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SIMPLE PREPARATIONS OF TRICYCLIC ORTHOAMIDES AND MACROCYCLIC TRIAMINES

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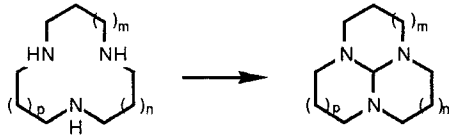
Abstract: Hexahydropyrimidopyrimidine **3** is condensed with an alkyl ditosylate **4** at room temperature in DME or toluene. The resulting tricyclic salt is reduced with sodium borohydride to provide orthoamides **6a-c**. Acidic hydrolysis of these orthoamides gives the corresponding macrocyclic triamines **8a-c** in high yield.

In 1980, Wuest[1a,c] and Atkins[1b] reported on the synthesis and chemistry of tricyclic orthoamides of the general structure **2**. These materials were prepared by condensation of the corresponding macrocyclic triamines **1** with DMF-dimethyl acetal, triethyl orthoformate, or formamidinium acetate. Particularly interesting properties of **2** include hydrolytic stability in some cases, metal complexing ability, and facile oxidation of the orthoamide moiety.



1 **2**

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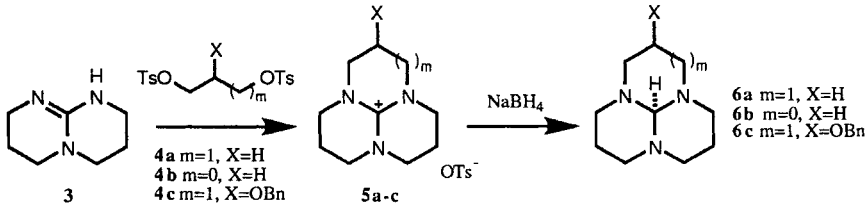
We are interested in using hydrolytically stable orthoamides for applications in molecular recognition. Since we will require functionalized versions of **2** for which the corresponding macrocycles might not be conveniently prepared, we have explored the feasibility of the alkylation/reduction sequence depicted in the Scheme below as an alternative route to orthoamides. In this protocol, a third ring is appended to bicyclic triamine **3**.[2] During the course of our work, a protocol for this two step approach was reported by Alder *et al.*[3] In the present communication, we describe our own protocols of which various aspects are noteworthy. In particular, our one-pot procedure is more convenient, yields of the orthoamides are higher, and we demonstrate access to new functionalized triamines.

Scheme



We have examined several alkylating agents and many sets of conditions for use in the alkylation/reduction sequence. The range of success was narrow: two specific protocols were found to be satisfactory, and three alkylating agents have provided good yields of tricyclic products. These results are shown in Table 1.[4]

Table 1 Alkylation/reduction of Bicyclic Triamine **3**.

Alkylating agent	Method[a]	Product
4a (m = 1, X = H)	A	**6a** (66%)
4b (m = 0, X = H)	B	**6b** (79%)
4c[5] (m = 1, X = OBn)	B	**6c** (100%)

Table 2 Hydrolysis of Orthoamides.

Orthoamide	Product
6a (m = 1, X = H)	**8a** (94%)
6b (m = 0, X = H)	**8b** (86%)
6c[6] (m = 1, X = OBn)	**8c** (89%)

[a] Method A: 1 equiv. **3**, 1.2 equiv. **4**, 3 equiv. KOH (finely ground with equal weight of KBr), 5 equiv. $NaBH_4$, toluene, rt, 48h; Method B: 1) 2-3 equiv. **3**, 1 equiv. **4**, DME, rt, 24-48h; 2) add $NaBH_4$; rt, 24h.

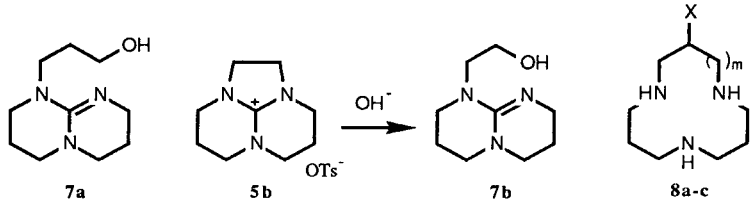
Only with tosylate as the leaving group were satisfactory results obtained. Furthermore, alkylating agents which bear both leaving groups on secondary or neopentyl carbons, which are allylically or benzylically activated, or which would produce a seven-membered ring in the orthoamide are unsuitable under the conditions listed. We emphasize, however, that products **6a-c** were prepared without need of isolating the intermediate guanidinium-type salts **5a-c**. Perhaps for this reason, our yields of orthoamides **6a** (66%) and **6b** (79%) are significantly higher than the previous literature yields (49% and 54%, respectively).[2]

The novel material **6c** is the first such tricycle to incorporate a "handle" that would not nullify the reductive[1a,c] or metal-complexing[7] abilities of the orthoamide functionality. We envision the use of this substructure as a reducing or binding domain in designed organic catalysts.

It is interesting to note that the tricyclic salts **5a** and **5b** (derived from **4a** and **4b**, respectively) react with hydroxide ion in the absence of borohydride to give in each case a ring-opened product. In this mode, **5a** can only give **7a**, but the transformation occurs regioselectively in the case of **5b**, giving only **7b**.

As demonstrated by Alder *et al.*,[2] hydrolysis of the orthoamide functionality can provide the corresponding macrocyclic triamine. We hydrolyzed orthoamide **6c** (Table 2) by heating in 0.53 M aqueous sulfuric acid at reflux (9.5 h). Subsequent addition of excess NaOH, concentration *in vacuo*, addition of Na_2SO_4, and extraction of the resulting solid with ether/toluene (1:1) afforded the novel macrocycle **8c** in 89% yield.

In summary, we have developed convenient, high-yielding protocols to prepare tricyclic orthoamides. Application of the methods to target more functionalized orthoamides, as well as our examinations of those materials' properties, will be reported in due course.



Representative Procedures:

Preparation of orthoamide **6a**.[4] Hexahydropyrimidopyrimidine **3** (1.03 g, 7.40 mmol), ditosylate **4a** (3.42 g, 8.90 mmol), KOH and KBr (1.25 g each, finely ground), and $NaBH_4$ (0.30 g, 7.93 mmol) were added to toluene (45 mL) and the mixture was stirred vigorously for 42.5 h at ambient temperature. Ethyl acetate (50 mL) was then added and the mixture was extracted with 1N NaOH (4 x 25 mL). Combined aqueous extracts were washed with ethyl acetate (25 mL) and this organic extract was back-extracted with 1N NaOH (25 mL). All aqueous layers were combined, saturated with NaCl (40 g), and extracted with methylene chloride (5 x 50 mL). Drying over sodium sulfate and concentration in vacuo gave an amber colored oil (1.13 g). Addition of diethyl ether (25 mL), drying over sodium sulfate, filtration, and concentration in vacuo gave spectroscopically pure **6a** (0.89 g, 66%) as a colorless oil which solidified on standing.

Preparation of macrocycle **8c**. Orthoamide **6c** (1.84 g, 6.40 mmol) in aqueous H_2SO_4 (0.53 M, 155 mL) was heated at reflux for 9.5 h. After cooling, solid NaOH (10.75 g) was added slowly, and the mixture was concentrated in vacuo. Drying was achieved by concentration from a mixture of EtOH and toluene (37:51). Addition of diethyl ether and toluene (1:1, 100 mL) and sodium sulfate, filtration (washing with ether), concentration, and concentration from toluene solution gave spectroscopically pure **8c** (1.58 g, 89%) as a colorless oil. ^1H NMR (300 MHz,

$CDCl_3$) δ 7.35-7.28 (m, 5H), 4.57 (s, 2H), 3.62-3.58 (m, 1H), 2.90-2.72 (m, 12H), 1.65-1.58 (m, 4H). IR (neat) 3272, 2925, 2821, 1669, 1468, 1454, 1142, 1101, 1073, 740, 705 cm^{-1}. HRMS (EI) 278.2235 (M+H); calc'd for $C_{16}H_{28}ON_3$, 278.2232.

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2. Available from Fluka Chemical Corporation, Ronkonkoma, NY.
3. Alder, R. W., Mowlam, R. W., Vachon, D. J., and Weisman, G. R., J. Chem. Soc., Chem. Commun., 1992, 507.
4. Known compounds **6a** and **6b** gave carbon-13 NMR spectra (75 MHz, $CDCl_3$) consistent with literature data. **6a**: δ 99.85, 53.82, 23.87. **6b**: δ 96.39, 51.53, 48.80, 47.36, 23.12. See Weisman, G. R., Johnson, V., Fiala, R. E., Tetrahedron Lett., 1980, 21, 3635. Our carbon-13 NMR data for known compound **8a** ($CDCl_3$; δ 48.56, 26.81) was consistent with a spectrum obtained using commercially available material (Aldrich). Known compound **8b** was converted to its tris-hydrochloride. This salt gave a carbon-13 NMR spectrum (D_2O; δ 44.36, 42.41, 20.38) consistent with literature data. Dioxane (δ 66.5) was used as an internal standard. See Buttafava, A., Fabbrizzi, L., Perotti, A., Poggi, A., Poli, G., Seghi, B., Inorg. Chem., 1986, 25, 1456.
5. Ditosylate **4c** was prepared from glycerol by successive ditritylation, benzylation, detritylation, and tosylation. The detritylation (HCl, MeOH, toluene, 60 °C) must be quenched with excess NaOH before concentration

and further extractive work-up in order to avoid partial retritylation.

6. Orthoamide **6c** crystallized from EtOAc/hexanes, giving colorless plates, m.p. 87.5-91.5°C; *Anal.* Calcd. for $C_{17}H_{25}N_3O$: C, 71.05; H, 8.77; N, 14.62. Found: C, 70.94; H, 8.91; N, 14.63.

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