SYNTHESIS OF 2-ALKYLPYRIMIDINES VIA 2-ALKYL-1,4,5,6-TETRAHYDROPYRIMIDINES

Richard Garth Pews

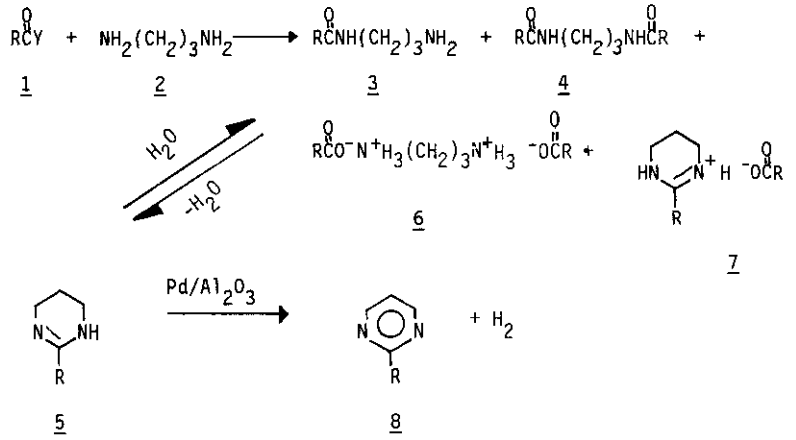
Organic Specialties Laboratory, Central Research, The Dow Chemical Company, 1776 Building, Midland, Michigan USA 48674

Abstract- The condensation of 1,3-diaminopropane with alkanoic acids gives 2-alkyl-1,4,5,6-tetrahydropyrimidines. Dehydrogenation of the tetrahydropyrimidine derivatives over a palladium catalyst produces the 2-alkylpyrimidines in high yields.

The direct synthesis of 4,6-unsubstituted 2-alkylpyrimidines from the condensation of malonaldehyde (or its acetal) with alkylamidines is well documented[1]. The intermediates, however, are not always readily available and inexpensive, and other methodology such as the reduction of halogenated 2-alkylpyrimidines is employed. We describe herein a high yield synthesis of 2-alkyl-1,4,5,6-tetrahydropyrimidines from readily available starting materials, and dehydrogenation of the tetrahydro derivatives to the desired aromatic pyrimidines.

The 1,4,5,6-tetrahydropyrimidine system is the most intensively investigated and the one most readily obtained via the condensation of 1,3-diaminopropanes with carboxylic acid or derivatives[2]. Although a popular monograph on pyrimidine chemistry notes that "it is preferable to use an acid derivative, usually an ester"[3], we have found, on the contrary, that the acid is the preferred derivative. The chemistry of 1,3-diaminopropane with 2,2-dimethylpropionic acid is illustrated in Scheme 1 (R=t-butyl).

Scheme 1



When methyl trimethylacetate, 1 (Y=OH), is heated with excess 1,3-diaminopropane 2 under reflux and then under azeotropic conditions, a mixture of products 3-7 are formed. Under these conditions, water formed from the cyclization of aminoamide, 3, hydrolyzes the ester 1 ($Y=OCH_3$), to the carboxylic acid 1 (Y=OH). 2,2-Dimethylpropionic acid is then available to form the salts with the diamine 2, and amidine 5. Interestingly, n-butyl trimethylacetate was unreactive with 1,3-diaminopropane in refluxing o-xylene. Preliminary experiments with 2,2-dimethylpropionic acid and 2 indicated that at longer reaction times, the desired amidine 5 and the amidinium salt 7 were formed. These results demonstrate that in order to convert all the carboxylic acid 1 (Y=OH), to aminoamide 3, it is necessary to maintain water in the reaction mixture so that the equilibrium favors aminoamide 3 and not the amidine 5. The removal of water favors amidine formation and hence the amidinium salt 7. Under azeotropic conditions, the carboxylic acid cannot be completely converted to aminoamide 3. When 1 (Y=OH) and 2 are allowed to react in a Parr bomb at 200-225°C for 7 h, the aminoamide 3 is formed in near quantitative yield, the minor by-product is 4% of the diamide 4. Removal of the excess diamine by distillation and ring closure of 3 to 5 under azeotropic conditions with boiling diethylbenzene gave essentially a quantitative yield of 2-t-butyl-1,4,5,6-tetrahydropyrimidine (5, R-t-butyl).

Few investigations have been described in the literature on the oxidations of tetrahydropyrimidines. The attempted dehydrogenation of the 1,4,5,6-tetrahydropyrimidine with sulfur led to insertion of sulfur in the molecule and formation of 1,4,5,6-tetrahydrobipyrimidine[4]. The synthesis of 2-methylpyrimidine via the passage of a stream of acetic acid, ester or amide and 1,3-diaminopropane over a platinum on alumina catalyst has been reported[5]. Our efforts to reproduce the data using methyl isobutyrate and 1,3-diaminopropane were unsuccessful. However, if the intermediate

aminoamide 3 (R=t-butyl) was passed over either a platinum or palladium on alumina catalyst at 320-350°C, a low yield, 20-40% of the desired 2-t-butylpyrimidine 8 was obtained. The preferred substrate for the dehydrogenation is the 2-alkyl-1,4,5,6-tetrahydropyrimidine. With a 0.5% palladium on neutral α-alumina catalyst and temperatures of 300-320°C, the desired 2-t-butylpyrimidine was obtained in 80% yield. The 2-methyl, ethyl, isopropyl, benzyl and phenyl derivatives were prepared in a similar manner and purified by distillation.

EXPERIMENTAL

Preparation of 2-Alkyl-1,4,5,6-tetrahydropyrimidines.

2,2-Dimethylpropionic acid (136g, 1.33 mol) was added with stirring to 1,3-diaminopropane (880 ml, 7.5 mol) and the mixture placed in a 2-litre Parr bomb and heated overnight at 225°C. After cooling and removal of the excess 1,3-diaminopropane with a rotary evaporator, the residue was diluted with o-xylene (250 ml) and refluxed for 48 hrs with a Dean and Stark apparatus. Gas chromatographic analysis (Hewlett Packard 5710A instrument equipped with 6'x3/16" glass columns packed with 3% by weight OV-101 on 100/120 gas chrom Q) gave an assay of >90% of the desired tetrahydropyrimidine and 3.5% of the diamide 4 (R=t-butyl). Evaporation of the o-xylene and slurrying the product with hexane, filtering and drying gave 167g (90%) of 2-t-butyl-1,4,5,6-tetrahydropyrimidine, mp 132.5°C (after recrystallization from toluene). Other tetrahydropyrimidines were prepared in a similar manner.

Preparation of 2-Alkylpyrimidines.

2-t-Butyl-1,4,5,6-tetrahydropyrimidine (193.3g, 1.38 mol) was placed in a 250 ml of dropping funnel wrapped with an electrical heating tape and maintained under a small positive pressure. The dehydrogenator consisted of a 1"x20" Vycor tube that was heated with an electric furnace (320-350°C). The tube was packed in the center with 6" (50g) of 1/8" 0.5% Pd/ Al_2O_3 pellets with small graphite chips at the top and bottom. The dropping funnel was positioned on top of the Vycor tube and the liquified tetrahydropyrimidine fed at the rate of 1.0 + 0.25g/min. The product was collected in a cooled receiver and distilled. The crude material was distilled to give 1.1 mol (80%) of 2-t-butylpyrimidine, bp 155-157°C. The other derivatives were prepared in a similar manner.

TABLE I.[a]

Prod	R	mp°C	bp°C	lit.	Yield	H-5,6	H-5	R	N-H
5	CH_3-	68-71		72[6]	95	3.10 (t,4)	1.60 (m,2)	1.72 (s,1)	7.10 (s,1)
5	CH_3CH_2-	50-53		54-55[6]	97	3.10 (t,4)	1.65 (m,2)	1.05 (t,3) 2.00 (g,2)	7.10 (s,1)
5	$(CH_3)_2CH$-	87-89		c	85	3.10 (t,4)	1.65 (m,2)	1.05 (d,6) 2.15 (m,1)	7.10 (s,1)
5	$(CH_3)_3C$-	132-133		c	96	3.15 (t,4)	1.65 (m,1)	1.10 (s,9)	4.5 (s,1)
5	$C_6H_5CH_2$-	115-118		115-118[7]	95	3.30 (t,4)	1.65 (m,1)	3.40 (t,2), 7.35 (s,5)	4.5 (s,1)
5	C_6H_5-	82-85		86.5[6]	75	3.30 (t,4)	1.70 (m,1)	7.15-7.70 (m,5)	4.5 (b,1)
8	CH_3-		130-131	130-135[8]	65	8.26 (d,2)	6.75 (t,1)	2.60 (s,3)	
8	CH_3CH_2-		148-150	147-150[9]	68	8.30 (d,2)	6.75 (t,1)	1.33 (t,3), 2.90 (q,1)	
8	$(CH_3)_2CH$-		153-154	153-154[10]	76	8.30 (d,2)	6.75 (t,1)	1.35 (d,6), 3.05 (m,1)	
8	$(CH_3)_3C$-		155-157	160-163[11]	80	8.38 (d,2)	6.80 (t,1)	1.35 (s,9)	
	$C_6H_5CH_2$-		97-99 2.0mm	c	53	8.30 (d,2)	6.50 (t,1)	4.10 (s,2), 6.70-7.10 (m,5)	
8	C_6H_5	36-38		38-39[12]	50	8.72 (d,2)	7.00 (t,1)	7.50 (m,2), 8.60 (m,3)	

a ^{1}H-Nmr spectra were obtained on a Varian EM-360A spectrometer at 60 MHz in $CDCl_3$.

b Solvent for recrystallization; methyl (hexane); ethyl (hexane); 1-methylethyl(hexane-toluene) 2-[1,1-dimethylethyl](toluene); benzyl (acetone); phenyl (acetone).

c Satisfactory C, H, and N analyses were obtained for these compounds.

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