.5 (m, 3H), 8.0 (S, 1H).
13e	H	$C_{10}H_7$ (β)	208	70	$C_{20}H_{16}N_2OS$	72.28 (72.54)	4.85 (4.80)	8.43 (8.43)	ir: 1675 cm^{-1}; nmr (deuteriochloroform): δ 1.8-2.0 (b, 4H), 2.7-3.1 (b, 4H), 2.7-3.1 (b, 4H), 7.5-7.9 (b, 7H), 8.1 (S, H).
13f	H	$(CH_2)_2C_6H_5$	120	65	$C_{18}H_{18}N_2OS$	69.66 (69.27)	5.85 (5.76)	9.03 (9.03)	ir: 1680 cm^{-1}; nmr (deuteriochloroform): δ 1.8-2 (b, 4H), 2.5-2.7 (b, 4H), 3.0 (t, 2H, J = 7 Hz), 4.1 (t, 2H, J = 7 Hz), 7.2 (S, 5H), 7.5 (S, 1H).
18a(14)	CH_3	$C_6H_4CH_3$ (*p*)	202	65	$C_{18}H_{18}N_2OS$				
18b(14)	CH_3	$C_6H_4OCH_3$ (*p*)	195	60	$C_{19}H_{18}N_2O_2S$				
18c	CH_3	C_6H_4Cl (*o*)	148-150	10	$C_{17}H_{15}ClN_2OS$	61.70 (61.72)	4.58 (4.53)	8.62 (8.47)	ir: 1675 cm^{-1}; nmr (deuteriochloroform): δ 1.7-1.9 (b, 4H), 1.9 (S, 3H), 2.7-2.9 (b, 4H), 6.5-7.2 (m, 4H).

as eluent. Recrystallization from dichloromethane-hexane gave **13a**, m.p. 150° (60%). The 3-substituted thienopyrimidones (**13b-13f**) and (**18a-18c**) were similarly prepared from the corresponding *o*-amino ester derivative and amines.

The main product isolated during the reaction between *o*-chloroaniline and **19** was the diamide **20** in 73% yield, m.p. 165-167°; ir (nujol): 1680, 1700 and 3100 cm^{-1}; nmr (deuteriochloroform): δ 1.7-2.0 (b, 4H), 2.25 (s, 3H), 2.7-3.0 (b, 4H), 7.1-7.5 (b, 4H), 8.2-8.5 (b, 2H).

Anal. Calcd. for $C_{17}H_{17}ClN_2O_2S$: C, 58.53; H, 4.87; N, 8.03. Found: C, 58.52; H, 4.97; N, 7.72.

A suspension of **20** (0.6 g.) and phosphorus pentoxide (0.3 g.) in xylene (20 ml.) were refluxed for 3 hours. Excess xylene was removed under reduced pressure. The residue was dissolved in methylene chloride, washed with water and dried (magnesium sulfate). Removal of the solvent provided a dark material which on chromatography over Florisil gave 50 mg. of **18c**.

Analytical and spectral data on these compounds are given in Table I.

o-Amino-*N*-(*p*-methoxyphenyl)benzamide (**15**).

Platinum oxide (0.1 g.) was added to a solution of the nitroamide (**14**) (1 g.) in ethyl acetate and the mixture hydrogenated at 40 psi overnight. The reactants were filtered. Evaporation of the solvent gave **15**, m.p. 119°; ir (nujol): 1640, 3250, 3330, 3400 cm^{-1}; nmr (deuteriochloroform): δ 3.75 (s, 3H), 5.3-5.5 (b, 2H), 6.7-7.5 (m, 8H), 7.8-7.95 (b, 1H). This compound was used as such for further reactions without additional purification.

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(20) Compounds **8** and **9** were also prepared by an alternative method by Mr. M. Sugiura in our laboratories.