[5,6-*h*]-1,3-benzodioxin-5-carboxylate (11b). Compound **4b** (1.02 g, 1.98 mmol) in 200 mL of benzene was degassed for 10 min and then was irradiated in a Pyrex tube in a Rayonet reactor with 350-nm light for 9 h. The solvent was removed in vacuo, and the residue was separated by sgc (H:EA = 4:1) to afford 0.520 g (51% yield) of compound **11b** as a white solid.

Compound **11b**: ^{1}H NMR ($CDCl_3$) δ 6.99 (s, 1 H), 6.55 (s, 2 H), 6.38 (s, 1 H), 5.91 (d, J = 1.2 Hz, 1 H), 5.88 (d, J = 1.2 Hz, 1 H), 5.31 (d, J = 6.3 Hz, 1 H), 5.18 (s, 1 H), 4.97 (d, J = 6.3 Hz, 1 H), 4.56 (d, J = 9.0 Hz, 1 H), 4.05 (dd, J = 10.8 Hz, 3.6 Hz, 1 H), 3.84 (s, 3 H), 3.81 (s, 6 H), 3.65 (t, J = 10.2 Hz, 1 H), 2.94–2.82 (m, 2 H), 1.25 (s, 9 H); IR (film) 3385, 1695 cm^{-1}; HRMS m/z for $C_{27}H_{32}O_{10}$ calcd 516.199 55, found 516.199 15; TLC (Et_2O:H:EtOH = 20:10:1) R_f = 0.65; mp 209–210.5 °C. Anal. Calcd: C, 62.78; H, 6.24. Found: C, 63.37; H, 6.61.

***tert*-Butyl (4aα,11bα)-4a,11b-Dihydro-6-(3,4,5-trimethoxyphenyl)-4*H*-[1,3]benzodioxolo[5,6-*h*]-1,3-benzodioxin-5-carboxylate (12b).** To **11b** (0.356 g, 0.688 mmol) in 150 mL of CH_2Cl_2 under argon was added Et_3SiH (0.16 mL, 1.03 mmol) in one portion followed by BF_3·Et_2O (0.093 mL, 0.76 mmol) dropwise at −78 °C. The mixture was then stirred for 1.5 h and was quenched with 20 mL of H_2O at −78 °C. The solution was allowed to slowly warm to rt, was washed with brine, and was dried over Na_2SO_4. The solvent was removed in vacuo, and the residue was purified by sgc (H:EA = 4:1) to afford 0.257 g (75% yield) of **12b** as a white solid.

Compound **12b**: ^{1}H NMR ($CDCl_3$) δ 7.08 (s, 1 H), 6.44 (s, 1 H), 6.33 (d, J = 4.8 Hz, 2 H), 5.95 (s, 2 H), 5.31 (d, J = 6.0 Hz, 1 H), 4.89 (d, J = 6.3 Hz, 1 H), 4.65 (d, J = 13.8 Hz, 1 H), 4.55 (dd, J = 10.8 Hz, 4.8 Hz, 1 H), 3.89 (s, 3 H), 3.80 (s, 6 H), 3.69 (t, J = 10.8 Hz, 1 H), 3.07 (m, 1 H), 1.19 (s, 9 H); IR (film) 2924, 2853, 1699 cm^{-1}; HRMS m/z for $C_{27}H_{30}O_9$ calcd 498.188 98, found 498.187 62; TLC (Et_2O:H:EtOH = 20:10:1) R_f = 0.67; mp 186–187 °C.

***tert*-Butyl (4aα,5α,6β,11bα)-4a,5,6,11b-Tetrahydro-6-(3,4,5-trimethoxyphenyl)-4*H*-[1,3]benzodioxolo[5,6-*h*]-1,3-benzodioxin-5-carboxylate (13b).** Compound **12b** (0.103 g, 0.21 mmol) in 100 mL of EtOH/THF (v/v = 1/1) was hydrogenated at 1 atm of H_2 with 10% Pd/C (0.030 g) for 4 days. The solution was then purified by sgc (CH_2Cl_2) to afford 0.094 g (91% yield) of compound **13b** as a white solid.

Compound **13b**: ^{1}H NMR ($CDCl_3$) δ 6.99 (s, 1 H), 6.34 (s, 1 H), 6.28 (s, 2 H), 5.90 (s, 2 H), 5.31 (d, J = 6.3 Hz, 1 H), 4.94 (d, J = 6.0 Hz, 1 H), 4.41 (dd, J = 3.9, 10.8 Hz, 1 H), 4.33 (s, 1 H), 4.31 (s, 1 H), 3.80 (s, 3 H), 3.77 (s, 6 H), 3.46 (t, J = 10.8 Hz, 1 H), 3.79 (dd, J = 6.9, 12.3 Hz, 1 H), 2.55 (m, 1 H), 1.18 (s, 9 H); IR (film) 2939, 2837, 1695 cm^{-1}; HRMS m/z for $C_{27}H_{32}O_9$ calcd 500.204 63, found 500.204 10; ^{13}C NMR ($CDCl_3$) δ 171.63, 152.34, 147.33, 146.92, 141.00, 136.66, 132.89, 128.61, 108.66, 103.65, 100.34, 93.90, 82.41, 78.95, 76.59, 75.43, 68.56, 60.46, 55.88, 52.59, 36.37, 27.42; TLC (H:EA = 3:1) R_f = 0.45; mp 158.2–159 °C.

(4aα,5α,6β,11bα)-4a,5,6,11b-Tetrahydro-6-(3,4,5-trimethoxyphenyl)-4*H*-[1,3]benzodioxolo[5,6-*h*]-1,3benzodioxin-5-carboxylic Acid (5). To **13b** (93.3 mg, 0.187 mmol) was added 15 mL of 0.5M CF_3COOH in CH_2Cl_2. The mixture was stirred for 30 h, and the solvent was removed in vacuo. The residue was purified by sgc (H:EA = 2:1) to give 73.8 mg (89% yield) of **5** as a white solid.

Compound **5**: ^{1}H NMR ($CDCl_3$) δ 7.01 (s, 1 H), 6.35 (s, 1 H), 6.23 (s, 2 H), 5.92 (dd, J = 1.0, 1.0 Hz, 2 H), 5.29 (d, J = 6.0 Hz, 1 H), 4.93 (d, J = 6.0 Hz, 1 H), 4.44–4.34 (m, 3 H), 3.79 (s, 3 H), 3.72 (s, 6 H), 3.42 (t, J = 10.5 Hz, 1 H), 2.91 (dd, J = 12.3, 6.6 Hz, 1 H), 2.52 (m, 1 H); IR (film) 3395, 2930, 1707 cm^{-1}; HRMS m/z for $C_{23}H_{24}O_9$ calcd 444.142 03, found 444.144 82; TLC (Et_2O:H:EtOH = 20:10:1) R_f = 0.36.

Acknowledgment. We thank the Hermann Frasch Foundation for partial support of this work.

Registry No. (±)-**1**, 77519-37-0; **3**, 6642-34-8; (*E*)-**4a**, 139896-27-8; (*Z*)-**4a**, 139896-28-9; (*E*)-**4b**, 139896-29-0; **5**, 139896-30-3; **6**, 139896-31-4; **6** alcohol, 139896-32-5; **7**, 139896-33-6; **9**, 86-81-7; **10**, 139896-34-7; **10** alcohol, 139896-35-8; **11a**, 139896-36-9; **11b**, 139896-37-0; **12a**, 139896-38-1; **12b**, 139896-39-2; **13a**, 139896-40-5; **13b**, 139896-41-6; **14**, 77519-38-1; **15**, 64937-82-2; $ClCH_2OCH_2CH{=}CH_2$, 3970-20-5; benzaldehyde, 100-52-7; ethyl triphenylphosphoranylideneacetate, 1099-45-2; *tert*-butyl triphenylphosphoranylideneacetate, 35000-38-5.

Supplementary Material Available: ^{1}H NMR spectra for title compounds and X-ray data for compounds **5** and **14** (28 pages). Ordering information is given on any current masthead page.

Multigram Preparation of 2-Alkylpyrimidines in the Vapor Phase from Carboxylic Acids and 1,3-Diaminopropane over a Dual Catalyst System

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2-Alkylpyrimidines **2** were obtained from cofeeding a carboxylic acid such as pivalic acid (**3a**) or propionic acid (**3b**) and 1,3-diaminopropane (**4**) over first an alumina catalyst at 250–290 °C and second a palladium dehydrogenation catalyst at 300–340 °C to give **2** directly in 56–68% overall yields. On the alumina bed, initial amidation of organic acid occurs to give the monoacyltrimethylenediamine **5**, followed by ring closure to the tetrahydropyrimidine intermediate **6**. An equilibrium between **5**, **6**, and water is established on the alumina bed, with an apparent equilibrium constant of 53 ± 7 mol/Kg at 290 °C. The high temperature of the alumina bed shifts the equilibrium in favor of **6**, which is directly dehydrogenated to **2** over the palladium catalyst. The method avoids the need to isolate and purify solid intermediates. The presence of low levels of sulfur acts as a strong palladium catalyst deactivator. Gradual decline of palladium catalyst activity was observed due to carbon buildup. No decline in alumina catalyst activity was observed. The continuous process allows for the preparation of multigram quantities of **2** with a laboratory-scale reactor.

2-Alkylpyrimidinyl thiophosphates **1** are known as a general class of insecticides.[1] Particularly effective are compounds bearing a bulky group at the 2-position of the pyrimidine ring, such as an isopropyl,[1] *tert*-butyl,[1] or methylcyclopropyl[2] group, as well as fluoroalkyl groups.[3]

(1) Reifschneider, W. U.S. Pat. 4429125, 1984; *Chem. Abstr.* 1984, *100*, P210153m.

(2) Reifschneider, W.; Larson, L. U.S. Pat. 4444764, 1984; *Chem. Abstr.* 1984, *101*, 91233w.

(3) Reifschneider, W.; Larson, L. U.S. Pat. 4558039, 1985; *Chem. Abstr.* 1986, *104*, 125074z.

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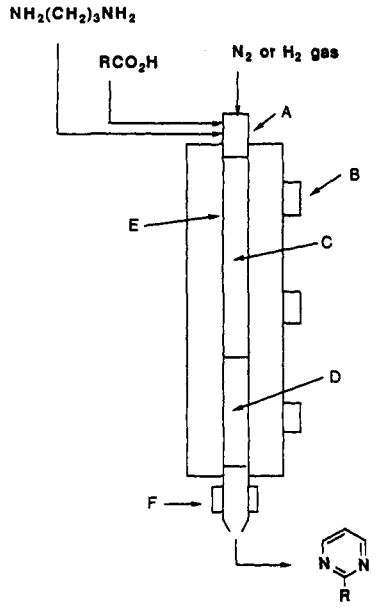
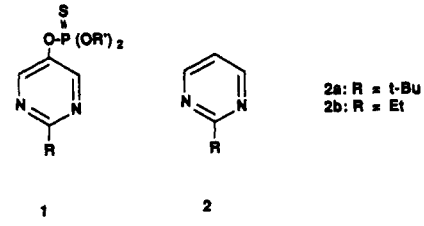


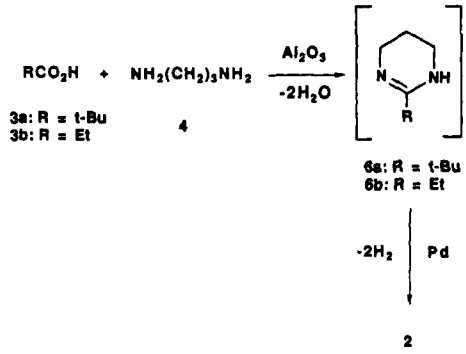
Figure 1. Vapor-phase reactor: (A) preheater zone, (B) three-zone electric furnace with 1.25-in. center hole, (C) alumina catalyst zone, (D) palladium catalyst zone, (E) 1-in.-diameter quartz reactor tube, (F) cold water condenser.

Production of this class of compounds requires an efficient route to the 2-alkylpyrimidines **2**.



1 **2**

Since previously reported routes to pyrimidines require multiple steps from relatively expensive reagents,[4] we sought a more efficient route to **2** from readily available starting materials. Pews has reported[5] the vapor-phase dehydrogenation of tetrahydropyrimidines **6** over a palladium catalyst to give **2**. We have extended this approach to a dual catalyst system where **6** is prepared in situ over an alumina catalyst and subsequently dehydrogenated over a palladium catalyst without isolation to give 2-alkylpyrimidines directly.[6]



We report here a continuous vapor-phase preparation of **2**, especially 2-*tert*-butylpyrimidine (**2a**) from carboxylic acids and 1,3-diaminopropane using a relatively simple vapor-phase reactor comprised of two catalysts. This method provides multigram quantities of 2-alkylpyrimidines on a laboratory scale in good yields. During the course of our study a similar approach was disclosed by another group[7] reporting the preparation of 2-alkylpyrimidines in the vapor phase, prompting us to report our results here.

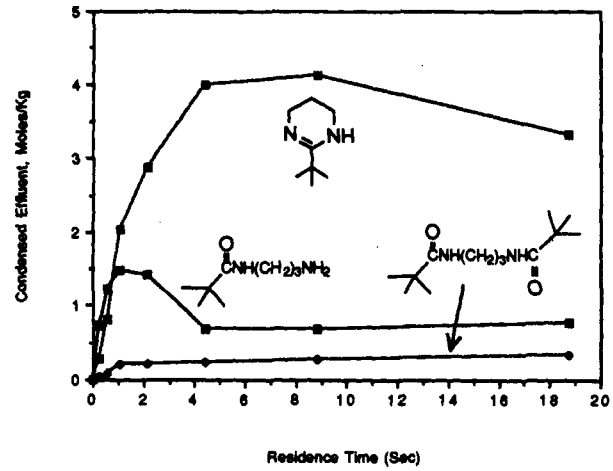
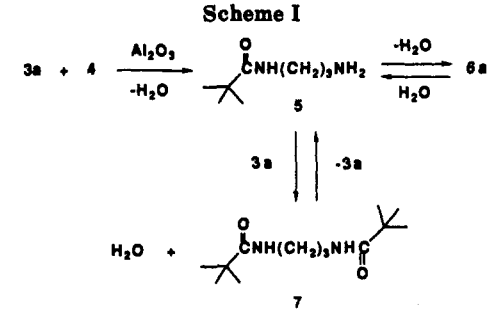


Figure 2. Products of the alumina catalyst bed at 290 °C.

Scheme I



Results and Discussion

Reactions carried out in the vapor phase can be synthetically advantageous. The availability of higher reaction temperatures with short contact time broadens the synthetic scope, especially of endothermic reactions or transformations where a light molecule such as water or hydrogen is a reaction coproduct and can be emitted as a gas.[8] As with our present study, additional advantage is gained when multiple reaction steps can be carried out by linking catalytic reactors, thereby producing molecules of higher value from inexpensive feeds with minimal handling of intermediates. Furthermore, the continuous nature of such a reactor scheme can result in the production of relatively large quantities of material, even in a small laboratory-scale reactor.

Vapor-Phase Reactor. The vapor-phase reactor system used to prepare 2-alkylpyrimidines is shown in Figure 1. In its simplest form, the two catalysts can be mounted in one tube, one over the other. For a more complex reactor system, two separate catalyst tubes can be used. For a study of the alumina bed chemistry only, the palladium catalyst was omitted.

Alumina Bed Chemistry. There have been few reports on the preparation of tetrahydropyrimidines over a solid catalyst such as alumina.[6,7] Aspinall has reported the

(4) Brown, D. J. *The Pyrimidines, Supplement II*; John Wiley and Sons: New York, 1985.
(5) (a) Pews, R. G. U.S. Pat. 4493929, 1985; *Chem. Abstr.* **1985**, *102*, 166775f. (b) Pews, R. G. *Heterocycles* **1988**, *27*, 1867.
(6) Hull, J., Jr. U.S. Pat. 4999427, 1991; *Chem. Abstr.* **1990**, *112*, 198408m.
(7) Teunissen, A. J. J. M.; Klop, W.; Delahaye, H. J. A. V. U.S. Pat. 4880929, 1989; *Chem. Abstr.* **1988**, *109*, 231056h.
(8) Prasad, A. R.; Subrahmanyam, M. *Synth. Commun.* **1990**, *20*, 3385.

preparation of 6 by lime dehydration of monoacyltrimethylenediamines,[9] but most methods of preparation of tetrahydropyrimidines involve multiple-step batch reactions.[4,5b]

The alumina catalyst used in this study is an activated γ-alumina, which readily catalyzes the amidation reactions due to a high degree of Lewis acidity.[10] The formation of **6a** from pivalic acid and 1,3-diaminopropane in the vapor phase was carried out using different alumina bed lengths and feed flow rates to vary the residence time and develop a reaction profile. Because the alumina bed effluent solidifies above room temperature, methanol was added at the reactor exit port for ease of analysis of a liquid solution. An internal standard was required to calculate predilution concentrations. Pyrimidine **2a** was chosen for this purpose due to its stability on alumina and ease of condensing (bp = 165 °C) and was added to the pivalic acid feed. From reaction samples taken from the alumina bed effluent at different residence times, the composition flowing to the palladium dehydrogenation bed was determined and is shown in Figure 2. From this, the alumina bed chemistry can be deduced and is shown in Scheme I.

An initial amidation of pivalic acid occurs to give aminoamide intermediate **5** followed by subsequent ring closure to give tetrahydropyrimidine **6a**. In a side reaction, the free amine group of **5** can be amidated with a second equivalent of pivalic acid to give diamide **7**. Since each of the amidation and cyclization reactions produce 1 equiv of water, the cyclization reaction of **5** is established as an equilibrium with **6a** and water (Figure 2). At 290 °C, the equilibrium is established after 4 s of residence time, and the apparent equilibrium constant was 53 ± 7 mol/kg. The high degree of uncertainty is due to the small number of samples taken at steady-state conditions. At room temperature, aqueous solutions of tetrahydropyrimidine **6a** favor the ring-opened form; **6a** is unstable and gives complete reversion to aminoamide **5**. However, the higher temperature of the alumina catalyst bed shifts the equilibrium in favor of the ring-closed product **6a**.

The reversibility of the second amidation reaction which gives **7** was demonstrated by feeding pure **7** and excess water to the reactor; **3a**, **5**, and **6a** were observed by HPLC effluent analysis. This reversibility prevents a large buildup of unwanted diamide **7** over longer residence times (Figure 2). No diamine **4** was observed in this experiment, an indication that the first amidation reaction to give **5** is essentially irreversible under the reaction conditions.

Longer residence times result in a dropoff of **6a** (Figure 2), along with a corresponding drop in diamine functional group mass balance. Under these conditions, product analysis indicates the presence of increasing levels of ethyl- and methylamine, products arising from the breakup of the primary amine chain of **5** on the acid catalyst. This effect is also observed at bed temperatures above 300 °C, at which point the reactor effluant darkened considerably. The most effective alumina bed temperature range was 275–290 °C.

In order to determine if the observed rates of formation of **5** and **6a** were limited by intrinsic chemistry or diffusion of reactants to the catalyst, conversion data from different catalyst bed lengths but with identical residence times were compared. At 250 °C, no effect of feed rate was observed on the conversions. However, at 290 °C somewhat higher conversions were observed with faster linear feed velocities for a given residence time. This implicates some diffusion limitation effects at temperatures in which the amidation occurs within 1–2 s.

Table I. GC Weight % Analysis of Crude 2a Condensed Reactor Effluent

		0.1% thiophene feed	
component	normal run (%)	4.1 h	5.6 h
2a	51.1	35.1	28.7
6a	0.3	11.5	14.8
trimethylacetamide	1.9	2.8	2.9
N-ethylpivalamide	6.5		
5	0.0	1.8	2.5
7	14.9	11.3	8.5
3a	8.0	5.0	
totals	83.0	67.5	57.4

From Figure 2, the size of the alumina bed or the feed flow rates can be adjusted to achieve the optimal equilibrium composition of **5** and **6a**. From the measured concentrations of reactor effluent, a 79% yield of **6a** was obtained based on pivalic acid at a residence time of 9 s. The yield of amino amide **5** was 13%. Thus, the total amidation yield was 92% based on pivalic acid.

No limitation of activity of the alumina catalyst was observed. The alumina bed could be reused in subsequent runs without a noticeable decrease in rates of the amidation and cyclization reactions.

Dehydrogenation Chemistry. Pews has reported[5] the vapor-phase dehydrogenation of **6a** which had been isolated and purified as a solid. A key difficulty is handling larger quantities of high-melting solid tetrahydropyrimidines such as **6a**, which also readily sublimes at elevated temperatures and can plug condensers and feed lines. Tetrahydropyrimidines are also sensitive to moisture.[9] With the current method, **6** is prepared in situ and passed directly into the subsequent palladium bed without isolation. The resulting 2-alkylpyrimidines are stable, easily handled liquids which are readily condensed and distilled.

Without prior removal of water from the alumina bed, a minor amount of ring-opened **5** is passed into the palladium dehydrogenation bed. This results in a somewhat lower overall yield of **2a**, since passage of **5** directly over a palladium catalyst gives only low yields of pyrimidines **2a** and substantial light amine organics from fragmentation of the alkyl amine chain.[5b] Table I lists the reactor effluent composition after passage of the stream over the palladium dehydrogenation catalyst. Pivalic acid is present since that reagent was used in excess. If diamine **4** is used in excess, 2-ethylpyrimidine is also formed from the reaction of **4** over the palladium catalyst.[11] Diamide **7** formed on the alumina bed appears to pass through the palladium bed as an inert heavy organic. Pyrimidine **2a** represented 51% by weight of the crude effluent and was obtained in overall yields of 57% and 68% based on pivalic acid and diamine **4**, respectively. Additional products were also formed from breakup of the amine hydrocarbon chain (Table I). Much of the 17% unaccounted for assay in Table I consists of water from the alumina bed reactions.

In the preparation of the ethyl derivative **2b**, optimization of the distilled yield was not attempted, but a 1-lb sample of purified **2b** was obtained from a 33-h run.

The endothermic nature of the dehydrogenation reaction[12] was observed by measuring the temperature dif-

(9) Aspinall, S. R. *J. Am. Chem. Soc.* **1940**, *62*, 2160.
(10) Anderson, J. R. *Structure of Metallic Catalysts*; Academic Press: New York, 1975; p 46.
(11) Okada, J.; Morita, S.; Tsuchiya, M. *Yakugaku Zasshi* **1976**, *96*, 801.
(12) Ritchie, A. W.; Nixon, A. C. *Am. Chem. Soc., Div. Petrol. Chem.* **1967**, *12*, 117.

Table II. Elemental Analysis of Fresh and Spent Palladium Catalysts

catalyst sample	%C	%H	%N	%S	run time (h)
unused	nd[a]	0.16	nd[a]	0.002	0
normal run	2.27	0.18	nd[a]	nd[a]	91.25
thiophene spiked[b]	1.97	0.21	nd[a]	0.044	6.0
pretreated catalyst[c]	0.42	0.06	nd[a]	0.082	0
pretreated catalyst[d]	2.03	0.20	nd[a]	0.092	1.7

[a] nd = nondetectable at less than 0.01%. [b] Diamine feed spiked with 0.1% thiophene. [c] Pretreatment with 12% thiophene in methanol at 300 °C, unused. [d] Pretreated with 12% thiophene in methanol and used in run.

ference between the center and skin of the reactor tube. The reactor center was typically 20–40 °C cooler than the skin temperature at the position of the bed where dehydrogenation was occurring. In this manner the dehydrogenation reaction front was observed moving down the bed in the direction of feed flow as the palladium catalyst gradually deactivated. This was a convenient measure of the remaining palladium catalyst capacity. Runs were terminated when levels of unreacted **6a** in the reactor effluent exceeded 1–2% by weight.

Palladium Catalyst Poisoning by Sulfur. From the experiments with thiophene additive, sulfur was found to be a potent deactivator for the dehydrogenation of **6a**. The feeds **3a** and **4** as obtained from commercial sources contained no sulfur at a 2 ppm detection limit. Although sulfur is known as a poison for noble metal catalysts, it is also known as a selective poison for undesired reaction paths such as hydrogenolysis, while suppressing dehydrogenation and aromatization to a lesser extent.[13] From the results shown in Table I, using a sulfided catalyst unreacted **6a** is present in the reactor effluent in high levels and increases rapidly during the first few hours, indicating significantly lower catalyst activity compared to the nonsulfided catalyst.

Elemental analysis results of sulfided and nonsulfided catalyst samples are shown in Table II. Normal deactivation of the palladium catalyst after a 91-h run arises from carbon formation, which can be reversed by air oxidation of the bed. The sulfided catalysts, either pretreated or sulfur poisoned during a run, showed rapid carbon formation and associated loss of dehydrogenation activity. No improvement of selectivity for the desired dehydrogenation reaction of **6a** to **2a** was observed. A fully sulfided 0.5% palladium on alumina catalyst sample purchased commercially[14] gave similar results to the thiophene treated examples above, that is rapid loss of dehydrogenation activity.

Conclusions

Starting from a carboxylic acid and 1,3-diaminopropane, three consecutive reactions over two catalysts were carried out without isolation of the amidation intermediates, giving 2-alkylpyrimidines directly in good yields. The catalyst life is determined by the palladium dehydrogenation activity, with the alumina catalyst showing no indication of decline. Gradual deterioration of the palladium bed occurs from the buildup of carbon, and the presence of 0.1% thiophene in the reactor feed leads to rapid deterioration of the palladium catalyst activity. The continuous nature of the dual catalyst reactor makes possible the preparation of significant quantities of pyrimidines, even in a laboratory-scale reactor.

(13) Wilde, M.; Stolz, T.; Feldhaus, R.; Anders, K. *Appl. Catal.* **1987**, *31*, 99 and references cited therein.

(14) Purchased from Engelhard Corp. Fully sulfided refers to a 1/1 molar ratio of sulfur to palladium.

Experimental Section

General. Analyses in weight % of the dehydrogenation reactor samples were carried out using a GC internal standard method, using a Quadrex 007 5% phenyl methyl silicone capillary column, 5-μm film thickness, and 0.32 i.d. A temperature program of 100-260 °C was used at 16 °C/min and a 250 °C FID. 1,2-Dichlorobenzene was added to samples as an internal standard. Analyses of reactor samples from the alumina bed were carried out using a dual column HPLC system consisting of a reversed-phase Zorbax ODS column (4.6 mm × 150 mm) followed by a Particil SCX cationic column (4.6 mm × 25 cm). The eluant consisted of 70/30 water/acetonitrile containing 0.01 M phosphoric acid and 0.05 M potassium hydrogen phosphate and was pumped at 1.0 mL/min. The method was calibrated with an external standard to give analyses in mol/Kg. The alumina catalyst was CSS-300 LDS $^1/_8$-in. macroporous spheres obtained from Alcoa Chemicals Division, which have a BET surface area of 300 m^2/g and contained 0.35% Na_2O. The palladium catalyst was a standard eggshell 1% palladium on alumina, $^1/_8$-in. pellets, obtained from Engelhard Corp. Palladium catalysts obtained from different lots, as well as from different companies, such as Degussa Corp., gave similar dehydrogenation results. Technical-grade pivalic acid and 1,3-diaminopropane were purchased from Exxon and BASF, respectively. However, material obtained from different sources, such as Aldrich, behaved similarly. Propionic acid was obtained from Aldrich and used without further purification.

The preparations of 2-*tert*-butylpyrimidine (**2a**), 2-*tert*-butyl-1,4,5,6-tetrahydropyrimidine (**6a**), (3-aminopropyl)pivalamide (**5**), and *N*,*N*′-1,3-propanediylbispivalamide (**7**) have been reported previously.[5b] Diamide **7** was obtained from the amidation of **3a** with a deficiency of **4** in a pressure vessel[5b] and purified by recrystallization of crude material from acetonitrile, mp 123 °C, bp 326 °C. Purified **6a** was prepared by recrystallization from warm hexane. Analytical standards of trimethylacetonitrile and trimethylacetamide were obtained from Aldrich. *N*-Methylpivalamide and *N*-ethylpivalamide, required for GC standards, were prepared by bubbling an excess of anhydrous methylamine or ethylamine into a toluene solution of trimethylacetyl chloride.

Proton (300-MHz) and carbon (75-MHz) NMR spectra were obtained on a Bruker AC 300 spectrometer. Melting points and boiling points are uncorrected.

All dehydrogenation reactions should be carried out in an efficient fume hood due to the production of hydrogen and gaseous odor-causing amine byproducts. Care should be exercised in the handling of hot reactor tubes. The reactor furnace should be allowed to cool to room temperature prior to dismantling of the reactor system.

Reactor. A diagram of the reactor system is shown in Figure 1. The catalyst was held in a 1-in.-diameter quartz tube filled 27 in. in length. The tube was fitted with a 6-mm center tube along its length to allow for the insertion of thermocouples. The top inch consisted of quartz chips followed by about 16-in. of the alumina catalyst. The lower portion contained an 8-in. zone of 1% Pd/alumina dehydrogenation catalyst, followed by 2 in. of inert quartz chips. For preparation of only the tetrahydropyrimidine intermediate **6**, palladium catalyst was omitted from the tube. The catalyst tube was heated by a three-zone electrical furnace with 8-in. heated zone lengths (24 in. total heated length) and each zone controlled by a separate three-mode controller. Control thermocouples were taped to the outside of the quartz tube with temperature-resistant tape to give control of "skin" temperatures. In addition, the internal temperatures were monitored by thermocouples inserted into the internal thermowell. A high-temperature cutoff with a separate thermocouple taped to the outer tube wall was used with the controllers for emergency shutdown. The alumina catalyst zones were typically operated at 250–290 °C, and the palladium catalyst zone typically at 280–340 °C.

Two separate FMI pumps were used to pump carboxylic acid and 1,3-diaminopropane into the preheater zone. In the case of pivalic acid, the feed was kept warm (70 °C) using a hotplate/stirrer, and the feed line was kept at 70 °C with a heat tape and

controller. The two feed bottles were placed on top-loading balances to monitor the feed flow rates during a run. The feed flow rates were adjusted to the desired stoichiometry. A short (6-in.) preheater tube filled with quartz chips was fitted onto the top of the reactor tube and heated by wrapping with heat tape and controlled with a separate controller to a skin temperature of approximately 200 °C.

During heating of the reactor, a mixture of hydrogen and nitrogen were passed over the beds at a rate of about 100 and 55 mL/min, respectively, in order to reduce the palladium catalyst. During a run, the hydrogen was turned off, maintaining only a slow nitrogen flow through the reactor.

Uncatalyzed Thermal Reaction. A control experiment was carried out with the reactor tube filled with only quartz chips and held at 290 °C. Very little amidation of pivalic acid or subsequent cyclization was observed without the alumina catalyst present, and difficulty with salt plugging (pivalate salt of diaminopropane) at the exit port of the reactor was encountered. HPLC analysis of the effluent indicated only very low levels of amidation products **5**, **6a**, and **7**.

2-*tert*-Butyl-1,4,5,6-tetrahydropyrimidine (6a). An alumina catalyst bed size of 3-in. length × 1-in. diameter was used (15.4 g alumina spheres) with the remainder of the reactor tube filled with quartz chips. Longer alumina bed lengths of 6 in., 12 in., and 24 in. were used to obtain conversion data at longer residence times. Pivalic acid containing 10% of **2a** as an internal standard and 1,3-diaminopropane were pumped into the reactor at a **4**/**3a** mole ratio of 1.04 and a bed temperature of 290 °C. Four total feed flow rates were used: 1.10, 2.17, 4.26, and 0.56 g/min, with nitrogen diluent flow rates of 52, 107, 214, and 27 mL/min, respectively. Methanol solvent was pumped at flow rates of 1.3, 1.8, 4.1, and 0.8 g/min, mixed with the reactor effluent at the bed exit port, and condensed as a liquid product. Samples of the liquid solution were monitored by HPLC at 20-min intervals. Four to six replicate samples were taken at each flow rate to ensure steady-state conditions. The product concentrations in the methanol-diluted solution were determined in mol/kg units and adjusted to nondiluted concentration values using the internal standard as a reference. The feed flow rates were used to calculate residence times using the ideal gas law and assuming a catalyst void volume of 0.45. At a residence time of 9 s the molar yields of **6a** and **5** were 79% and 13% based on pivalic acid and 75% and 12% based on diaminopropane.

Purified **6a** was obtained by evaporation of the methanol/water solution and recrystallization of the white solid residue from warm hexane: mp 131–134 °C (lit.[5b] mp 132–133 °C); bp 205 °C; $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 162.68 (1 C), 41.77 (2 C), 36.36 (1 C), 28.23 (3 C), 20.55 ppm (1 C).

***N*-(3-Aminopropyl)pivalamide (5).** An aqueous solution of tetrahydropyrimidine **6a** was stirred overnight at 25 °C. After evaporation of water, **5** was obtained in quantitative yield and was recrystallized from toluene, mp 56–58 °C: ^1H NMR ($CDCl_3$) δ6.82 (br, 1 H), 3.28 (q, J = 6 Hz, 2 H), 2.74 (t, J = 6 Hz, 2 H), 1.56 (quintet, J = 6 Hz, 2 H), 1.40 (br, 2 H), 1.12 ppm (s, 9 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 178.6 (1 C), 40.3 (1 C), 38.6 (1 C), 38.3 (1 C), 32.2 (1 C), 27.6 ppm (3 C).

2-*tert*-Butylpyrimidine (2a). The top two heated reactor zones (16 in.) consisted of 73.0 g of alumina spheres. The bottom 8 in. heated zone consisted of 66.3 g of 1% palladium on alumina pellets. The skin temperatures of the alumina and palladium catalyst zones were maintained at 275 °C and 320 °C, respectively. Pivalic acid (4466.2 g, 43.7 mol) and **4** (2708.9 g, 36.5 mol) were pumped to the reactor at rates of about 0.82 and 0.50 g/min, respectively, over a period of 91.3 h. The feed molar ratio was maintained in a range such that pivalic acid was used in excess; the **4**/**3a** molar ratio was typically 0.84. The crude liquid product was condensed and collected at the exit port of the reactor as a light yellow two-phase solution. A total of 6605 g of crude **2a** was obtained, for a mass recovery of 92%. Analysis of the well-stirred crude product by GC gave an assay for **2a** of 51.1%, or 3375.9 g (24.8 mol), for yields of 56.7% and 67.8% based on **3a** and **4**, respectively. Additional major components found in the crude product from GC analysis are listed in Table I.

During the final 20 h, the activity of the palladium catalyst gradually declined, and the run was terminated when the level of unreacted **6a** in the reactor effluent reached 1.7% by weight.

Crude **2a** was purified by atmospheric distillation through an Oldershaw column using a 10/1 reflux splitter ratio. After initial aqueous and light organics fractions, pure fractions of 97% purity or greater (by GC assay) of **2a** were taken overhead, bp 165 °C (lit.[5b] bp 155–157 °C). Alternatively, the crude product was washed with dilute aqueous NaOH solution to remove unreacted pivalic acid, the phases were separated, and purified **2a** was distilled overhead from the organic phase: $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 177.4 (1 C), 156.4 (2 C), 117.9 (1 C), 39.4 (1 C), 29.5 ppm (3 C).

2-Ethylpyrimidine (2b). The alumina bed consisted of 77.2 g of alumina spheres and was held at 290 °C. The palladium bed consisted of 66.2 g of 1% palladium on alumina pellets and was held at 320 °C. Propionic acid (1112.2 g, 15.01 mol) and **4** (1181.1 g, 15.93 mol) were pumped into the reactor at a rate of approximately 0.54 and 0.60 g/min, respectively, for a period of 33 h. A total of 1947.1 g of crude product was condensed and collected as a single phase, representing a mass recovery of 84.9%. Analysis of the crude product by GC/MS showed the presence of 2-methylpyrimidine, propionic acid, *N*-ethylpropanamide, and *N*-propylpropanamide as minor components and **2b** as the major component.

Purification of **2b** was carried out by atmospheric distillation of the crude reactor effluent through an Oldershaw column using a 10/1 reflux splitter ratio. A preliminary 737-g fraction taken overhead contained some 2-methylpyrimidine, and this fraction was redistilled in a similar manner, collecting a 454 g fraction (bp = 152 °C) that gave a GC area % analysis of 99.8% **2b** and 0.11% 2-methylpyrimidine. The yield of the purified fraction of **2b** was 27.9% based on propionic acid: $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 172.3 (1 C), 156.6 (2 C), 118.2 (1 C), 32.6 (1 C), 12.4 ppm (1 C).

Preparation of 2a with Feed Spiked with 0.1% Thiophene. In this experiment diamine **4** was spiked with 0.1% by weight thiophene, and **3a** (337.7 g, 3.3 mol) and **4** (173.1 g, 2.3 mol) were pumped into the reactor as above for a period of 6 h at average rates of 0.89 and 0.48 g/min, respectively. During this time increasingly high levels of tetrahydropyrimidine **6a** were found in the reactor effluent. A total of 452.3 g of light yellow liquid product was condensed from the reactor, representing a mass recovery of 89%. Table I shows the composition of a sample of reactor condensate taken after 4.1 and 5.6 h.

Pretreatment of Palladium Catalyst with Thiophene. The standard 1% palladium on alumina catalyst was loaded into the reactor tube. The bed was heated to 300 °C, and a 12% by weight thiophene solution in methanol was pumped through the reactor at 1.25 g/min for 2.17 h. The reactor was cooled under a slow nitrogen stream, and the catalyst was removed for analysis. Catalyst analysis results are shown in Table II.

Preparation of 2a with a Thiophene Pretreated Catalyst. In this run a 74.8-g alumina catalyst bed and a 64.7-g 1% palladium on alumina catalyst bed was used. This bed was pretreated with thiophene solution as above for 2.25 h. The reactor was flushed by pumping deionized water at reactor temperature for about 30 min. Pivalic acid (97.4 g, 0.95 mol) and **4** (47.0 g, 0.63 mol) were pumped into the reactor at average rates of 0.91 and 0.47 g/min, respectively, over a period of 1.66 h. Samples condensed from the reactor effluent showed a high level of unconverted **6a**, indicating rapid palladium catalyst deactivation. Analysis of the spent palladium catalyst from this run is shown in Table II.

Registry No. **2a**, 61319-99-1; **2b**, 60544-11-8; **3a**, 75-98-9; **3b**, 79-09-4; **4**, 109-76-2; **5**, 85727-25-9; **6a**, 92328-13-7; **7**, 93667-57-3; Al_2O_3, 1344-28-1; Pd, 7440-05-3; trimethylacetamide, 754-10-9; *N*-ethylpivalamide, 14278-29-6.