Pyrimidones. 2. Synthesis and Reactions of 2-Chloropyrimidines

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The treatment of 1-alkyl-5-aryl and 1-alkyl-4,5-diaryl-2-(1*H*)pyrimidones with phosphorus oxychloride and phosphorus pentachloride resulted in chlorination and dealkylation to furnish 2-chloro-5-aryl (or 4,5-diaryl)-pyrimidines. These chlorpyrimidines were reacted with a variety of nitrogen, oxygen, sulfur, and carbon nucleophiles to produce the corresponding 2-substituted pyrimidines. In the case of phenyllithium, attack occurred at the 4-position of the pyrimidine ring yielding **11**. Triazolopyrimidine **9** was synthesized *via* the treatment of **2d** with hydrazine followed by reaction with triethyl orthoformate.

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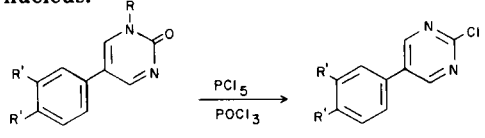
In a continuing search for compounds exhibiting pharmacological activity, our interest was channeled into the area involving the synthesis and biological evaluation of various functionalized pyrimidines. In an earlier report (1) we described the preparation of some 1-substituted-5-aryl and 4,5-diaryl-2-(1*H*)pyrimidones. We now would like to report on chemical conversions of these compounds.

Our prime objective was to functionalize the 2-position of the pyrimidine nucleus. The introduction of an easily displaceable moiety (*e.g.* halogen) into the 2-position would fit this requirement.

The treatment of 1-substituted-5-aryl-2-(1*H*)pyrimidones (**1**) with phosphorus oxychloride at elevated temperatures resulted in the dealkylation of the substituent on the nitrogen at the 1-position and the introduction of a chlorine atom into the 2-positon of the pyrimidine which furnished 2-chloro-5-arylpyrimidines (**2**) in low yields. It was found that incorporation of phosphorus pentachloride in the reaction mixture significantly increased the yield of **2**.

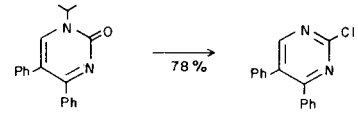
The reaction was performed with a variety of *N*-alkyl substituents and it appears that the yield of **2** decreases as the size of the alkyl group increases (see table).

Transformations of this type are not without precedent. The reaction of 2-methyl-1-isoquinolone, using phosphorus oxychloride and phosphorus pentachloride, has been reported to yield 1-chloroisoquinoline (2,3). An analogous reaction with 6-methyl-1,6-naphthyridin-5-(6*H*)-one furnished a mixture of mono and dichloronaphthyridines (4). However, to the best of our knowledge, this is the first example of this reaction being applied to the pyrimidine nucleus.



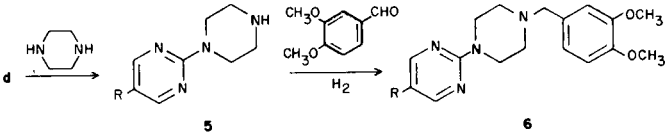
	1 R	R'	2 Yield, %
a)	CH_3	H	57
b)	C_2H_5	H	45
c)	$CH(CH_3)_2$	H	25
d)	CH_3	OCH_3	75

The reaction has also been applied successfully to a pyrimidone bearing aryl substituents at the 4- and 5-position (*e.g.* **3**). The corresponding 2-chloro-4,5-diarylpyrimidine (**4**) was isolated in high yield even though the 1-position contains an isopropyl group.

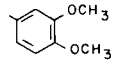


3 4

Reactions of the 2-chloropyrimidines with different nucleophiles enabled the isolation of a variety of 2-substituted pyrimidines. Treatment of **2d** with amines resulted in the formation of the corresponding 2-aminopyrimidine (see Scheme 1). More complex systems (*e.g.* **6**) were produced by the interaction of **2a** or **2d** with piperazine followed by reductive alkylation with 3,4-dimethoxylbenzaldehyde.



5 6

a) R = C_6H_5 b) R = 

Generation of the *s*-triazolo[4,3-*a*]pyrimidine ring system can be accomplished in two steps (Scheme 1). The treatment of **2d** with hydrazine results in the formation of hydrazino adduct **8** in 93% yield. Its subsequent reaction with triethyl orthoformate furnished the desired product (**9**) in moderate yield.

When **2a** or **2d** was allowed to react with ethyl glycolate or ethyl thioglycolate in the presence of sodium hydride, the corresponding esters **12** were isolated. Alkaline hydrolysis furnished acids **13** in good yield (Table 1).

The reaction of carbon nucleophiles with the 2-chloropyrimidines gave mixed results. For example, the reaction of **2a** with diethyl methylmalonate in the presence of sodium hydride afforded **14** in 70% yield. However, when

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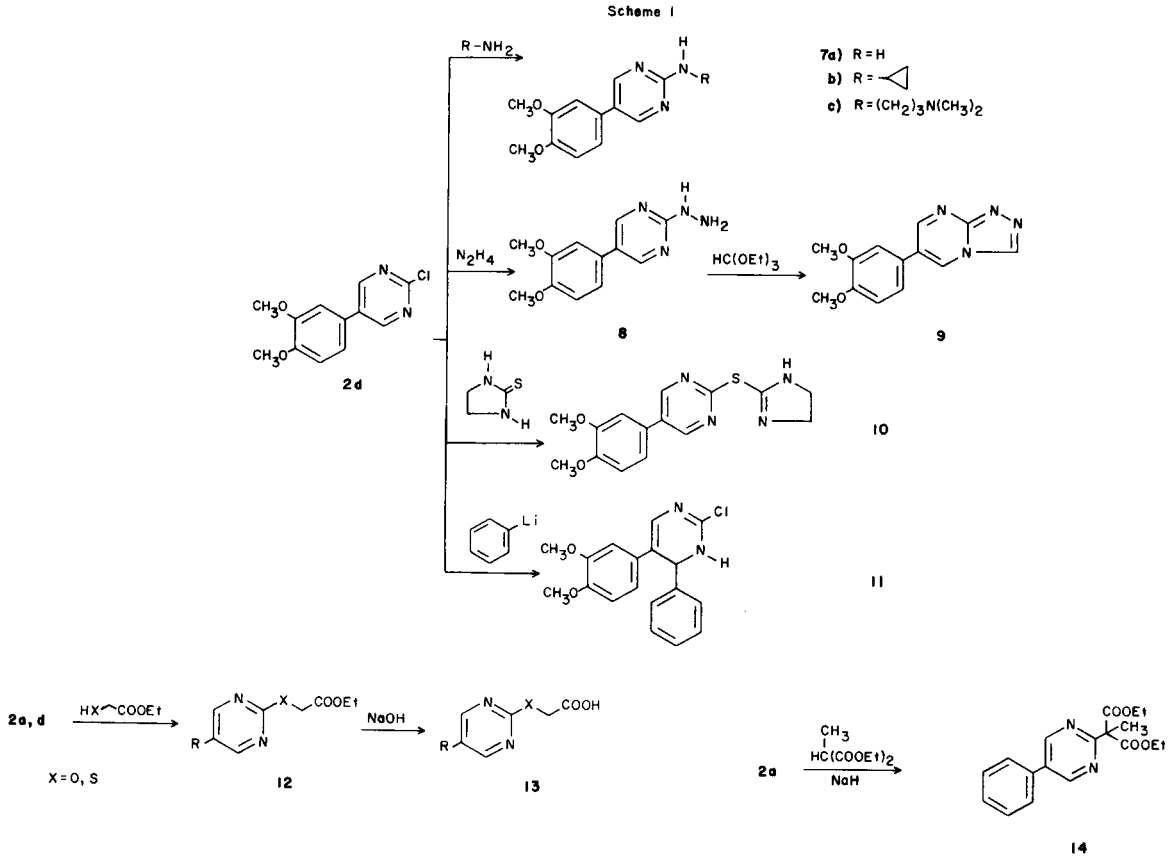
Scheme I

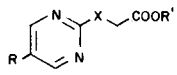


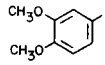
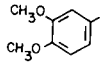
2d was allowed to react with phenyllithium at 0°, the expected 2-phenylpyrimidine was not formed. Instead, reaction occurred at the 4-position of the pyrimidine ring and **11** was isolated in 82% yield (Scheme 1).

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover unimelt apparatus and are uncorrected. The infrared spectra were recorded on a Perkin-Elmer Model 257 and 457 spectrophotometers. Absorption frequencies are quoted in reciprocal centimeters. Nuclear magnetic

Table 1



Compound No.	R	X	R'	M.p., °C	Yield, %	Molecular Formula	Analysis Calcd. (Found) C	H	N
12a	C_6H_5	O	C_2H_5	71-73	90	$C_{14}H_{14}N_2O_3$	65.1	5.5	10.9
							(65.4	5.6	11.2)
12b	C_6H_5	S	C_2H_5	54-57	66	$C_{14}H_{14}N_2O_2S$	57.7	5.9	15.0
							(57.6	5.6	15.1)
12c		O	C_2H_5	95-97	75	$C_{16}H_{18}N_2O_5$	60.4	5.7	8.8
							(60.6	5.7	8.6)
13a	C_6H_5	O	H	192-194	92	$C_{12}H_{10}N_2O_3$	62.6	4.4	12.2
							(62.4	4.5	12.0)
13b	C_6H_5	S	H	177-180	93	$C_{12}H_{10}N_2O_2S$	58.5	4.1	11.4
							(58.1	4.2	11.2)
13c		O	H	205-207	82	$C_{14}H_{14}N_2O_5$	57.9	4.9	9.7
							(57.6	5.3	9.8)

resonance spectra were determined on Varian A-60 and T-60 spectrometers using tetramethylsilane as an internal reference. Chemical shifts are quoted in parts per million (s = singlet, d = doublet, t = triplet, q = quarter, m = multiplet).

Unless otherwise stated, all solutions of organic compounds were washed with brine and dried over sodium sulfate. No attempt has been made to optimize the yields of the described reactions.

2-Chloro-5-phenylpyrimidine (**2a**).

A mixture of 17.2 g. of **1a** (1), 4.2 g. of phosphorus pentachloride and 40.0 ml. of phosphorus oxychloride was heated at 120° for 3 hours. Excess phosphorus oxychloride was removed under reduced pressure and to the cooled residue was added cold water. The resulting precipitate was extracted into methylene chloride and dried over sodium sulfate. Removal of the solvent under reduced pressure furnished 10.0 g. (57%) of **2a**, m.p. 124-128°; ir (chloroform): 1580, 1400 cm^{-1}; nmr (deuteriochloroform): δ 8.9 (s, 2), 7.6 (s, 5).

Anal. Calcd. for $C_{10}H_7ClN_2$: C, 63.0; H, 3.7; Cl, 18.6. Found: C, 62.6; H, 4.0; Cl, 18.6.

2-Chloro-5-(3,4-dimethoxyphenyl)pyrimidine (**2d**).

A mixture of 5.0 g. of **1d**, 3.5 g. of phosphorus pentachloride and 55 ml. of phosphorus oxychloride was heated at 120° for 20 hours. Excess phosphorus oxychloride was removed under reduced pressure and to the residue was added cold water. The mixture was extracted into methylene chloride and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was crystallized from ethanol to give 3.8 g. (75%) of **2d**, m.p. 128-131°; nmr (deuteriochloroform): δ 8.8 (s, 2), 7.05 (m, 3), 3.95 (s, 6).

Anal. Calcd. for $C_{12}H_{11}ClN_2O_2$: C, 57.5; H, 4.4; Cl, 14.1; N, 11.2. Found: C, 57.1; H, 4.6; Cl, 14.2; N, 11.2.

2-Chloro-4,5-diphenylpyrimidine (**4**).

A mixture of 5.1 g. of **3**, 5.0 g. of phosphorus pentachloride and 70 ml. of phosphorus oxychloride was refluxed for 48 hours. Excess phosphorus oxychloride was removed under reduced pressure and to the residue was added cold water. The mixture was extracted into methylene chloride and dried over sodium sulfate. The solvent was removed under reduced pressure and the crude product was crystallized from ethyl acetate/pentane to give 3.6 g. (78%) of **4**, m.p. 135-139°; ir (chloroform): 1550, 1400 cm^{-1}; nmr (deuteriochloroform): δ 8.65 (s, 1), 7.6-7.0 (m, 10).

Anal. Calcd. for $C_{16}H_{11}ClN_4$: C, 72.0; H, 4.2; Cl, 13.3; N, 10.5. Found: C, 71.7; H, 4.4; Cl, 13.5; N, 10.8.

5-Phenyl-2-(1-piperazinyl)pyrimidine (**5a**).

To a warm solution of 8.0 g. of piperazine in 150 ml. ethanol was added 8.0 g. of **2a** and the resulting mixture was heated at 60° for 2 hours. The solvent was removed under reduced pressure and 2*N* sodium hydroxide was added to the residue. The mixture was extracted into methylene chloride and dried over sodium sulfate. Evaporation of the solvent furnished 8.1 g. (81%) of **5a**, m.p. 101-104°; ir (chloroform): 1605 cm^{-1}; nmr (deuteriochloroform): δ 8.6 (s, 2), 7.4 (m, 5), 3.85 (m, 4), 2.95 (m, 4), 1.85 (s, 1).

Anal. Calcd. for $C_{14}H_{16}N_4$: C, 70.0; H, 6.7. Found: C, 69.8; H, 7.1.

5-(3,4-Dimethoxyphenyl)-2-(1-piperazinyl)pyrimidine (**5b**).

The reaction was performed similar to the one described for the preparation of **5a**, and the product, **5b**, was isolated in 89% yield, m.p. 142-145°; nmr (deuteriochloroform): δ 8.6 (s, 2), 7.0 (s, 3), 3.9 (s, 6), 3.85 (m, 4), 3.0 (m, 4), 1.9 (s, 1).

Anal. Calcd. for $C_{16}H_{20}N_4O_2$: C, 64.0; H, 6.7; N, 18.7. Found: C, 64.1; H, 6.5; N, 18.3.

2-[4-(3,4-Dimethoxyphenyl)methyl]piperazinyl-5-phenylpyrimidine (**6a**).

A mixture of 1.0 g. of **5a**, 0.8 g. of 3,4-dimethoxylbenzaldehyde and 0.2 g. of 10% palladium on carbon in 25 ml. of methanol was hydrogenated at 3.5 atmospheres for 17 hours. Methylene chloride was added to the mixture to dissolve any solids, the catalyst was filtered, and the filtrate was evaporated to give 0.4 g. (25%) of **6a**, m.p. 116-120°; ir (chloroform) 1600, 1450, 1255 cm^{-1}; nmr (deuteriochloroform): δ 8.5 (s, 2), 7.4 (m, 5), 7.0-6.75 (m, 3), 3.85 (m, 10), 3.47 (s, 2), 2.5 (m, 4).

Anal. Calcd. for $C_{23}H_{26}N_4O_2$: C, 70.7; H, 6.7; N, 14.3. Found: C, 71.0; H, 6.9; N, 14.3.

5-(3,4-Dimethoxyphenyl)-2-[4-(3,4-dimethoxyphenyl)methyl]piperazinylpyrimidine (**6b**).

The reaction was performed similar to the one described for the preparation of **6a**, but with a reaction time of 4 days, and the product, **6b**, was isolated in 73% yield, m.p. 148-150°; ir (chloroform): 1600, 1495 cm^{-1}; nmr (deuteriochloroform): δ 8.6 (s, 2), 7.0 (m, 6), 3.9 (m, 16), 3.5 (s, 2), 2.5 (m, 4).

Anal. Calcd. for $C_{25}H_{30}N_4O_4$: C, 66.6; H, 6.7; N, 12.4. Found: C, 66.9; H, 7.0; N, 12.4.

2-Amino-5-(3,4-dimethoxyphenyl)pyrimidine (**7a**).

A mixture of 10.0 g. of **2d** and 25 ml. of ammonia was heated in a steel cylinder at 90° for 24 hours. Evaporation of the ammonia at room temperature furnished 9.8 g. (100%) of **7a**. An analytical sample was crystallized from dimethylacetamide, m.p. 229-232°; ir (Nujol): 3305, 3160 cm^{-1}; nmr (DMSO-d_6): δ 8.55 (s, 2), 7.15 (m, 3), 6.65 (s, 2), 3.85 (d, 6).

Anal. Calcd. for $C_{12}H_{13}N_3O_2$: C, 62.3; H, 5.7; N, 18.2. Found: C, 62.3; H, 5.7; N, 18.4.

2-Cyclopropylamino-5-(3,4-dimethoxyphenyl)pyrimidine (**7b**).

A mixture of 5.0 g. of **2d**, 10.0 g. of cyclopropylamine and 10 drops of methanol was heated in a steel cylinder at 120° for 20 hours. Any excess cyclopropylamine was removed under reduced pressure and the residue was crystallized from ethanol to give 4.1 g. (81%) of **7b**, m.p. 139-142°; nmr (deuteriochloroform): δ 8.6 (s, 2), 7.0 (s, 3), 6.15 (m, 1), 3.9 (d, 6), 2.85 (m, 1), 1.0-0.5 (m, 4).

Anal. Calcd. for $C_{15}H_{17}N_3O_2$: C, 66.4; H, 6.3; N, 15.5. Found: C, 66.5; H, 6.4; N, 15.5.

2-(3-Dimethylaminopropyl)amino-5-(3,4-dimethoxyphenyl)pyrimidine (**7c**).

To a suspension of 0.5 g. of **2d** in 10 ml. of ethanol at 70° was added 0.8 g. of 3-dimethylaminopropylamine. The resulting mixture was stirred at 70° for 24 hours. The solvent was removed under reduced pressure and to the residue was added 1*N* sodium hydroxide. The mixture was extracted with methylene chloride and was dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was crystallized from ether/pentane to give 0.35 g. (55%) of **7c**, m.p. 77-79°; ir (chloroform): 3450, 1600 cm^{-1}; nmr (deuteriochloroform): δ 8.6 (s, 2), 6.95 (s, 3), 6.15 (m, 1), 3.95 (d, 6), 3.5 (m, 2), 2.35 (m, 2), 2.25 (s, 6), 1.85 (m, 2).

5-(3,4-Dimethoxyphenyl)-2-hydrazinopyrimidine (**8**).

A mixture of 16.0 g. of **2d** and 16.0 ml. of hydrazine in 1 liter of ethanol was refluxed for 90 minutes. The reaction mixture was concentrated to one third volume and allowed to cool. The resuting precipitate was filtered and recrystallized from ethanol to give 15.0 g. (93%) of **8**, m.p 160-163°; nmr (DMSO-d_6): δ 8.7 (s, 2), 8.3 (s, 1), 7.2 (m, 3), 4.3 (s, 2), 3.85 (d, 6).

Anal. Calcd. for $C_{12}H_{14}N_4O_2$: C, 58.5; H, 5.7; N, 22.8. Found: C, 58.5; H, 5.8; N, 22.9.

6-(3,4-Dimethoxyphenyl)-s-triazolo[4,3-*a*]pyrimidine (**9**).

A suspension of 8.0 g. of **8** and 0.8 g. of *p*-toluenesulfonic acid in 80 ml. of triethyl orthoformate was refluxed for 20 hours. The resulting yellow precipitate was filtered and recrystallized from methylene chloride to give 3.0 g. (36%) of **9**, m.p. 264-266°; nmr (DMSO-d_6): δ 9.2 (m, 3), 7.4-6.9 (m, 3), 3.85 (d, 6).

Anal. Calcd. for $C_{13}H_{12}N_4O_2$: C, 60.9; H, 4.7; N, 21.9. Found: C, 60.7; H, 4.8; N, 22.0.

2-(4,5-Dihydro-1*H*-imidazo-2-ylthio)-5-(3,4-dimethoxyphenyl)pyrimidine (**10**).

A mixture of 11.0 g. of **2d** and 4.5 g. of 2-imidazolidinethione in 100

ml. of ethanol was refluxed for 3 days. The resulting precipitate (the hydrochloride of the product) was filtered, washed with ethanol, then ether and it was then dissolved in 2 l. of water. The solution was made alkaline by the addition of 50% sodium hydroxide. The resulting precipitate was filtered, washed with water, and dissolved in methylene chloride. After drying over sodium sulfate, the solvent was removed under reduced pressure and the product was recrystallized from methylene chloride/ether to give 9.7 g. (69%) of **10**, m.p. 138-140°; ir (chloroform): δ 3330, 1570, 1395 cm^{-1}; nmr (deuteriochloroform): δ 8.7 (s, 2), 6.9 (m, 4), 3.95 (s, 6), 3.75 (s, 4).

Anal. Calcd. for $C_{15}H_{16}N_4O_2S$: C, 56.9; H, 5.1; N, 17.7; S, 10.1. Found: C, 57.5; H, 5.1; N, 18.1; S, 10.2.

Reanalysis of carbon did not improve the value.

2-Chloro-5-(3,4-dimethoxyphenyl)-1,6-dihydro-6-phenylpyrimidine (**11**).

To a solution of 5.0 g. of **2d** in 100 ml. of tetrahydrofuran (cooled to 0°) was added dropwise 10 ml. of phenyllithium (2.1*M* in ether). After addition, the reaction mixture was stirred at 0° for 15 minutes, and then was poured on cold water. The organic phase was separated, washed with saturated sodium chloride, and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue crystallized from methylene chloride/ether to give 5.3 g. (82%) of **11**, m.p. 137-140°; ir (chloroform) 3425, 1670, 1620, 1455, 1020 cm^{-1}; nmr (deuteriochloroform): δ 7.5-7.2 (m, 5), 6.7 (s, 3), 6.65 (m, 1), 5.55 (s, 1), 3.77 (s, 3), 3.7 (s, 3).

Anal. Calcd. for $C_{18}H_{17}ClN_2O_2$: C, 65.7; H, 5.2; Cl, 10.8; N, 8.5. Found: C, 65.5; H, 5.2; Cl, 11.1; N, 8.2.

(5-Phenyl-2-pyrimidinyloxy)acetic Acid Ethyl Ester (**12a**).

To a solution of 8.2 g. of ethyl glycolate in 150 ml. of benzene was added 4.0 g. of sodium hydride (57% in mineral oil, pentane washed) in portions. The mixture was stirred at room temperature for 30 minutes; then 11.6 g. of **2a** was added. The reaction was then stirred at 60° for 3 days. The mixture was poured into water and the organic phase was separated, washed with saturated sodium chloride, and dried over sodium sulfate. Removal of the solvent under reduced pressure gave 14.2 g. (90%) of **12a**. An analytical sample was crystallized from ether/pentane, m.p. 71-73°; ir (chloroform): 1760, 1591, 1450 cm^{-1}; nmr (deuteriochloroform): δ 8.75 (s, 2), 7.6 (s, 5), 5.1 (s, 2), 4.35 (q, 2), 1.3 (t, 3).

Anal. Calcd. for $C_{14}H_{14}N_2O_3$: C, 65.1; H, 5.5; N, 10.9. Found: C, 65.4; H, 5.6; N, 11.2.

Compounds **12b** (using ethylmercaptoacetate) and **12c** (using **2d**) were prepared similarly and the results are listed in Table 1.

(5-Phenyl-2-pyrimidinyloxy)acetic Acid (**13a**).

To a solution of 0.55 g. of **12a** in 15 ml. of ethanol was added 2.25 ml. of 1.0*N* sodium hydroxide and the mixture was stirred at room temperature for 1 hour. Water was added to dissolve the precipitate which formed and the ethanol was removed under reduced pressure. The resulting solution was acidified (under ice cooling) with 2*N* hydrochloric acid and the precipitate which formed was filtered, washed with water, and dried to give 0.45 g. (92%) of **12a**, m.p. 192-194°; ir (potassium bromide): 3425, 1730 cm^{-1}; nmr (DMSO-d_6): δ 13.65-10.0 (s, broad, 1), 9.0 (s, 2), 7.65 (m, 5), 5.0 (s, 2).

Anal. Calcd. for $C_{12}H_{10}N_2O_3$: C, 62.6; H, 4.4; N, 12.2. Found: C, 62.4; H, 4.5; N, 12.0.

Compouds **13b** and **13c** were prepared similarly and the results are listed in Table 1.

Methyl-(5-phenyl-2-pyrimidinyl)propanedioic Acid Diethyl Ester (**14**).

A mixture of 0.42 g. of sodium hydride (57% in mineral oil, pentane washed) in 20 ml. of DMSO was stirred at 70° for 30 minutes. After cooling to room temperature, 1.75 g. of diethyl methylmalonate was added dropwise. The mixture was stirred at room temperature for 1 hour and then 1.9 g. of **2a** was added. The reaction was stirred at 80° for 18 hours and then was poured into water. The mixture was extracted into methylene chloride, washed with water, then with saturated sodium chloride, and was dried over sodium sulfate. Evaporation of the solvent under reduced pressure furnished an oil which was chromatographed on a column of silica gel using chloroform to elute the product, 2.1 g. (70%) of **14**; ir (chloroform): 1730 cm^{-1}; nmr (deuteriochloroform): δ 8.95 (s, 2), 7.5 (m, 5), 4.35 (q, 4), 2.05 (s, 3), 1.3 (t, 6).

Anal. Calcd. for $C_{18}H_{20}N_2O_4$: C, 65.8; H, 6.1; N, 8.9. Found: C, 65.7; H, 6.1; N, 9.1.

Reanalysis of nitrogen did not improve the value.

Acknowledgement.

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