N-Alkylation of Pyrimidine and Purine Derivatives (Uracils, Xanthines, Adenine) using Solid/Liquid Phase-Transfer Catalysis without Solvent

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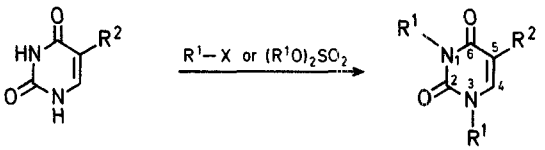
The *N*-alkylation of pyrimidine and purine derivatives has attracted interest in connexion with the investigation of carcinogenesis[1] and as an access to therapeutic agents such as

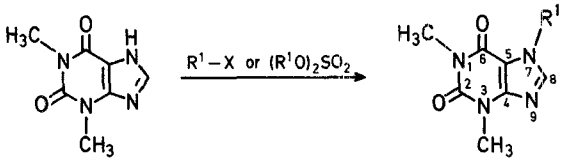
antiviral adenine dervivatives[2] and antimitotic pyrimidine derivatives[3]. Most of the known methods for the alkylation of an anionic (deprotonated) N—H group[4-11] have been used with pyrimidine and purine derivatives, recent work including alkylation using potassium fluoride on alumina[12] or tetrabutylammonium fluoride[13] as a base or using liquid/liquid phase-transfer catalysis[14,15].

It has recently been shown that acetate[16], alkoxide[17], fluoride[18], and indole[19] anions can be efficiently alkylated without the use of a solvent in the presence of catalytic amounts of quaternary ammonium salts. We describe here the alkylation of uracils (**1, 2, 3**), xanthines (**4, 5, 6**), and adenine (**11**) using phase-transfer catalysis under these conditions.

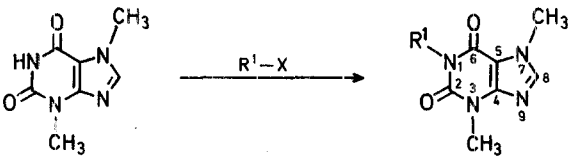


1 R^2 = H
2 R^2 = CH_3
3 R^2 = F

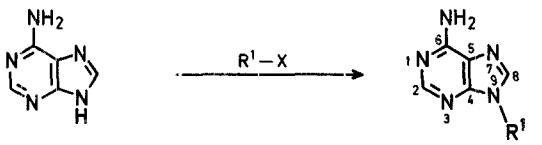
4 R^2 = H
5 R^2 = CH_3
6 R^2 = F



7 **8**



9 **10**



11 **12**

From the results obtained, our method appears to be superior to reported procedures. Thus, an only 22% yield has been reported for the alkylation reaction leading to **10e**[15] and compounds **4e** and **8e** did not form at all under the conditions of Ref.[15], whereas our method affords the mentioned three products in 80% yield. Further, our method requires smaller amounts of catalyst (3%, for each nucelophilic site) than the reported phase-transfer procedures.

For comparison, we also tested other heterogeneous-phase procedures: methylation of uracil (**1**) impregnated on basic alumina or on silica gel in dry media[20] using dimethyl sulfate afforded lower yields of methylation product **1a**; with iodomethane, no alkylation took place (Table 2).

In summary, the procedure described here does not require the use of a reaction solvent, the reaction time is short and work-up simple, and the yields are high.

Table 1. *N*-Alkylation of Pyrimidine and Purine Derivatives in the Absence of Solvent or Support

Product	Alkylating Agent	Catalyst[a]	Reaction Temperature [°C]	Yield [%]	m.p. [°C]	Molecular Formula[b] or m.p. [°C] reported
4a	$(H_3CO)_2SO_2$	TBAB	20°	96	119°	120°[22]
4b	C_6H_5—CH_2—Br	TBAB	20°	38	75.5°	76°[14]
		TBAB	80°	96		
	C_6H_5—CH_2—Cl	TBAB	20°	47		
		Aliquat 336	20°	58		
		18-Crown-6	20°	63		
		TBAF	20°	87		
		—	20°	0		
4c	*n*-C_4H_9—Br	Aliquat 336	80°	63	oil	$C_{12}H_{20}N_2O_2$ (297.2)
4d	*n*-C_8H_{17}-Br	Aliquat 336	80°	61	oil	$C_{20}H_{36}N_2O_2$ (336.5)
4e	*n*-$C_{18}H_{37}$—Br	Aliquat 336	80°	98	83°	$C_{40}H_{76}N_2O_2$ (617.1)
5b	C_6H_5—CH_2—Br	TBAB	20°	53	90°	91°[14]
		TBAB	80°	98		
6b	C_6H_5—CH_2—Br	TBAB	20°	34	oil	oil[23]
		TBAB	80°	79		
8a	$(H_3CO)_2SO_2$	Aliquat 336	20°	90	234–235°	235°[15]
8b	C_6H_5—CH_2—Cl	TBAB	20°	75	153–156.5°	156°[15]
8d	*n*-C_8H_{17}—Br	Aliquat 336	80°	96	41.5°	$C_{15}H_{24}N_4O_2$ (292.4)
8e	*n*-$C_{18}H_{37}$—Br	Aliquat 336	80°	96	79.5°	$C_{25}H_{44}N_4O_2$ (432.6)
10b	C_6H_5—CH_2—Cl	Aliquat 336	80°	97	138–139°	140°[15]
10d	*n*-C_8H_{17}—Br	Aliquat 336	80°	75	65.5°	$C_{15}H_{24}N_4O_2$ (292.4)
10e	*n*-$C_{18}H_{37}$—Br	Aliquat 336	80°	87	79°	$C_{25}H_{44}N_4O_2$ (432.6)
12b	C_6H_5—CH_2—Cl	Aliquat 336	80°	47	230–232°	234°[15]
12d	*n*-C_8H_{17}—Br	Aliquat 336	80°	52	127–128.5°	$C_{13}H_{21}N_5$ (247.3)

[a] TBAB = $(n\text{-}C_4H_9)_4N^{\oplus}Br^{\ominus}$; Aliquat 336 = (essentially) $H_3C(n\text{-}C_8H_{17})_3N^{\oplus}Cl^{\ominus}$; TBAF = $(n\text{-}C_4H_9)_4N^{\oplus}F^{\ominus}$.
[b] The microanalyses were in good agreement with the calculated values: C ±0.19, H ±0.19, N ±0.21.

Table 2. Reaction of Uracil (**1**) with Methylating Agents in the Presence of a solid Support and in the Absence of a Solvent, using TBAB as Catalyst

Methylating Agent	Solid Support	Yield of **4a** [%]
$(H_3CO)_2SO_2$	alumina/$NaOCH_3$	63
H_3C—J	alumina/$NaOCH_3$	0
$(H_3CO)_2SO_2$	silica gel/$NaOCH_3$	40
H_3C—J	silica gel/$NaOCH_3$	0

Table 3. ^{1}H-N.M.R. ($CDCl_3$/TMS_{int}) Data of Alkylation Products **4**, **5**, **6**, **8**, **10**, **12** (unless otherwise stated)

Compound	δ [ppm]
4a	3.40 (s, 3H); 3.53 (s, 3H); 5.73 (d, 1H); 7.2 (d, 1H)
4b	4.76 (s, 2H); 5.1 (s, 2H); 5.56 (d, 1H); 7.00 (d, 1H); 7.1–7.5 (m, 10H)
4c	0.90 (t, 3H); 0.94 (t, 3H); 1.10–1.88 (m, 8H); 3.8 (t, 3H); 3.97 (t, 3H); 5.53 (d, 2H); 7.16 (d, 2H)
4d	0.80 (t, 3H); 0.90 (t, 3H); 1.10–1.83 (m, 24H); 3.78 (t, 2H); 3.86 (t, 2H); 5.53 (d, 1H); 7.16 (d, 1H)
4e	0.84 (t, 3H); 0.9 (t, 3H); 1.10–1.85 (m, 60H); 3.64 (t, 2H); 3.85 (t, 2H); 5.66 (d, 1H); 7.1 (d, 1H)
5b	1.94 (s, 3H); 4.94 (s, 2H); 5.27 (s, 2H); 7.00 (s, 1H); 7.16–7.66 (m, 10H)
6b	4.74 (s, 2H); 5.16 (s, 2H); 7.10–7.66 (m, 11H)[a]
8a	3.43 (s, 3H); 3.63 (s, 3H); 4.06 (s, 3H); 7.80 (s, 1H)
8b	3.39 (s, 3H); 3.66 (s, 3H); 5.06 (s, 2H); 7.33 (s, 1H)
8d	0.84 (t, 3H); 1.22–1.58 (m, 10H); 1.68–2.16 (m, 4H); 3.32 (s, 3H); 3.48 (s, 3H); 4.32 (t, 2H); 7.6 (s, 1H)
8e	0.84 (t, 3H); 1.00–1.44 (m, 30H); 1.64–2.04 (m, 2H); 3.40 (s, 3H); 4.64 (s, 3H); 4.24 (t, 2H); 7.48 (s, 1H)
10b	3.60 (s, 3H); 3.97 (s, 3H); 5.51 (s, 2H); 7.20–7.66 (m, 5H); 7.5 (s, 1H)
10d	0.93 (t, 3H); 1.10–1.88 (m, 12H); 3.56 (s, 3H); 4.06 (s, 3H); 4.03 (t, 2H); 7.53 (s, 1H)
10e	0.90 (t, 3H); 1.16–1.93 (m, 32H); 3.60 (s, 3H); 4.01 (t, 2H); 4.06 (t, 3H)
12b	[b]5.41 (s, 2H); 7.23 (br. s, 2H); 7.33 (s, 5H); 8.20 (s, 1H); 8.30 (s, 1H)
12d	0.90 (t, 3H); 1.04–1.5 (m, 10H); 1.80–2.06 (m, 2H); 4.13 (t, 2H); 6.1 (br. s, 2H); 7.64 (s, 1H); 8.24 (s, 1H)

[a] The signal of the pyrimidine H is superimposed by that of the aromatic protons.
[b] Solvent DMSO-d_6.

A Heidolph apparatus was used for shaking the reaction mixture at room temperature; a magnetic stirrer was used when the reaction mixture was heated. Melting points were not corrected. The ^{1}H-N.M.R. spectra were recorded on a Varian EM 390 spectrometer.

***N*-Alkylation of *NH*-Heterocyclic Compounds (1, 2, 3, 7, 9, 11); General Procedure:**

A mixture of the *NH*-heterocyclic compound (10 mmol), potassium hydroxide (0.67 g, 11.5 mmol, for each alkylation site), and catalyst (see Table 1; 0.3 mmol) is shaken at room temperature or stirred (if the mixture is heated) at the temperature given in Table 1. After 2 h, the alkylating agent (see Table 1; 10 mmol for each alkylation site) is added and shaking or stirring is continued for another hour. The mixture is then cooled, if necessary, and Florisil® (0.5 g) is added and the mixture extracted with dichloromethane (3 × 20 ml). The extract is evaporated in vacuo and the residual product purified by recrystallization from ethyl acetate (for **4e**), diisopropyl ether (for **10d**, **10e**, and **12e**), acetone (for **8e**), or chloroform (for **8d**) or by column chromatography on silica gel using ether (for **4c**), ethyl acetate/dichloromethane (1/9; for **12b**) or dichloromethane/acetone (1/1; for **12d**) as eluent.

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