Reaction of Diimines with Carbonyl Compounds. Synthesis of Dihydropyrimidines

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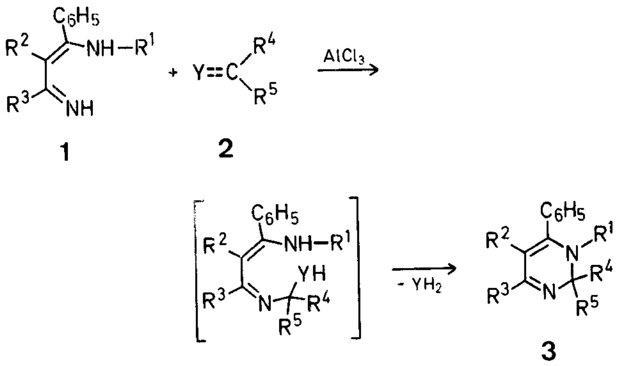
It has been shown that diimines **1** react with saturated nitriles[1], imines[2], and acetylenedicarboxylic acid esters[3]. These reactions are suitable general methods for the synthesis of pyrimidines, dihydropyrimidines, and pyridines, respectively.

1,2-Dihydropyrimidines **3** are always obtained in the reaction of **1** with aldimines **2** ($Y=N-R^6$, $R^5=H$) regardless of the nature of R^1 and R^6. These observation suggests that **3** arises from an aluminium chloride-catalyzed condensation.

On the basis of the preceding results, diimines **1** should be able to react with different condensation agents leading to heterocyclic systems with at least two nitrogen atoms in the ring. This possibility, in addition to the easy preparation of systems **1**[4], induced us to study the scope of application and limitations of these types of synthesis.

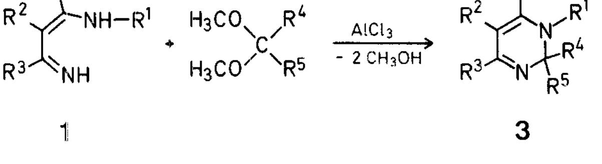
In the present communication, the results of the reaction of 1,3-diimines with carbonyl compounds and derivatives such as acetals are described.



1,2-Dihydropyrimidines **3** are generated in high yields (Table 1) when diimines **1** are allowed to react with aldehydes **2** ($Y=O$, $R^5=H$), in dioxan at 90° in the presence of aluminium chloride as catalyst in a 1 : 1 : 1 molar ratio[5].

The reaction of **1** with ketones ($Y=O$, $R^5 \neq H$), does not lead to the formation of the corresponding dihydropyrimidine **3**[6]. However, dihydropyrimidines **3** ($R^4=R^5=CH_3$) are obtained by reaction at 85° of diimines **1** with 2,2-dimethoxypropane (Table 2).

Acetals derived from phenylacetaldehyde or formaldehyde are also able to undergo condensation with diimines **1** (Table 2). These latter reactions extend the method now reported to the synthesis of dihydropyrimidines which cannot be directly prepared from the corresponding aldehydes[7].



5-Methyl-1-(4-methylphenyl)-2,4,6-triphenyl-1,2-dihydropyrimidine (3n):

To a stirred solution of 3-imino-2-methyl-1,3-diphenyl-*N*-(4-methylphenyl)prop-1-enamine (2.6 g, 8 mmol) and benzaldehyde (0.85 g, 8 mmol) in dioxan, aluminium chloride (1.1 g, 8 mmol) is added under argon. The mixture is heated and stirred at 90° for 12 h, allowed to cool, acidified with 2 normal sulfuric acid (80 ml), and then treated with 3 normal potassium hydroxide solution

Table 1. 1,2-Dihydropyrimidines **3** from Diimines **1** and Aldehydes **2** ($Y=O$, $R^5=H$).

Product	R^1	R^2	R^3	R^4	Yield [%]	m.p. or b.p./torr	Molecular formula[a]	^{1}H-N.M.R. (CCl_4)[b] δ [ppm]
3a	C_6H_5	CH_3	$4-H_3C-C_6H_4$	2-furyl	89	140°/0.001	$C_{28}H_{24}N_2O$ (404.5)	1.8 (s, CH_3); 2.3 (s, CH_3); 6.15–6.25 (m, 2H_{fur}); 6.6 (s, CH); 6.7–7.6 (m, 14H_{arom} and 1H_{fur})
3b	$2-H_3C-C_6H_4$	CH_3	$4-H_3C-C_6H_4$	$4-Cl-C_6H_4$	80	124–125°	$C_{31}H_{27}ClN_2$ (463.0)	1.8 (s, CH_3); 2.2 (s, CH_3); 2.4 (s, CH_3); 6.2 (s, CH); 6.8–7.7 (m, 17H_{arom})
3c	$c-C_6H_{11}$	CH_3	$4-H_3C-C_6H_4$	$4-Cl-C_6H_4$	73	206–208°	$C_{30}H_{31}ClN_2$ (455.1)	0.9–2.1 (m, CH_2); 1.55 (s, CH_3); 2.4 (s, CH_3); 2.6–3.0 (m, CH–N); 6.2 (s, CH); 7.0–7.6 (m, 13H_{arom})
3d	$c-C_6H_{11}$	CH_3	C_6H_5	$4-Cl-C_6H_4$	87	170–172°	$C_{29}H_{29}ClN_2$ (441.0)	0.9–2.0 (m, CH_2); 1.5 (s, CH_3); 2.7–3.0 (m, CH–N); 6.2 (s, CH); 7.1–7.5 (m, 14H_{arom})
3e	C_6H_5	CH_3	C_6H_5	$4-Cl-C_6H_4$	89	163–165°	$C_{29}H_{23}ClN_2$ (435.0)	1.8 (s, CH_3); 6.5 (s, CH); 6.8–7.7 (m, 19H_{arom})
3f	C_6H_5	H	C_2H_5	$4-Cl-C_6H_4$	70	100°/0.001	$C_{24}H_{21}ClN_2$ (372.9)	1.1–1.35 (t, CH_3); 2.3–2.65 (q, CH_2); 5.8 (s, CH); 6.4 (s, CH); 6.7–7.7 (m, 14H_{arom})

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Table 1. (Continued)

Product	R^1	R^2	R^3	R^4	Yield [%]	m.p. or b.p./torr	Molecular formula[a]	^{1}H-N.M.R. (CCl_4)[b] δ [ppm]
3g	C_6H_5	CH_3	4-$H_3C—C_6H_4$	4-$H_3CO—C_6H_4$	90	135–137°	$C_{31}H_{28}N_2O$ (444.6)	1.8 (s, CH_3); 2.4 (s, CH_3); 3.7 (s, OCH_3); 6.6 (s, CH); 6.8–7.6 (m, 18 H_{arom})
3h	C_6H_5	CH_3	C_6H_5	4-$H_3CO—C_6H_4$	90	132–134°	$C_{30}H_{26}N_2O$ (430.6)	1.8 (s, CH_3); 3.75 (s, OCH_3); 6.6 (s, CH); 6.7–7.7 (m, 19 H_{arom})
3i	C_6H_5	CH_3	4-$H_3C—C_6H_4$	4-$H_3C—C_6H_4$	92	156–158°	$C_{31}H_{28}N_2$ (428.6)	1.7 (s, CH_3); 2.3 (s, CH_3); 2.35 (s, CH_3); 6.6 (s, CH); 6.8–7.6 (m, 18 H_{arom})
3j	4-$H_3C—C_6H_4$	CH_3	C_6H_5	4-$H_3C—C_6H_4$	90	182–184°	$C_{31}H_{28}N_2$ (428.6)	1.8 (s, CH_3); 2.2 (s, CH_3); 2.3 (s, CH_3); 6.5 (s, CH); 6.8–7.7 (m, 18 H_{arom})
3k	C_6H_5	H	C_6H_5	4-$H_3C—C_6H_4$	91	128–130°	$C_{29}H_{24}N_2$ (400.5)	2.3 (s, CH_3); 6.4 (s, CH); 6.7 (s, CH); 6.8–8.0 (m, 19 H_{arom})
3l	C_6H_5	CH_3	4-$Cl—C_6H_4$	C_6H_5	80	143–145°	$C_{29}H_{23}ClN_2$ (435.0)	Ref. [2]
3m	*c*-C_6H_{11}	CH_3	4-$H_3C—C_6H_4$	C_6H_5	82	119–121°	$C_{30}H_{32}N_2$ (420.6)	1.0–2.1 (m, CH_2); 1.5 (s, CH_3); 2.4 (s, CH_3); 2.7–3.0 (m, CH—N); 6.2 (s, CH); 7.1–7.5 (m, 14 H_{arom})
3n	4-$H_3C—C_6H_4$	CH_3	C_6H_5	C_6H_5	87	186–188°	$C_{30}H_{26}N_2$ (414.6)	1.8 (s, CH_3); 2.2 (s, CH_3); 6.6 (s, CH); 6.8–7.8 (m, 19 H_{arom})
3o	2-$H_3C—C_6H_4$	CH_3	C_6H_5	C_6H_5	86	115–117°	$C_{30}H_{26}N_2$ (414.6)	1.8 (s, CH_3); 2.2 (s, CH_3); 6.2 (s, CH); 6.8–7.8 (m, 19 H_{arom})
3p	C_6H_5	CH_3	4-$H_3C—C_6H_4$	C_6H_5	91	158°	$C_{30}H_{26}N_2$ (414.6)	Ref. [2]
3q	*c*-C_6H_{11}	CH_3	C_6H_5	C_6H_5	88	174–176°	$C_{29}H_{30}N_2$ (406.6)	0.9–2.1 (m, CH_2); 1.5 (s, CH_3); 2.7–3.0 (m, CH—N); 6.2 (s, CH); 7.1–7.7 (m, 15 H_{arom})
3r	C_6H_5	CH_3	C_6H_5	C_6H_5	91	142–144°	$C_{29}H_{24}N_2$ (400.5)	Ref. [2]
3s	C_6H_5	H	C_6H_5	C_6H_5	88	193–194°	$C_{28}H_{22}N_2$ (386.5)	Ref. [2]
3t	C_6H_5	CH_3	*n*-C_3H_7	C_6H_5	88	110°/0.001	$C_{26}H_{26}N_2$ (366.5)	0.9–1.1 (t, CH_3); 1.6–1.9 (m, CH_2); 1.8 (s, CH_3); 2.3–2.6 (q, CH_2); 6.4 (s, CH); 6.7–7.7 (m, 15 H_{arom})
3u	C_6H_5	H	C_2H_5	C_6H_5	93	140–142°	$C_{24}H_{22}N_2$ (338.5)	1.1–1.3 (t, CH_3); 2.3–2.6 (q, CH_2); 5.8 (s, CH); 6.4 (s, CH); 6.8–7.6 (m, 15 H_{arom})
3v	C_6H_5	CH_3	4-$H_3C—C_6H_4$	*n*-C_3H_7	72	105°/0.001	$C_{27}H_{28}N_2$ (380.5)	1.1–1.3 (t, CH_3); 1.7–1.9 (m, $CH_2—CH_2$); 1.9 (s, CH_3); 2.3 (s, CH_3); 5.4–5.6 (t, CH); 6.7–7.4 (m, 14 H_{arom})
3w	2-$H_3C—C_6H_4$	CH_3	C_6H_5	*n*-C_3H_7	80	101°/0.001	$C_{27}H_{28}N_2$ (380.5)	0.95–1.1 (t, CH_3); 1.6–1.9 (m, $CH_2—CH_2$); 1.8 (s, CH_3); 2.2 (s, CH_3); 5.05–5.25 (t, CH); 6.8–7.6 (m, 14 H_{arom})
3x	C_6H_5	CH_3	C_6H_5	C_2H_5	91	110°/0.001	$C_{25}H_{24}N_2$ (352.5)	1.2–1.4 (t, CH_3); 1.6–1.9 (m, CH_2); 1.9 (s, CH_3); 5.35–5.55 (t, CH); 6.7–7.7 (m, 15 H_{arom})
3y	C_6H_5	CH_3	4-$H_3C—C_6H_4$	CH_3	88	95°/0.001	$C_{25}H_{24}N_2$ (352.5)	1.45–1.55 (d, CH_3); 1.9 (s, CH_3); 2.35 (s, CH_3); 5.55–5.8 (q, CH); 6.7–7.5 (m, 14 H_{arom})
3z	2-$H_3C—C_6H_4$	CH_3	C_6H_5	CH_3	89	90°/0.001	$C_{25}H_{24}N_2$ (352.5)	1.45–1.55 (d, CH_3); 1.8 (s, CH_3); 2.2 (s, CH_3); 5.1–5.35 (q, CH); 6.7–7.9 (m, 14 H_{arom})
3aa	C_6H_5	H	C_6H_5	CH_3	90	115°/0.001	$C_{23}H_{20}N_2$ (324.4)	1.55–1.65 (d, CH_3); 5.65–5.9 (q, CH); 6.45 (s, CH); 6.8–8.0 (m, 15 H_{arom})
3ab	C_6H_5	H	C_2H_5	CH_3	90	114–116°	$C_{19}H_{20}N_2$ (276.4)	1.1–1.3 (t, CH_3); 1.45–1.55 (d, CH_3); 2.25–2.55 (q, CH_2); 5.45–5.7 (q, CH); 5.85 (s, CH); 6.7–7.5 (m, 10 H_{arom})

[a] The microanalyses for all products were in satisfactory agreement with the calculated values (C ±0.23, H ±0.24, N ±0.18).

[b] Measured at 90 MHz with a Varian EM-390 spectrometer.

Table 2. 1,2-Dihydropyrimidines **3** from Diimines **1** and Acetals

Product	R^1	R^2	R^3	R^4	R^5	Yield [%]	m.p. or b.p./torr	Molecular formula[a]	^{1}H-N.M.R. (CCl_4)[b] δ [ppm]
3ac	C_6H_5	CH_3	4-H_3C—C_6H_4	CH_3	CH_3	92	154–155°	$C_{26}H_{26}N_2$ (366.5)	1.55 (s, 2CH_3); 1.75 (s, CH_3); 2.3 (s, CH_3); 6.7–7.7 (m, 14H_{arom})
3ad	C_6H_5	CH_3	C_6H_5	CH_3	CH_3	93	130°/0.001	$C_{25}H_{24}N_2$ (352.5)	1.6 (s, 2CH_3); 1.8 (s, CH_3); 6.8–7.7 (m, 15H_{arom})
3ae	2-H_3C—C_6H_4	CH_3	C_6H_5	CH_3	CH_3	90	129–131°	$C_{26}H_{26}N_2$ (366.5)	1.55 (s, 2CH_3); 1.8 (s, CH_3); 2.2 (s, CH_3); 6.8–7.6 (m, 14H_{arom})
3af	C_6H_5	H	C_2H_5	CH_3	CH_3	85	85°/0.001	$C_{20}H_{22}N_2$ (290.4)	1.15–1.3 (t, CH_3); 1.55 (s, 2CH_3); 2.2–2.45 (q, CH_2); 5.8 (s, CH); 6.9–7.5 (m, 10H_{arom})
3ag	2-H_3C—C_6H_4	CH_3	4-H_3C—C_6H_4	C_6H_5—CH_2	H	70	143–145°	$C_{32}H_{30}N_2$ (442.6)	1.9 (s, CH_3); 2.0 (s, CH_3); 2.4 (s, CH_3); 3.1–3.2 (d, CH_2); 5.3–5.45 (t, CH); 6.7–7.5 (m, 18H_{arom})
3ah	C_6H_5	CH_3	C_6H_5	C_6H_5—CH_2	H	80	146–148°	$C_{30}H_{26}N_2$ (414.6)	2.0 (s, CH_3); 3.1–3.2 (d, CH_2); 5.65–5.8 (t, CH); 6.3–7.6 (m, 20H_{arom})
3ai	C_6H_5	H	C_6H_5	C_6H_5—CH_2	H	75	160–161°	$C_{29}H_{24}N_2$ (400.5)	3.1–3.3 (m, CH_2); 5.65–5.8 (q, CH); 6.2–8.0 (m, 21H_{arom})
3aj	2-H_3C—C_6H_4	CH_3	4-H_3C—C_6H_4	H	H	85	98°/0.01	$C_{25}H_{24}N_2$ (352.5)	2.0 (s, CH_3); 2.35 (s, CH_3); 2.4 (s, CH_3); 5.1 (s, CH_2); 6.8–7.6 (m, 13H_{arom})
3ak	c-C_6H_{11}	CH_3	4-H_3C—C_6H_4	H	H	81	100°/0.001	$C_{24}H_{28}N_2$ (344.5)	0.9–1.8 (m, CH_2); 1.5 (s, CH_3); 2.3 (s, CH_3); 2.5–2.9 (m, CH—N); 4.8 (s, CH_2); 7.0–7.6 (m, 9H_{arom})
3al	C_6H_5	CH_3	4-H_3C—C_6H_4	H	H	90	110°/0.001	$C_{24}H_{22}N_2$ (338.5)	1.9 (s, CH_3); 2.3 (s, CH_3); 5.3 (s, CH_2); 6.8–7.7 (m, 14H_{arom})
3am	C_6H_5	CH_3	C_6H_5	H	H	90	115°/0.001	$C_{23}H_{20}N_2$ (324.4)	1.9 (s, CH_3); 5.25 (s, CH_2); 6.8–7.7 (m, 15H_{arom})

[a] The microanalyses for all products were in satisfactory agreement with the calculated values (C ±0.22, H ±0.17, N ±0.16).

[b] Measured at 90 MHz with a Varian EM-390 spectrometer.

until basic. The mixture is extracted with ether, all solvent is removed from the ether extract under reduced pressure, and the crude solid recrystallised from hexane; yield: 2.9 g (87 %); m.p. 186–188°.

$C_{30}H_{26}N_2$	calc.	C 86.92	H 6.32	N 6.76
(414.5)	found	87.02	6.08	6.74

M.S.: m/e = 414 (M^+), 337, 310, 194, 91.

I.R. (nujol): $\nu_{C=N} = 1630\ cm^{-1}$.

Dihydropyrimidines can be obtained by a similar procedure via acetals. Longer reaction times (48 h) have to be used in these cases.

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[1] H. Hoberg, J. Barluenga, *Synthesis* **1970**, 363.

[2] V. Gómez Aranda, J. Barluenga, V. Gotor, S. Fustero, *Synthesis* **1974**, 720.

[3] J. Barluenga, S. Fustero, V. Gotor, *Synthesis* **1975**, 191.

[4] H. Hoberg, J. Barluenga, *Synthesis* **1970**, 142.

[5] Reaction of **1** with acetaldehyde, propanal, and butanal are performed at the reflux temperature of the corresponding aldehyde.

[6] Product **1** does not react at 65° with acetone even in large excess and reaction times over 100 h. Reactions with acetophenone or propiophenone at 150° lead to the decomposition of the starting diimine **1**.

[7] Reactions with phenylacetaldehyde at 90° and $AlCl_3$ as the catalyst lead to the recovery of the starting diimine **1** and to the polymerisation of the aldehyde.

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