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The 'Eenie–Meenie reaction'. Displacement reactions of bisanilinopyrimidines

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Abstract—A novel acid-catalysed nucleophilic displacement reaction of pyrimidines is described, involving quinone–methide type chemistry. A wide range of nucleophiles can be tolerated. A similar mechanism is also applied to the synthesis of a tricyclic system.

During our quest to find a novel anti-cancer agent, we have discovered an unexpected and previously unreported reaction of 5-substituted 2,4-bisanilinopyrimidines. Few methods are described for the preparation of these compounds. We wished to explore this area further, with the aim of developing new pharmacologically active molecules.

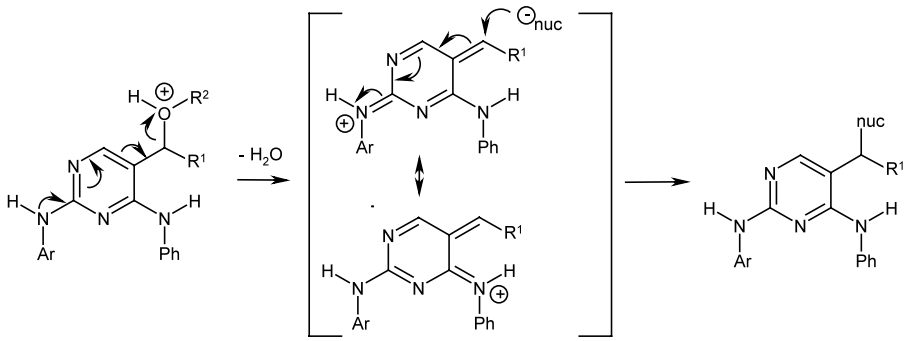
We have found that 5-(alkoxymethyl)-2,4-bisanilinopyrimidines[1,2] undergo acid-catalysed displacement with a wide range of nucleophiles (Scheme 1).

The intermediate cation is stabilised by the mesomeric donating effects of the two anilines. This stabilised species contains *ene* and *iminium* functionalities; therefore, we have named this process '*the Eenie–Meenie reaction*'. Similar nucleophilic displacements have been described for 4,4′-dimethoxybenzhydrol.[3] We believe this is the first example of quinone–methide type chemistry applied to a heteroaromatic system.

2,4-Bisanilino-5-(ethoxymethyl)pyrimidine **1** is easily prepared by sequential nucleophilic displacements of the known 2,4-dichloro-5-(ethoxymethyl)pyrimidine[2] in a two stage process with optionally substituted anilines (Scheme 2).

Treatment of **1** with nucleophiles in the appropriate solvents under acidic catalysis at 100°C gives novel 5-substituted pyrimidines.[4,6] A wide range of nucleophiles is tolerated, including alcohols, amides, ureas, anilines, various substituted heterocycles and amines (Table 1).

A similar 'Eenie–Meenie' mechanism can be applied to pyrimidines bearing hydroxymethyl anilines in the 2- or



Scheme 1. $R^1 = H$, Ph; $R^2 = H$, alkyl.

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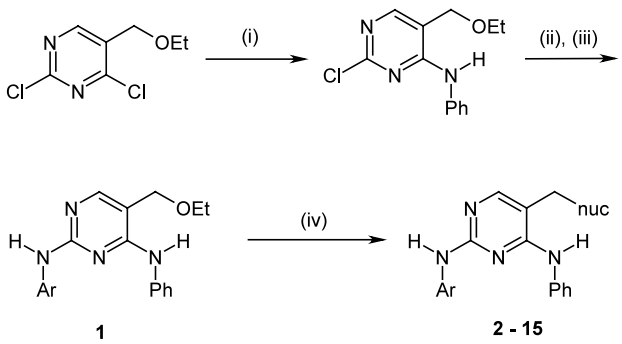


Scheme 2. *Reagents and conditions*: (i) $PhNH_2$, Et^iPr_2N, *n*-BuOH, 100°C, 16 h; (ii) *p*-$H_2NC_6H_4OCH_2CH(OH)CH_2NMe_2 \cdot 2HCl$, *n*-BuOH, MeOH, 100°C, 16 h; (iii) EtOH, 100°C, 16 h; (iv) nucleophile, $Et_2O \cdot HCl$, 100°C.

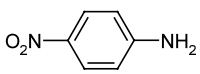
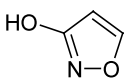
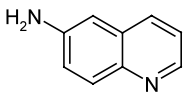
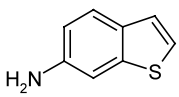
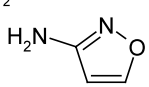
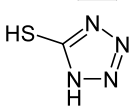
4-positions. Treatment of **16** with 4-aminobenzyl alcohol in *n*-butanol under acidic catalysis gave **17**.[5] We propose the following mechanism (Scheme 3).

Reaction of **16** with 2-aminobenzyl alcohol in *n*-butanol under acidic catalysis generates a similar 'Eenie–Meenie' intermediate, which undergoes electrocyclic rearrangement to generate the novel pyridoquinazoline system **18** (Scheme 4). The regioselectivity of the cyclisation was confirmed by NOE ^1H NMR. A strong NOE is seen from Ha to Hb and Hc; the alternative isomer **19** would only show one NOE, from Hd to He. Formation of **19** was not observed, presumably due to the lower electron density on the 3-nitrogen relative to the 1-nitrogen of the pyrimidine ring.

The reaction of **1** with 3-aminobenzyl alcohol under the same conditions gave only formation of the initial bisanilinopyrimidine, as there can be no mesomeric stabilisation of the benzylic cation at the 3-position.

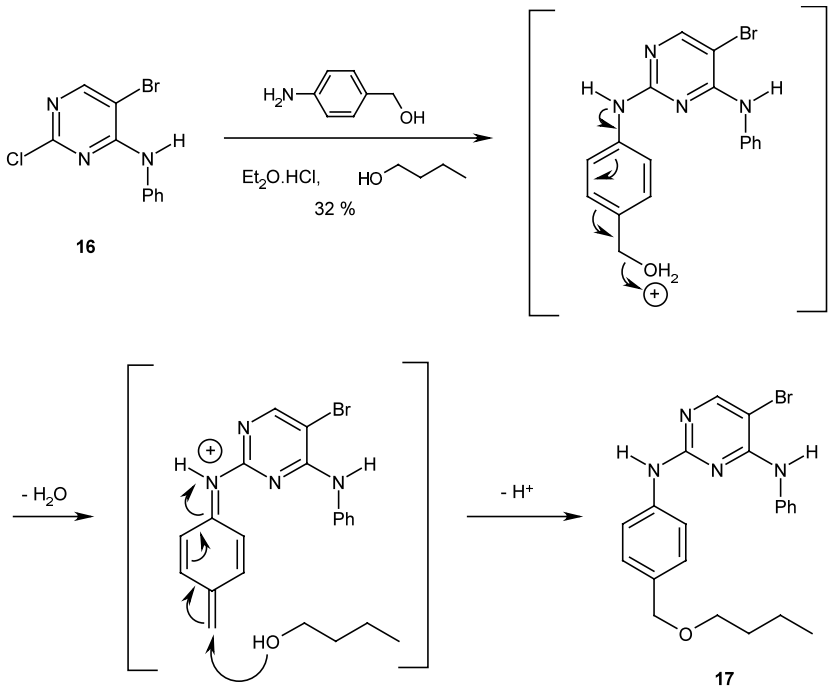
Further applications of this reaction will appear in future publications.

Table 1. Reactions of **1** with various nucleophiles

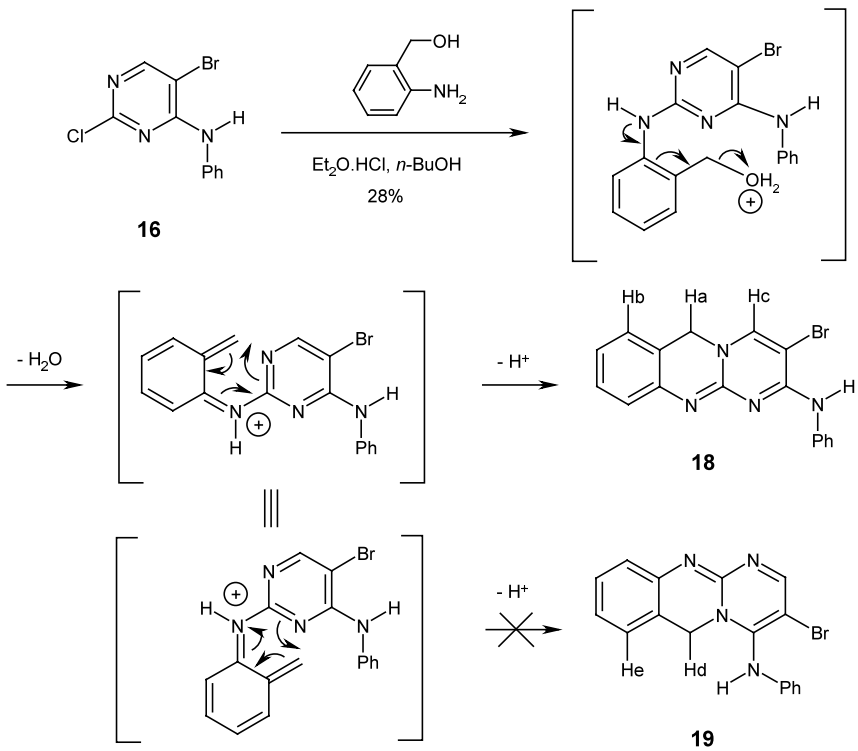
Product	Nucleophile	Solvent	No. of equiv.	Time/h	Yield
2	H_2O	solvolysis		3	75
3	$HOCH_2CH_2OH$	solvolysis		16	100
4	$PhCH_2OH$	solvolysis		16	100
5	$MeCONH_2$	dioxan	2	16	18
6	H_2NCONH_2	dioxan	1.2	16	28
7		dioxan	1.2	16	44
8	imidazole	dioxan	1.2	16	25
9		NMP	2	16	62
10		NMP	2	2	69
11		NMP	2	2	31
12		NMP	2	2	24
13		NMP	2	2	45
14	$MeNH_2$	NMP	2.5	2[a]	33
15	Me_2NH	DMF	1.2	4[b]	38

[a]Reaction performed at 160°C

[b]Reaction performed at 120°C



Scheme 3. Reaction with 4-aminobenzyl alcohol.



Scheme 4. Reaction with 2-aminobenzyl alcohol.

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2. Brossmer, R.; Röhm, E. *Justus Leibigs Ann. Chem*. **1966**, *692*, 119–133.
3. Hennuse, C.; Boxus, T.; Tesolin, L.; Pantano, G.; Marchant-Brynaert, J. *Synthesis* **1996**, 495–501.
4. In a typical procedure, the nucleophile (0.50 mmol) and Et_2O·HCl (0.50 mmol) were added to a solution of bisanilinopyrimidine **1** (0.25 mmol) in 3 ml *N*-methyl pyrrolidinone, and the mixture was heated to 100°C for 2 h. The reaction was monitored by TLC. The solution was cooled to room temperature and 30 ml Et_2O were added, causing a solid or gum to fall out of solution. The supernatant was decanted off and the residue purified by flash chromatography (MeOH/DCM system, containing 0.5% conc. aqueous ammonia).
5. 4-Anilino-5-bromo-2-chloropyrimidine (626 mg, 2.20 mmol) and 4-aminobenzyl alcohol (246 mg, 2.00 mmol) were dissolved in *n*-butanol (20 ml). Ethereal HCl (1 M, 4.00 ml, 4.00 mmol) was added at room temperature, and the solution heated at 100°C for 16 h. The yellow solid, which precipitated was removed by filtration, and the filtrate was concentrated in vacuo. The crude product was twice purified by flash chromatography (firstly eluting with DCM, then eluting with 0–15% EtOAc in *iso*-hexane). Product (**17**) (270 mg, 32%) was obtained as a white solid.
6. **Selected data**: Chemical shifts are reported relative to tetramethylsilane, and coupling constants are reported in Hertz. **1**: ^{1}H NMR ($CDCl_3$): $\delta=1.28$ (3H, t, $J=6.5$), 2.33 (6H, s), 2.3–2.6 (2H, m), 3.54 (2H, q, $J=6.5$), 3.97 (2H, d, $J=4.4$), 4.07 (1H, m), 4.48 (2H, s), 6.87 (2H, d, $J=8.5$), 6.89 (1H, s), 7.08 (1H, t, $J=7.0$), 7.31 (2H, dd, $J=7.0$, 8.1), 7.44 (2H, d, $J=8.5$), 7.57 (2H, d, $J=8.1$), 7.87 (1H, s), 7.93 (1H, br. s); MS (M+H$^+$) 438.5. **3**: ^{1}H NMR ($CDCl_3$): $\delta=2.34$ (6H, s), 2.3–2.6 (2H, m), 3.63 (2H, t, $J=5.0$), 3.73 (1H, s), 3.86 (2H, t, $J=5.0$), 3.96 (2H, d, $J=4.5$), 4.08 (1H, m), 4.54 (2H, s), 6.86 (2H, d, $J=8.5$), 6.88 (1H, s), 7.08 (1H, t, $J=7.0$), 7.30 (2H, dd, $J=7.0$, 7.4), 7.43 (2H, d, $J=8.5$), 7.58 (2H, d, $J=7.4$), 7.88 (2H, m); MS (M+H$^+$) 454.3. **9**: ^{1}H NMR ($CDCl_3$): $\delta=2.20$ (6H, s), 2.25–2.5 (2H, m), 3.75–3.9 (3H, m), 4.79 (1H, br. s), 5.06 (2H, s), 6.05 (1H, d, $J=2.5$), 6.80 (2H, d, $J=8.3$), 7.02 (1H, t, $J=7.3$), 7.29 (2H, dd, $J=7.3$, 7.9), 7.50 (2H, d, $J=8.3$), 7.70 (2H, dd, $J=7.9$), 8.05 (1H, s), 8.54 (1H, d, $J=2.5$), 8.73 (1H, s), 9.07 (1H, s); MS (M+H$^+$) 477.5. **17**: ^{1}H NMR (DMSO-d_6): $\delta=0.87$ (3H, t, $J=6.7$), 1.31 (2H, tq, $J=6.7$, 6.7), 1.49 (2H, tt, $J=6.7$, 6.7), 3.36 (2H, t, $J=6.7$), 4.31 (2H, s), 7.07 (2H, d, $J=7.8$), 7.13 (1H, t, $J=7.4$), 7.35 (2H, dd, $J=7.4$, 8.1), 7.54 (2H, d, $J=8.1$), 7.60 (2H, d, $J=7.8$), 8.20 (1H, s), 8.75 (1H, s), 9.30 (1H, s); MS (M+H$^+$) 427.3, 429.3. **18**: ^{1}H NMR (DMSO-d_6): $\delta=4.92$ (2H, s), 6.85–6.95 (3H, m), 6.95–7.0 (2H, m), 7.12 (1H, d, $J=6.9$) 7.15–7.25 (3H, m), 7.69 (1H, s), 10.0 (1H, br. s); MS (M+H$^+$) 352.9, 354.9.