Selective *N*-Protection of Medium-ring Triamines

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Efficient schemes for selective *N*-protection of 1,4,7-triazacyclononane and 1,5,9-triazacyclododecane and for synthesis of related bis-coronands are based upon the synthetic intermediacy of tricyclic orthoamides.

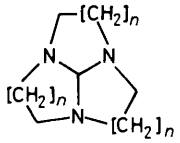
Interest in azacoronands (medium and macrocyclic polyamines) bearing pendant arms is currently high, because of the possibilities these systems offer for systematic variation of the type of ligand donor group and geometry of metal-ion complexation.

Consequently, efficient synthetic methods for preparation of selectively protected precursors are essential. Available methods have recently been reviewed by Kaden.[1] Most approaches to date have involved selective protection of a ring segment prior to cyclization by Stetter–Richman–Atkins methods.[2] While most of the reported work in this area has been directed toward macrocyclic tetra-amines,[1,3] Bulkowski and his co-workers have applied the methodology to the synthesis of selectively protected medium-ring triamines.[4]

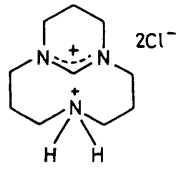
As part of an effort aimed at synthesis and complexation studies of triazacoronands bearing pendant arms, we have developed short, efficient, and conceptually novel syntheses of *N*-protected derivatives of 1,4,7-triazacyclononane (9[ane]N_3) (**1**) and 1,5,9-triazacyclododecane (12[ane]N_3) (**2**).

We report herein methods for synthesis of derivatives (**3**)—(**9**).† The general approach relies upon the introduction of a single *N*-formyl group masked as a tricyclic orthoamide and subsequent reaction of the orthoamide functional group. Thus, (**1**) and (**2**) (prepared by the literature method[2]) were treated with 1 equiv. of $Me_2NCH(OMe)_2$ (85 °C, 3 h) to give orthoamides (**10**) and (**11**), respectively, in typical yields of *ca.* 90%.[5] Monoprotection of (**1**) was achieved by hydrolytic unmasking of (**10**) and diprotection was effected by subsequent reaction with toluene-*p*-sulphonyl chloride (TsCl) followed by hydrolytic removal of the formyl group (Scheme 1). Compound (**5**) has also been reported by Bulkowski[4] and by Wieghardt *et al.*,[6] the latter workers preparing it by statistical tosylation of (**1**) followed by separation from tritosyl-(**1**). Our attempts to apply the approach of Scheme 1 to synthesis of selectively protected (**2**) met with failure. Treatment of (**11**) with aqueous HCl gave bicyclic amidinium salt (**12**) quantitatively, as previously reported by Wuest.[7] Interestingly, treatment of (**12**) with aqueous NaOH, the usual conditions for amidinium salt hydrolysis, simply regenerated (**11**). (Compare this behaviour with that of acyclic orthomides, which are instantly hydrolysed in H_2O.) Reaction of (**11**) with aqueous HCl at elevated temperatures or for extended periods led to the slow formation of hydrochlorides of (**2**) and we were able to isolate any *N*-formyl derivative of (**2**).

A successful alternative scheme for protection of (**2**) which relies upon irreversible bicyclic amidinium salt formation is shown in Scheme 2. Orthoamide (**11**) was monoalkylated cleanly by $PhCH_2Br$ to yield the stable salt (**13**) [i.r.(KBr)



(**10**; *n* = 1)
(**11**; *n* = 2)

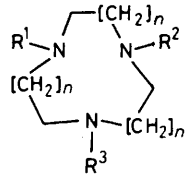


(**12**)

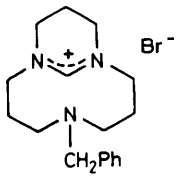
Scheme 1

(**10**) —a→ (**3**) —b→ (**4**) —c→ (**5**)
(81—87%) (81%) (92%)

Reagents: a, (i) 2.8 M aq. HCl, 25 °C, 7 h; (ii) aq. NaOH (pH 10), 0 °C, immediate $CHCl_3$ extraction; b, TsCl (2.1 equiv.), Et_3N (22.5 equiv.), tetrahydrofuran (THF), 25 °C, 24 h; c, NaOH (25 equiv.), EtOH, reflux, 22 h.



	n	R^1	R^2	R^3
(**1**)	1	H	H	H
(**2**)	2	H	H	H
(**3**)	1	CHO	H	H
(**4**)	1	CHO	Ts	Ts
(**5**)	1	H	Ts	Ts
(**6**)	2	H	CHO	CH_2Ph
(**7**)	2	Ts	CHO	CH_2Ph
(**8**)	2	Ts	H	CH_2Ph
(**9**)	1	H	CHO	CH_2Ph



(**13**)

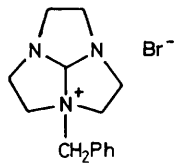
Scheme 2

(**11**) —d→ (**13**) —e→ (**6**)
(96%) (81%)

—f→ (**7**) —g→ (**8**)
(72%) (92%)

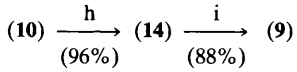
Reagents: d, $PhCH_2Br$ (1.1 equiv.), $CHCl_3$ 25 °C, 1.5 h; e, 0.34 M-aq. NaOH (3.0 equiv.), Et_2O, 25 °C, 40 h; f, TsCl (1.0 equiv.), Et_3N (14.7 equiv.), THF, 25 °C, 72 h; g, 0.66 M-NaOH (25 equiv.), EtOH–H_2O (3:1), reflux, 72 h.

† Satisfactory C,H,N analyses or high-resolution mass spectra were obtained for all new compounds except for (**16a**), which was taken on to (**15a**) directly. I.r., ^1H n.m.r., and ^{13}C n.m.r. spectra are consistent with the reported structures.

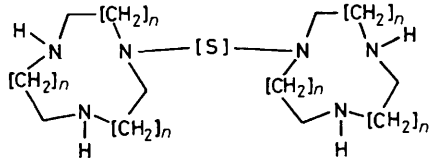


(14)

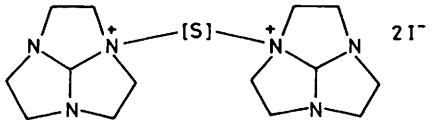
Scheme 3



Reagents: h, $PhCH_2Br$ (1.0 equiv.), THF, 25 °C, 24 h; i, (i) H_2O, reflux, 3.5 h; (ii) NaOH (pH 10), 0 °C, immediate $CHCl_3$ extraction.



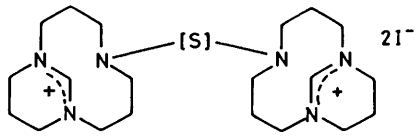
	n	[S]	% Yield
(15) a;	1	$-[CH_2]_3-$	88
b;	1	$-[CH_2]_4-$	87
c;	1	$-[CH_2]_2O[CH_2]_2-$	58
d;	2	$-[CH_2]_3-$	80
e;	2	$-[CH_2]_4-$	71



	[S]	% Yield
(16) a;	$-[CH_2]_3-$	83
b;	$-[CH_2]_4-$	77
c;	$-[CH_2]_2O[CH_2]_2-$	46

1675 cm^{-1}; ^1H n.m.r. (60 MHz, $CDCl_3$) δ 1.1—2.4 (m, 6H), 2.9—3.45 (m, 10H), 3.6 (s, 2H), 4.1—4.7 (m, 2H), 7.0—7.55 (m, 5H), 9.8 (br. s, 1H); ^{13}C n.m.r. ($CDCl_3$) δ_C 19.8, 23.8, 42.3, 54.6, 55.3, 57.1, 127.8, 128.4, 130.4, 135.8, 158.7 (amidinium C)]. This, in turn, was hydrolysed under basic conditions to benzyl/formyl derivative (**6**). Thus, all three nitrogens of (**2**) are differentiated in three high-yield steps. Further replacement of formyl with the less easily hydrolysed tosyl protecting group was also accomplished straightforwardly as shown in Scheme 2.

Our success with the versatile approach exemplified by Scheme 2 led us to apply it to protection of (**1**) as well. As shown in Scheme 3, reaction of (**10**) with $PhCH_2Br$ (1 equiv.) in tetrahydrofuran gave tricyclic monoalkylation product (**14**)



	[S]	% Yield
(17) a;	$-[CH_2]_3-$	92
b;	$-[CH_2]_4-$	57

cleanly, the salt precipitating from solution upon formation [i.r.: no amidinium CN stretch; ^1H n.m.r. (60 MHz, $CDCl_3$) δ 3.2—4.2 (m, 12H), 4.95 (s, 2H), 5.9 (br. s, 1H), 7.4—7.9 (m, 5H); ^{13}C n.m.r. ($CDCl_3$) δ_C 52.3, 56.4, 57.8, 62.0, 123.1 (methine C), 129.1, 129.4, 130.5, 132.3]. We saw no evidence for opening of (**14**) to the corresponding strained bicyclic [5.2.1] amidinium salt. Compound (**14**) was converted into the desired selectively protected derivative (**9**) by hydrolysis in refluxing H_2O followed by basification.

The orthamide monoalkylation approach is also ideally suited for the synthesis of bis-coronands (**15**) of 9[ane]N_3 and 12[ane]N_3. Such 'earmuff'[8] ligands are potential mononuclear or binuclear metal complexing agents depending upon the nature of the spacer group [S] between the two rings and have therefore been the subject of a flurry of recent research activity.[6,9] Alkylation of (**10**) and (**11**) with α,β-di-iodoalkanes (0.5 equiv.) gave salts (**16**) and (**17**) respectively in fair to good yields. Hydrolyses of (**16a—c**) [(i) H_2O, reflux; (ii) aqueous NaOH, reflux] gave hygroscopic (**15a—c**) directly. Similarly, basic hydrolysis (aqueous NaOH, reflux) of (**17a—b**) gave (**15d—e**). Compound (**15a**) has also recently been prepared by other workers[6] through alkylation of (**5**), but (**15b—e**) are previously unreported.

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