Dynamic Protection of Amines using 18-Crown-6

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Summary The regioselectivity of diamine monoacylation has been controlled by selective complexation with 18-crown-6 and a proton source

RECENTLY we reported a convenient method for the selective acylation of secondary amines in the presence of primary amines [1] 18-Crown-6 forms complexes with alkylammonium salts *via* three hydrogen bonds and pole–dipole interactions in the 2 7 Å cavity [2] We expected that rapid selective complexation of one (or more) ammonium function(s) in a polyamine substrate should permit selective functionalisation of uncomplexed sites Since dialkylammonium salts form less stable complexes owing to a reduction in hydrogen bonding, selective acylation of a secondary amino function in the presence of a primary is possible

Herein we report dramatic improvements in diamine monoacylation using dynamic protection (Table 1) For example the reaction of *N*-methylethylenediamine with benzoyl and toluene-4-sulphonyl chlorides in sequence† gave *N*-benzoyl-*N*-methyl-*N'*-toluene-4-sulphonylethylenediamine (16%) In the presence of 18-crown-6 the yield was increased to 79% Surprisingly (entries 8—19) the selective monobenzoylation of ethylenediamine and homologues was also improved in the presence of 18-crown-6

The decrease in stability of crown–primary alkylammonium salt complexes with increasing steric congestion[3] should permit the selective acylation of a hindered primary amine in the presence of a non-hindered function Such selection is relevant to aminoglycoside chemistry As model systems, competition in the acylation and toluene-4-sulphonylation of mixtures of benzylamine and benzhydrylamine or 3α-(axial) and 3β-(equatorial) amino-5α-cholestanes[4] were studied (Table 2) Without crown ether the less hindered (benzyl- or 3β- respectively) amine was principally functionalised In the presence of 18-crown-6 the ratio of hindered non hindered amides was increased Consistent with sterically selective complexation[3] dicyclohexyl 18-crown-6 (entries 10, 11) was superior to 18-crown-6 In the steroid examples exclusive axial substitution was observed in the presence of *N*-benzylmono-aza-18-crown-6 [5]

The advantage of the aza-crown was emphasised by competition experiments between benzylamine and *N*-benzyl-iso-propylamine Since the rate of tosylation of the latter was slow, a 62% yield of *N*-benzyl-*N*-isopropyltoluene-4-sulphonamide was only obtained when the

TABLE 1 Selective acylation of diamines $RNH[CH_2]_nNH_2$[a]

Entry	Equiv of 18-crown-6	Percentage yields of products $RN(Ts)[CH_2]_n$-NHTs	$RN(COAr)[CH_2]_n$NHTs	$RN(Ts)[CH_2]_n$-NHCOAr	$RN(COAr)[CH_2]_n$-NHCOAr
1	0[b]	30	16	0·2	37
2	1	12	63	traces	4
3	2	traces	79	traces	15
4	0[b]	40	1	4	42
5	1	12	51	1	11
6	2	6	61	0 8	8
7	2	0	69	0	22
8	0[b]	43	8	—	27
9	1	20	56	—	17
10	2	4	76	—	3
11	0[b]	40	6	—	34
12	1	11	41	—	26
13	2	5	79	—	10
14	0[b]	42	1	—	47
15	1	18	49	—	23
16	2	5	64	—	24
17	0[b]	37	0	—	45
18	1[b]	15	31	—	29
19	2[b]	9	32	—	32

[a] R = Me (entries 1—7) and H (8—19) Ar = Ph (1—3, 7—19) and C_6H_4-4-NO_2 (4—6), n = 2 (1—6, 8—10), 3 (7, 11—13), 4 (14—16) and 8 (17—19) Typically benzoyl chloride and triethylamine were added in sequence to *N*-methylethylenediammonium di(toluene-4-sulphonate) and 18-crown 6 (1 mmol each) in dichloromethane (10 ml) When reactions were complete (t l c) toluene-4-sulphonyl chloride (1 mmol), triethylamine (4 mmol), and an excess of potassium chloride were added Yields refer to pure compounds isolated by direct chromatography on Merck Kieselgel H [b] Heterogeneous reactions It must be assumed that the high yield of RN(COAr)$[CH_2]_n$NHCOAr in the blank reactions followed in part from the low solubility of the $RNH_2^+[CH_2]_nNH_3^+2TsO^-$ salts How, ever, the increase in the yield of $RN(COAr)[CH_2]_nNH$ 1s with increase in crown ether from 1 to 2 equiv is consistent only with selective complexation

† The diamine was used as its di-toluene-4-sulphonate and, to facilitate chromatographic separation, after acylation remaining amino functions were toluene-4-sulphonylated

TABLE 2. Selective acylation and sulphonylation of amines[a]

Entry	Equiv of crown ether	Amine	Ammonium salt	% Amides[b]	Hindered amide[b] mol fraction
1	0[c]	$PhCH_2NH_2$	$Ph_2CHNH_3^+TsO^-$	96	0·61
2	1	"	"	85	0·78
3	2	"	"	79	1·00
4	0[c]	"	"	93	0·31
5	1	"	"	92	0·47
6	2	"	"	95	0·52
7	0[c]	"	"	95	0·04
8	1	"	"	97	0·30
9	2	"	"	91	0·44
10	1	"	"	98	0·59
11	2	"	"	98	0·71
12	0[c]	$PhCH_2NH_2$	$PhCH_2Pr^iNH_2^+TsO^-$	100	⩽0·02
13	1	"	"	98	0·31
14	2	"	"	99	0·46
15	2	"	"	96	0·60
16	1	"	"	97	0·55
17	2	"	"	97	0·62
18	2	"	"	95	0·65
19	0	3β- : 3α-Amino-5α-cholestanes: CF_3CO_2H 1 : 1 : 1		83	0·12
20	1	"		85	0·40
21	2	"		81	0·59
22	0	"		96	0·26
23	1	"		88	0·47
24	2	"		88	0·70
25	1	"		84	1·0
26	2	"		87	1·0

[a] Reactions were carried out using 18-crown-6 (entries 2, 3, 5, 6, 8, 9, 13—15, 20, 21, 23, and 24), dicyclohexyl-18-crown-6 (Fluka AG) (10, 11), and *N*-benzylmono-aza-18-crown-6 (16—18, 25, 26) with $(CF_3CO)_2O$ (1—3), PhCOCl (4—6), TsCl (7—18, 22—26), or Ac_2O (19—21) as electrophile. [b] The ratios of amides were determined by n.m.r. spectroscopy (± 0·02) (entries 12—18); all other ratios refer to pure isolated compounds. Typically toluene-4-sulphonyl chloride and then, over 5 min, triethylamine (1 mmol each) were added to a solution prepared from 18-crown-6, benzylamine, and benzhydrylammonium toluene-4-sulphonate (1 mmol each) in dichloromethane (10 ml) [or (entries 19—26) from 3α- and 3β-amino-5α-cholestanes and CF_3CO_2H (1 : 1 : 1)]. Chromatography on Merck Kieselgel H gave *N*-benzyl (0·68 mmol) and *N*-benzhydryl- (0·29 mmol) toluene-4-sulphonamides. In entries 15 and 18 the triethylamine was added over 1 week. [c] Heterogeneous reactions.

triethylamine was added slowly (1 week rather than 5 min) after the toluene-4-sulphonyl chloride (Table 2, entry 18).

Clearly dynamic protection provides a more convenient simple alternative to classical protection group methodologies.

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