A NEW METHOD FOR THE PREPARATION OF SUBSTITUTED 2-PYRIMIDINYL- AND s-TRIAZINYL-FORMAMIDE OXIMES FORMYLATION OF HETEROCYCLIC AMINES WITH TRISFORMAMINOMETHANE

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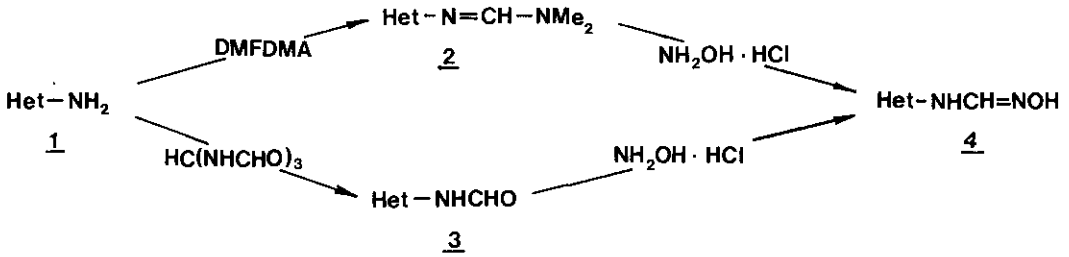
Abstract - A novel method for the preparation of substituted 2-pyrimidinyl- and s-triazinyl-formamide oximes is described. Heterocyclic amines 1 are first converted with trisformaminomethane, as the most powerful formylating agent, into formylamino derivatives 3. These give by treatment with hydroxylamine the corresponding formamide oximes 4 in yields up to 95%.

Heteroarylformamide oximes are versatile intermediates in the synthesis of various heterocyclic systems. On this basis, new routes leading to s-triazolo /1,5-x/azines [1-4], s-triazolo/1,5-x/azine 3-oxides [5,6], pyrido/2,3-d/pyrimidine 3-oxides [7,8], and pteridines and pteridine 3-oxides [9] have been developed recently. They are usually obtained from the heterocyclic amines 1 by treatment with dimethylformamide dimethylacetal (DMFDMA) to give dimethylaminomethyleneamino compounds 2, followed by treatment with hydroxylamine affording the corresponding heteroarylformamide oximes 4[1]. (Scheme I). However, in spite of the generality of this conversion, some side reactions, such as methylation of secondary amino groups and transformations of reactive methyl groups into olefins can occur [10,11].

In this communication we wish to report on a new simple method of preparation of s-triazinyl- and 2-pyrimidinyl-formamide oximes, which represents an alternative in comparison to the previously described method. In the first step, the corresponding 2-aminopyrimidine derivatives 1d-f and 2-amino-4,6-disubstituted 1,3,5-triazine derivatives 1h-l are converted into the corresponding formylamino derivatives 3. We found that the most useful formylating agent turned out to be trisformaminomethane, which has been previously used for the synthesis of various heterocyclic systems as a reagent for introducing of one carbon unit into a heterocyclic ring [12,13]. With this reagent even the least reactive heterocyclic amines afford the corresponding formylamino derivatives in yields up to 95% (Table I).

The second step represents the treatment of heterocyclic formylamino compounds 3 with hydroxylamine hydrochloride at room temperature to give the corresponding formamide oximes 4 in yields between 54 and 95%. (Scheme I) (Table II).



Het a) pyridyl-2
b) pyridyl-4
c) 6-chloropyridazinyl-3
d) pyrimidinyl-2
e) 2,4-dihydroxypyrimidinyl-5
f) 2,6-dimethylpyrimidinyl-4
g) pyrazinyl-2
h) 4-dimethylamino-6-chloro-1,3,5-triazinyl-2
i) 4-ethylthio-6-methylamino-1,3,5-triazinyl-2
j) 4,6-bisethylthio-1,3,5-triazinyl-2
k) 4,6-bismethylthio-1,3,5-triazinyl-2
l) 4,6-dimethoxy-1,3,5-triazinyl-2

S C H E M E I

However, the conversion of formylamino compounds 3 into formamide oxime derivatives 4 is limited only to 2-formylaminopyrimidines (3d-f) and formylamino--1,3,5-triazines (3h-l), i.e. to the heterocyclic amino compounds in which the amino group is a part of the guanidine structural element. Other heterocyclic formylamino compounds, such as 2-formylaminopyridine (3a), 4-formylaminopyridine (3b), 3-formylamino-6-chloropyridazine (3c), 5-formylaminouracil (3e), 2,6-dimethyl-4-formylaminopyrimidine (3f), 2-formylaminopyrazine (3g) do not react under these reaction conditions.

2-Amino-4-ethylthio-6-methylamino-1,3,5-triazine (1i).

A mixture of 2-amino-4,6-bisethylthio-1,3,5-triazine (1j)[14] (1.4 g), acetone (3 ml) and methylamine (45% aqueous solution, 25 ml) was heated under reflux for 4h. After standing overnight at room temperature the precipitate was collected by filtration, washed with water and recrystallized from ethanol, mp. 141-142°C, yield 63%.

Anal.: Calcd. for $C_6H_{11}N_5S$: C 39.00%, H 6.03%, N 37.62%, Found C 38.90%, H 5.99%, N 37.81%.

Heterocyclic formylamines (3). General procedure.

A heterocyclic amino compound 1 (1 mM) and trisformaminomethane (145 mg, 1 mM) were heated in a sealed vessel for 20-30 min. at 165-170°C. After cooling water or methanol was added, the precipitated formylamino compound 3 collected by filtration and recrystallized from appropriate solvent. The experimental details are given in Table I.

N-Heteroarylformamide oximes (4). General procedure.

To formylamino compound 3 (100 mg) dissolved in methanol or dimethylformamide (2-4 ml) hydroxylamine hydrochloride was added and the mixture left overnight at room temperature. The solvent was removed to one-half, water (4 ml)

Table I Formylaminoheterocycles (3)

Compound	Yield[a] [%]	mp [°C] (solvent) (Lit.mp.)	ms m/e M^+	Compound	Yield[a] [%]	mp [°C] (solvent) (Lit.mp.)	ms m/e M^+
3a	64	78-81 (EtOH) (76-77[15])	-	3g	59	161-162 (EtOH)	123
3b	68	149-152 (EtOH) (151-153[16])		3h	56	176-179 subl.140°C/ 3 torr)	201
3c	90	176-178 (MeOH)	157	3i	79	192-195 (EtOH)	213
3d	62	168 (EtOH) (208-10[16])		3j	92	70-73 (petroleum ether)	244
3e	94	320(decomp) (EtOH) (312(decomp[17])	-	3k	95	147-150 (CCl_4)	216
3f	87	109-112 (dioxane)	151	3l	56	144-153 ($CHCl_3$/ petroleum ether)	184

[a] Yield of purified product

Table II N-Heteroarylformamide oximes (4)

Compound	Yield[a] [%]	mp [°C] (Lit. mp.)	ms m/e M^+
4d	54	192-195 (198-200[1])	-
4h	63	251-253	216
4i	79	185-195 (dec.)	228
4j	81	175(dec.)	259
4k	72	170(dec.)	231
4l	95	220	199

[a] Yield of purified product. All new compounds gave satisfactory elemental analyses for C,H,N.

was added and the precipitate collected by filtration. The crude product was recrystallized from methanol or dimethylformamide/water 1:3. The experimental details are given in Table II.

REFERENCES AND NOTES

1. S.Polanc, B.Verček, B.Šek, B.Stanovnik, and M.Tišler, J.Org.Chem., 1974, 39, 2143.
2. S.Polanc, B.Verček, B.Stanovnik, and M.Tišler, Tetrahedron Letters, 1973, 1677.
3. B.Jenko, B.Stanovnik, and M.Tišler, Synthesis, 1976, 833.
4. B.Verček, B.Stanovnik, M.Tišler and Z.Zrimšek, Org.Prep.Proc., Int., 1978, 10, 293.
5. J.Bratož-Stres, S.Polanc, B.Stanovnik, and M.Tišler, Tetrahedron Letters, 1975, 4429.
6. K.Babič, S.Molan, S.Polanc, B.Stanovnik, J.Stres-Bratož, M.Tišler, and B.Verček, J.Heterocyclic Chem., 1976, 13, 487.
7. B.Verček, I.Leban, B.Stanovnik, and M.Tišler, J.Org.Chem., 1979, 44, 1695.
8. B.Verček, I.Leban, B.Stanovnik, and M.Tišler, Heterocycles, 1978, 9, 1327.
9. M.Kočevar, B.Stanovnik, and M.Tišler, Heterocycles, 1981, 15, 293.
10. B.Stanovnik, M.Tišler, A.Hribar, G.B.Barlin, and D.J.Brown, Austral.J.Chem., 1981, 34, in press.
11. For a review on the chemistry of formamide acetals see: R.F.Abdulla and R.S.Brinkmeyer, Tetrahedron, 1979, 35, 1675.
12. H.Bredereck, R.Gompper, H.G.v.Schuh, and G.Theilig, "Synthesen mit Säuereamiden, insbesondere mit Formamid." in "Neuere Methoden der Präparativen Organischen Chemie", W.Foerst, Ed., Verlag Chemie, Weinheim 1961, Band III, pp. 163-204.
13. Ch.Grundmann "Synthesen mit s-Trianin." in "Neuere Methoden der Präparativen Organischen Chemie", W.Foerst, Ed., Verlag Chemie, Weinheim 1967, Band V, pp. 156-184.
14. W.M.Pearlman and C.K.Banks, J.Amer.Chem.Soc.,1948, 70, 3726.
15. I.B.Romanova and Z.F.Panfilova, Khim.Geterots.Soed., 1971, 1368.
16. H.L.Yale, J.Org.Chem., 1971, 36, 3238.
17. Tsun-Yao Weng, Yao Hsüeh HsÜeh Pao, 1959, 7, 253; Chem.Abstr., 1960, 54, 14256c.

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