Tetrahedron Letters, Vol.32, No.38, pp 5031-5034, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

ONE-POT SYNTHESIS OF CYCLIC AMIDINIUM TETRAFLUOROBORATES AND HEXAFLUOROPHOSPHATES; THE SIMPLEST MODELS OF N^5,N^{10}-METHENYLTETRAHYDROFOLATE COENZYME

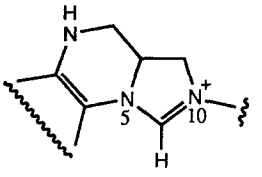
Shahrokh Saba,* AnneMarie Brescia, and Moses K. Kaloustian*

Department of Chemistry, Fordham University
Bronx, New York 10458

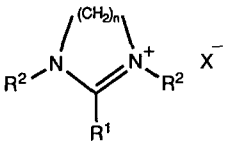
Abstract: Reaction of triethyl orthoesters with various *N,N'*-dialkyl-α,ω-alkanediamines in the presence of ammonium tetrafluoroborate or hexafluorophosphate, all in the same molar ratio, affords cyclic amidinium salts in excellent yields.

The role of tetrahydrofolate coenzymes in the transfer of a one-carbon unit at different oxidation levels has been well recognized.[1] N^5,N^{10}-Methenyltetrahydrofolate **1**, utilizes an imidazolinium moiety in the transfer of carbon at the formate oxidation level.[2] Pandit and co-workers,[3] have used simple imidazolinium systems, as models of N^5,N^{10}-methenyltetrahydrofolate, to mimic such carbon-transfer reactions. The utility of simple imidazolines and imidazolinium salts, as folate models, has also been demonstrated in recent years in the synthesis of ketones,[4] and indoloquinolizidine derivatives.[5]

For a project directed toward studies of stereoelectronic effects[6] in the generation and breakdown of model, tetrahydrofolate-type tetrahedral intermediates,[7a,b] in non-aqueous media and utilizing neutral oxygen nucleophiles, we required peralkylated cyclic amidinium systems (**2**-**4**) with gegenions of low nucleophilicity. We describe herein a simple and efficient one-pot process for the synthesis of amidinium tetrafluoroborates and hexafluorophosphates **2**, **3** and **4** from commercially available orthoesters.



1



2: n=2
3: n=3
4: n=4

Existing methodologies for the synthesis of such cyclic amidinium salts are sparse and, with relatively few exceptions, the majority of recorded salts possess a halide as the counterion. Cook and co-workers,[8] prepared 1,3-dimethyl-2-phenyl-4,5-dihydroimidazolium iodide from 1-methyl-2-phenylimidazoline and excess methyl iodide. Following a similar approach, Anderson and co-workers[4] also reported the synthesis of a series of 2-alkyl-1-benzyl-3-methyl-4,5-dihydroimidazolium iodides. Pandit and co-workers[3] also rerpoted the reactions between α,ω-alkanediamines with 1-acetyl or 1-tosyl-3,4,4-trimethyl-Δ^2-imidazolinium iodides as a route to some cyclic amidinium iodides.

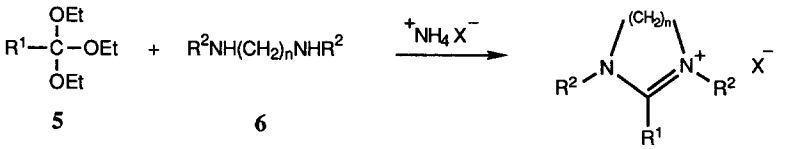
Several 1,3-dialkyl-5,5-dimethyl-1,4,5,6-tetrahydropyrimidinium iodides have been reported as by-products when the corresponding hexahydropyrimidines were treated with alkyl halides.[9] The perchlorate salts of a number of similar compounds have also been obtained from the reaction of the corresponding hexahydropyrimidines with mercuric acetate.[10]

Desmarchelier *et al.*[11] reported the synthesis of 2-methyl-4,5,6,7-tetrahydro-1,3-diazepinium chloride by the reaction of acetamidine hydrochloride with 1,4-butanediamine.

Benkovic and co-workers[7a] prepared a few formadinium fluoroborates by the reaction of substituted tetrahydroquinoxalines with triethyl orthoformate followed by treatment with aqueous fluoroboric acid. *N*-carbomethoxy-*N'*-methyl-2-ethyloxyimidazolinium fluoroborate has also been made by *O*-ethylation ($Et_3O^+BF_4^-$) of *N*-carbomethoxy-*N'*-methyl-2-imidazolidone, while *N*-carbomethoxy-*N'*-methyl-2-(2',6'-dimethylphenoxy)imidazolinium fluoroborate was obtained by *N*-methylation ($Me_3O^+BF_4^-$) of *N*-carbomethoxy-2-(2',6'-dimethylphenoxy)imidazoline.[12]

We have found that reaction of an orthoester **5**, with an *N,N'*-dialkyl-α,ω-alkanediamine **6**, in the presence of ammonium tetrafluoroborate or ammonium hexafluorophosphate (Scheme 1), all in equimolar amounts in the absence of a solvent, affords directly the corresponding dihydroimidazolium, tetrahydropyrimidinium and tetrahydro-1,3-diazepinium salts in excellent yields (Table).[13] The requisite diamines were either commercially available or were prepared by literature procedures or adaptation of literature procedures.

Scheme 1



5 **6** **2a-m** **3a-h** **4a-e**

N,N'-Di-*tert*-butylethylenediamine[14], *N,N'*-diisopropylethylenediamine,[15] and *N,N'*-dimethyl-1,4-butanediamine[16] were prepared as described in the literature, while *N,N'*-diethyl-1,4-butanediamine, *N,N'*-diisopropyl-1,4-butanediamine and *N,N'*-diisopropyl-1,3-propanediamine were prepared by adaptation of the method of Klemm *et al.*[15] from the corresponding diamines and alkyl halides.

Table. Amidinium Salts **2, 3, 4.**[17,18]

Product	R^1	R^2	X	Yield(%)	mp(°C)
2a	H	H	BF_4	92	252-255
2b	H	Me	BF_4	94	oil
2c	H	Et	BF_4	92	oil
2d	H	*i*-Pr	BF_4	96	152-153
2e	H	*i*-Pr	PF_6	94	200-203
2f	H	*t*-Bu	BF_4	36	277
2g	Me	Me	BF_4	97	215
2h	Me	Me	PF_6	97	195-198
2i	Et	Me	BF_4	99	210
2j	Et	Me	PF_6	93	204-207
2k	Et	Et	PF_6	76	199-200
2l	Ph	Me	BF_4	97	87-88
2m	Ph	Me	PF_6	94	119-120
3a	H	H	BF_4	98	263-264
3b	H	*i*-Pr	PF_6	97	163
3c	Me	Me	BF_4	94	204-205
3d	Me	Me	PF_6	98	223-224
3e	Et	Me	BF_4	88	239-241
3f	Et	Me	PF_6	97	240-245
3g	Ph	Me	BF_4	89	84.5-85
3h	Ph	Me	PF_6	95	145
4a	H	H	BF_4	90	gel
4b	H	Me	PF_6	92	semi-solid
4c	H	*i*-Pr	PF_6	88	semi-solid
4d	H	Et	BF_4	87	gel
4e	H	Et	PF_6	90	gel

2-Ethyl-1,3-dimethyl-1,4,5,6-terahydropyrimidinium tetrafluoroborate (3e); typical procedure. A 10 mL round-bottomed flask charged with triethyl orthopropionate (1.76 g, 0.010 mole), ammonium tetrafluoroborate (1.05 g, 0.010 mole) and *N,N'*-dimethyl-1,3-propanediamine (1.02 g, 0.010 mole) was heated at 120°C in an oil bath for 3 hrs. The ethanol formed during the reaction was removed on the rotary evaporator followed by further drying on the vacuum pump for 2 hrs. The crude product was crystallized from absolute ethanol to give white needles (see Table). Anal. calcd for $C_8H_{17}BF_4N_2$: C, 42.13; H, 7.52; N, 12.29. Found: C, 42.21; H, 7.53; N, 12.38. ^{1}H-NMR ($CDCl_3/CD_3CN$) δ 1.28 (t, 3H); 2.17 (m, 2H); 2.74 (q, 2H); 3.34 (s, 6H); 3.56 (t, 4H).

This work was supported in part by a grant from the Fordham University Research Council.

References and Notes

(1) Bruice, T. C. and Benkovic, S. J. *Bioorganic Mechanisms*, vol. 2, p. 350, Benjamin, New York, 1966. Benkovic, S. J. *Acc. Chem. Res.* **1978**, *11*, 314 and refs cited therein

(2) Benkovic S. J. *Ann. Rev. Biochem.* **1980**, *49*, 227 and refs cited therein. Pandit, U. K. *Recl. Trav. Chim. Pays-Bas* **1988**, *107*, 111.

(3) Bieraugel, H.; Plemp, R.; Hiemstra, H. C.; Pandit, U. K. *Tetrahedron*, **1983**, *39*, 3971 and refs cited therein.

(4) Anderson, M. W.; Jones, R. C. F.; Saunders, J. *J. Chem. Soc. Chem. Commun.* **1982**, 282.

(5) Stoit, A. R.; Pandit, U. K. *Tetrahedron*, **1989**, *45*, 849 and refs cited therein.

(6) Perrin, C. L.; Nunez, O. *J. Am. Chem. Soc.* **1987**, *109*, 522 and refs cited therein.

(7) (a) Benkovic, S. J.; Bullard, W. P.; Benkovic, P. A. *J. Am. Chem. Soc.* **1972**, *94*, 7542. (b) Robinson, D. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1967**, *89*, 7088.

(8) Cook, M. J.; Katritzky, A. R.; Page, A. D.; Tack, R. D.; Witeck, H. *Tetrahedron*, **1976**, *32*, 1773.

(9) Piotrowska, H.; Prejzner, H. *Bull. Acad. Pol. Sci., Ser. Sci. Chim.* **1981**, *29*, 329. *C. A.* **1983**, *98*, 215556.

(10) Piotrowska, H.; Prejzner, H.; Sas, W. *Rocz. Chem.* **1977**, *51*, 1775. *C. A.* **1978**, *88*, 74368.

(11) Desmarchelier, J. M.; Evans, N. A.; Evans, R. F., Johns, R. B. *Aus. J. Chem.* **1968**, *21*, 257.

(12) Cravey, M.; Kohn, H. *J. Am. Chem. Soc.* **1980**, *102*, 3928.

(13) While compounds **2a-4e** are the fully characterized products, NMR evidence indicates that the method described can be applied to the preparation of macrocyclic amidinium salts derived from diamines with longer chain lengths as well as other ammonium salts such as bromides.

(14) Shepard, R. G.; Wilkinson, R. G. *J. Med. Pharm. Chem.* **1962**, *5*, 823.

(15) Klemm, D.; Bellstedt, K.; Hoerhold, H. *J. Prakt. Chem.* **1979**, *321*, 680.

(16) Devinsky, F.; Lacko, I.; Krasnec, L. *Synthesis*, **1980**, 303.

(17) The products were characterized by their melting points, elemental analyses and ^{1}H-NMR. NMR spectra of the amidinium salts showed the expected downfield shifts of the *N*-alkyl signals associated with the partial positive charge on the nitrogens as compared to the absorptions of the corresponding groups in the starting diamines. Noncrystalline products were purified by shaking the crude products with Et_2O/EtOH (1:1; v/v) followed by decantation and vacuum drying for several hours.

(18) Two-step approaches to the same overall transformation have been worked out (Garza, V. and Kaloustian, M. K., unpublished results). In the first approach, an acyclic amidinium acetate is converted to the corresponding fluoroborate salt by treatment with $Et_3O^+BF_4^-$ and the product is then made to react with an *N,N'*-dialkyl-α,ω-alkanediamine. Alternatively, an acyclic amidinium acetate is made to react with the α,ω-alkanediamine, and the product is subsequently treated with $Et_3O^+BF_4^-$.

(Received in USA 22 May 1991)