Pergamon

Tetrahedron Letters 39 (1998) 3551–3554

TETRAHEDRON LETTERS

Novel Synthesis of Aliphatic Nitriles from Amidines

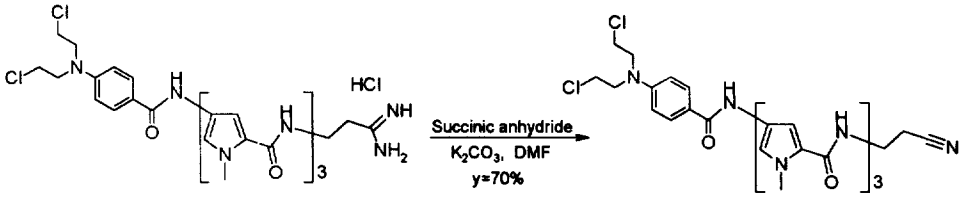
Marina Caldarelli*, Giovanni Biasoli, Paolo Cozzi and Nicola Mongelli

Pharmacia & Upjohn, Viale Pasteur 10, 20014 Nerviano (MI), Italy

Received 7 January 1998; revised 2 March 1998; accepted 6 March 1998

Abstract: Aliphatic nitriles were obtained through functional group transformation of the corresponding unsubstituded aliphatic amidines with penta-atomic anhydrides. The best results were obtained with succinic anhydride.

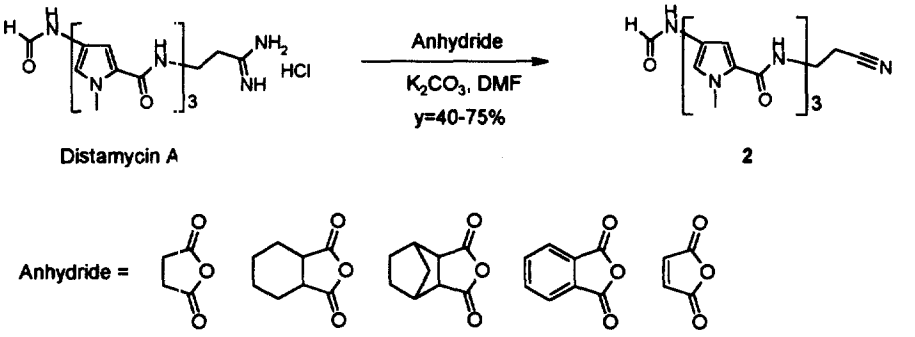
Although amidines are readily prepared from the corresponding nitriles,[1] there are only two publications dealing with the synthesis of nitriles from amidines. In one paper the nitrile is obtained by treatment of the amidine with $CHCl_3$ and $NaOH$[2], in the other, N-monosubstituted-N-silylated aromatic amidines are treated with $CSCl_2$ in EtO_2 giving the nitrile and starting amidine.[3] During our studies[4] aimed at modification of the structure of the antitumor agent tallimustine,[5] a benzoic acid mustard derivative of distamycin A,[6] we found that the reaction of tallimustine with succinic anhydride (SA) gave, in good yield, the corresponding nitrile instead of the expected N-acyl derivative.



Tallimustine 1

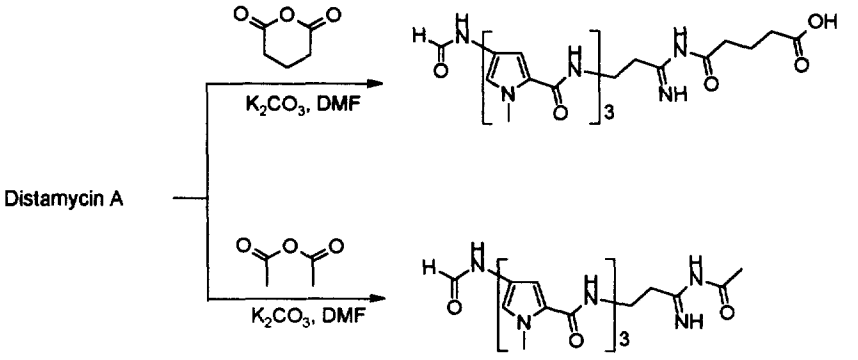
To the best of our knowledge, this kind of reaction has not been previously reported. To further investigate this reaction, we used first the more available and structurally similar distamycin A as an amidine substrate, which was reacted with several different cyclic anhydrides.

0040-4039/98/$19.00
PII: S0040-4039(98)00546-2

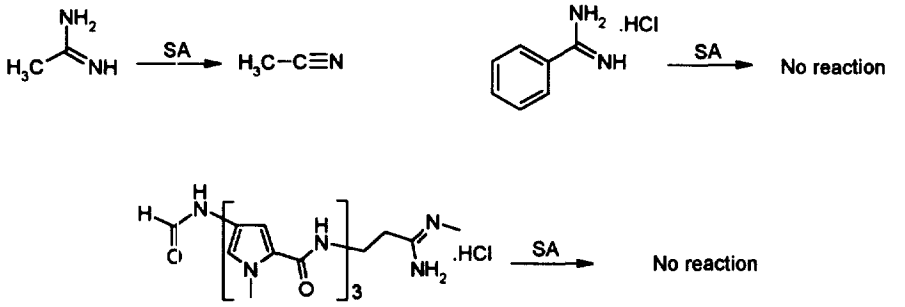


We noticed that all the 5-membered ring anhydrides we tested gave the nitrile **2**, independently of their electronic and steric features. The reaction was performed at room temperature except for the sterically hindered bicyclic norbornane anhydride for which heating at 80°C was required. The best yield was obtained with succinic anhydride (75%), while for the other anhydrides the yields were lower and the reaction was slow.

In the case of the 6-membered ring glutaric anhydride and of acetic anhydride we obtained in the same conditions the N-acylated product.

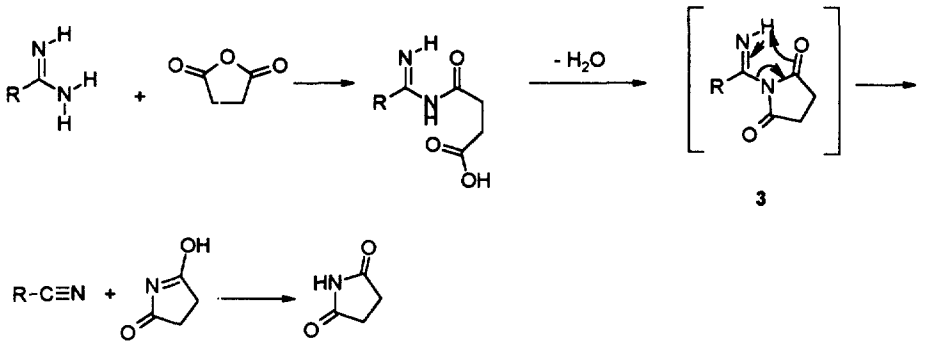


With the aim of extending the methodology to other amidines we examined the reaction of succinic anhydride, with acetamidine,[7] benzamidine and N-methylamidine derivative of distamycin A.[8] While the former gave cyanonitrile, the latters did not react.



The results of these experiments show that the method appears to be general for aliphatic amidines but it does not apply to aromatic and substituted amidines. The unreactivity of benzamidine is in accordance with the results of a recent paper reporting the acylation of 4-aminobenzamidine hydrochloride by SA on the amino but not on the amidino group.[9]

The reaction of distamycin A with SA lead to the formation of succinimide which was detected by HPLC. This suggests acylation of the amidino group and a subsequent or concomitant formation of penta-atomic ring, but we were not able to isolate the putative succinylamidine intermediate **3**.



In conclusion, even if this facile and simple reaction has no practical interest for the synthesis of simple nitriles, it may be used to circumvent the basicity and reactivity of amidine group present in complex substrates, by its transformation into a nitrile and a final restoration of the amidine function e.g. with classical Pinner synthesis.

A typical procedure: a mixture of distamycin A (100 mg, 0.19 mmol), succinic anhydride (38 mg, 0.38 mmol) and K_2CO_3 (48 mg, 0.38 mmol) in DMF (5 ml) was allowed to stand at room temperature for 3 h or until the reaction was complete (< 12h). The solvent was removed under reduced pressure and the residue was

chromatographed on silica gel column (eluant: CH_2Cl_2-MeOH) to give 65 mg of **2** (75%) as a white amorphous solid.

2: ESI: m/z 465, (100, $(M+H)^+$). IR (KBr): 2250 cm^{-1}.

^{1}H-NMR (DMSO-d_6, 200 MHz) δ: 10.00 (s, 1H), 9.91 (s, 1H), 8.32 (t, J=5.8Hz, 1H), 8.11 (s, 1H), 7.2 (m, 3H), 7.01 (d, J=1.8Hz, 1H), 6.9 (m, 2H), 3.83 (s, 6H), 3.80 (s, 3H), 3.39 (dt, J=6.5Hz and J=5.8Hz, 2H), 2.71 (t, J=6.5Hz, 2H).

1: FAB-MS: m/z 680, (8, $(M+H)^+$); 488, (10); 366, (15); 244, (100). IR (KBr): 2250 cm^{-1}.

^{1}H-NMR (DMSO-d_6, 200 MHz) δ: 10.01 (s, 1H), 9.96 (s, 1H), 9.94 (s, 1H), 8.34 (t, J=6.0Hz, 1H), 7.84 (m, 2H), 7.30 (d, J=1.8Hz, 1H), 7.25 (d, J=1.8Hz, 1H), 7.22 (d, J=1.8Hz, 1H), 7.07 (d, J=1.8Hz, 1H), 7.05 (d, J=1.8Hz, 1H), 6.94 (d, J=1.8Hz, 1H), 6.83 (m, 2H), 3.90-3.60 (m, 8H), 3.86 (s, 3H), 3.80 (s, 3H), 3.40 (m, 2H), 2.72 (t, J=6.4Hz, 2H).

REFERENCES AND NOTES

1. Boyd, G.V. *The Chemistry of Amidines and Imidates* Vol.2, Edited by S.Patai and Zvi Rappoport, John Wiley & Sons, N.Y., 1991, pp. 340-345.
2. Graefe, J. *Z. Chem.* **1975**, *15*, 301.
3. Barnikow, G.; Ebeling, H. *Z. Chem.* **1971**, *11*, 103.
4. Cozzi, P.; Beria, I.; Caldarelli, M.; Geroni, M. C.; Pesenti, E. Patent WO9728123.
5. Pezzoni, G.; Grandi, M.; Biasoli, G.; Capolongo, L.; Ballinari, D.; Giuliani, F. C.; Barbieri, B.; Pastori, A.; Pesenti, E.; Mongelli, N.; Spreafico, F. *Br.J.Cancer*, **1991**, *64*, 1047.
6. (a) Arcamone, F.; Orezzi, P. G.; Barbieri, W.; Nicolella, V.; Penco, S. *Gazz.Chim.Ital.* **1967**, *97*, 1097. (b) Penco, S.; Redaelli, S.; Arcamone, F. *Gazz.Chim.Ital.* **1967**, *97*, 1110.
7. The reaction was followed *via* GLC.
8. Cozzi, P.; Beria, I.; Biasoli, G.; Caldarelli, M.; Capolongo, L.; Geroni, M. C.; Mongelli, N. *Bioorg.Med.Chem.Lett.* **1997**, 7, 2979.
9. Cossy, J.; Schmitt, A.; Cinquin, C.; Buisson, D.; Belotti, D. *Bioorg.Med.Chem.Lett.* **1997**, *7*, 1699.