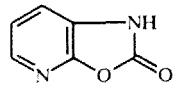
Chemistry of Heterocyclic Compounds, Vol. 32, No. 4, 1996

7-TRIFLUOROMETHYL-5-PHENYL-2-OXO-(1H)-OXAZOLO[5,4-*b*]PYRIDINE AND SOME OF ITS PROPERTIES

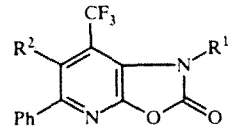
M. V. Yure, D. V. Shantare, and É. Yu. Gurdinietse

The potassium salt of 7-trifluoromethyl-5-phenyl-2-oxooxazolo[5,4-b]pyridine (IV) was prepared from 3-aminocarbonyl-4-trifluoromethyl-6-phenyl-2(1H)-pyridone by the Hofmann reaction and was converted into 3-amino-4-trifluoromethyl-6-phenyl-2(1H)-pyridone without isolation. 1-Substituted 7-trifluoromethyl-5-phenyl-2-oxooxazolo[5,4-b]pyridines were formed by alkylation of salt IV. 6-Halogeno-7-trifluoromethyl-5-phenyl-2-oxo-(1H)-oxazolo[5,4-b]pyridines have been prepared.

In contrast to the 2-oxooxazolo[4,5-*b*]pyridines, the synthesis, properties and biological activities of the 2-oxo-oxazolo[5,4-*b*]pyridines have been little studied [1-4]. The first derivative of 2-oxooxazolo[5,4-*b*]pyridine — its 6-arsinic acid — was prepared by acylating 3-amino-2(1H)-pyridone-5-arsinic acid with phosgene [1]: subsequently phosgene was replaced by bis(trichloromethyl) carbonate [5]. A single stage method for preparing 2-oxo-(1H)-oxazolo[5,4-*b*]pyridine (I) itself consisted of acylation 3-amino-2(1H)-pyridone with bis(trichloromethyl) carbonate ("triphosgene"), or with carbonyldiimidazole in the presence of base at −78°C [2, 3].



I



II, IV, VIa,b, VIIIa-i

II $R^1 = R^2 = H$; IV $R^1 = K$, $R^2 = H$; VIa $R^1 = H$, $R^2 = Cl$, b $R^1 = H$, $R^2 = Br$; VIII a $R^2 = H$, $R^1 = CH_3$, b $R^1 = C_2H_5$, c $R^1 = n\text{-}C_3H_7$, d $R^1 = n\text{-}C_4H_9$, e $R^1 = n\text{-}C_5H_{11}$, f $R^1 = i\text{-}C_5H_{11}$, g $R^1 = CH_2CH{=}CH_2$, h $R^1 = CH_2Ph$, i $R^1 = CH_2CO_2Me$

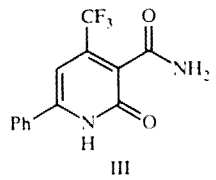
We have previously reported that 5,7-disubstituted 2-oxooxazolo[5,4-*b*]pyridines were obtained in high yield from the corresponding 3-aminocarbonyl-2(1H)-pyridones by the Hofmann reaction [4]. In a continuation of this work we have studied more thoroughly the behavior of 3-aminocarbonyl-4-trifluoromethyl-6-phenyl-2(1H)-pyridone (III) in the Hofmann reaction and we have investigated the properties of the 2-oxooxazolo[5,4-*b*]pyridine (II) obtained and its potassium salt IV.

In contrast to the report of Rufenacht et al. [6], we found that reaction of aminocarbonylpyridone (III) under Hofmann conditions at room temperature for 1 h gave the potassium salt of 2-oxoazolopyridine (IV) as its hydrate. The water of hydration was lost on heating the hydrate of IV to 105°C. When the reaction mixture was heated to 80-90°C without isolating the intermediate IV a readily separable mixture of the amine V and the salt IV was obtained (~3.5:1).

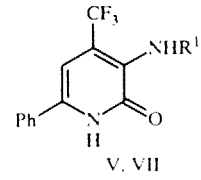
7-Trifluoromethyl-5-phenyl-2-oxo-(1H)-oxazolo[5,4-*b*]pyridine, identical to that prepared previously [4], was isolated on acidification of an aqueous solution of the potassium salt IV. 6-Chloro- and 6-bromo-derivatives (VIa and VIb respectively) were obtained by halogenating the oxazole II.

Riga Technical University, Riga, LV-1048. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 542-545, April, 1996. Original article submitted November 10, 1995.

0009-3122/96/3204-0473$15.00



III



V, VII

V R^1 = H, VII R^1 = COOEt

Boiling the oxazole II in a mixture of ethanol and DMF gave 3-ethoxycarbonylpyrimidone (VII). Study of cleavage of the oxazole ring is continuing.

N-Substituted 2-oxooxazolo[5,4-*b*]pyridines prepared by alkylation of the oxazolopyridine I with alkyl halides in DMF solution in the presence of a base [2, 3] have analgesic properties but do not have antinociceptive effects [3].

We used the hydrated potassium salt IV to prepare N substituted 2-oxooxazolo[5,4-*b*]pyridines VIII. When IV was heated in DMF solution with alkyl halides, benzyl chloride, and methyl chloroacetate the N-substituted oxazolopyridines VIIIa-i were obtained in good yields. Alkylation can also be done in ethanol solution but the yields of the N-alkyl derivatives are somewhat reduced, e.g., the N-allyl derivative VIIg was obtained in 74% yield. The yields of compounds VIIIa and VIIIf were increased to 93 and 79% respectively alkylating the anhydrous salt IV in absolute DMF.

Using 3-aminocarbonyl-4-trifluoromethyl-6-phenyl-2(1H)-pyridone as an example we have shown that it is possible to synthesize 2-oxooxazolo[5,4-*b*]pyridines via the Hofmann reaction. Alkylation of the potassium salt of 7-trifluoromethyl-6-phenyl-2-oxo-(1H)-oxazolo[5,4-*b*]pyridine is a suitable preparative method for the 1-substituted derivatives.

EXPERIMENTAL

^{1}H NMR spectra of $CDCl_3$ and DMSO-D_6 solutions with TMS as internal standard were recorded with a Bruker WH-90-DS (90 MHz) spectrometer. IR spectra of Nujol (1800-1500 cm^{-1}) and hexachlorobutadiene mulls (3600-2000 cm^{-1}) were recorded with Specord 71A spectrometer. The course of reactions and the purity of compounds obtained were monitored by TLC on Silufol UV-254 strips.

Elemental analyses for C, H, N, and halogen agreed with calculated values.

Properties of compounds IV-VIII are give in Table 1.

Potassium 7-Trifluoromethyl-5-phenyl-2-oxo-(1H)-oxooxazolo[5,4-*b*]pyridine Hydrate(IV, $C_{13}H_6F_3KN_2O_2 \cdot 2H_2O$). A solution of 3-aminocarbonyl-4-trifluoromethyl-7-phenyl-2(1H)-pyridone (III) (5.6 g, 20 mmole) in 10% KOH (100 cm^3) heated to 70-75°C was added slowly with constant stirring and cooling with ice to solution of potassium hypobromite [prepared from KOH (6.7 g, 120 mmole) and Br_2 (1.2 cm^3, 24 mmole)]. Stirring was continued for 1 h at room temperature. The precipitate was recrystallized from ethanol.

Acidification of an aqueous solution of the potassium salt IV gave the oxazolopyridine II, identical with a sample prepared previously [4].

3-Amino-4-trifluoromethyl-6-phenyl-2(1H)-pyridone (V, $C_{12}H_9F_3N_2O$). The reaction was carried out as in the previous example except, after stirring for 1 h at room temperature, the reaction mixture was heated for 1 h at 80-90°C. The anhydrous potassium salt IV (1.57 g, 22.3%) precipitated on cooling. The precipitate was filtered off and hydrochloric acid was added to bring the pH of the filtrate to 7. The light yellow precipitate of the amine V was recrystallized from ethanol.

7-Trifluoromethyl-5-phenyl-6-chloro-2-oxo-(1H)-oxazolo[5,4-*b*]pyridine (VIa, $C_{13}H_6ClF_3N_2O_2$). Solutions of oxazolopyridine II (1 g, 3.6 mmole) in DMF (15 cm^3) and Cl_2 (0.4 g, 5.4 mmole) in DMF (5 cm^3) were mixed and kept for 24 h at room temperature. The mixture was then added to water and the precipitate recrystallized from ethanol.

6-Bromo-7-trifluoromethyl-5-phenyl-6-chloro-2-oxo-(1H)-oxazolo[5,4-*b*]pyridine (VIb, $C_{13}H_6BrF_3N_2O_2$). Br_2 (0.14 cm^3, 2.7 mmole) was added to a stirred solution of oxazole (II) (0.5 g, 1.8 mmole) in DMF (5 cm^3) and the mixture was heated at 60°C for 5 h. The mixture was cooled, diluted with water and the precipitate was recrystallized from ethanol.

4-Trifluoromethyl-6-phenyl-3-ethoxycarbonylamino-2-(1H)-pyridone (VII, $C_{15}H_{12}F_3N_2O_3$). A solution of oxazole II (0.5 g, 1.8 mmole) in ethanol (2.5 cm^3) and DMF (2.5 cm^3) was boiled for 2 h and then cooled. The residue was recrystallized from 80% ethanol.

TABLE 1. Properties of Compounds IV to VIIIa-i

Compound	Molecular formula	M.p., °C	^{1}H NMR spectrum,* δ, ppm	IR spectrum, cm^{-1}	Yield, %
IV Hydrate	$C_{13}H_6F_3KN_2O_2 \cdot 2H_2O$	> 255 (dec.)	3,33 (H_2O), 7,13...7,60 (4H, m, Ph, CH), 7,91 (2H, m, Ph)	3434, 1722, 1650, 1625, 1594	65,2
IV	$C_{13}H_6F_3KN_2O_2$	> 255 (dec.)	7,22...7,56 (4H, m, Ph, 6-H), 7,13...8,00 (2H, m, Ph)	1768, 1626, 1594	
V	$C_{12}H_9F_3N_2O$	198...200 (dec.)	5,98 (2H, s, NH_2), 6,42 (1H, s, 5-H), 7,40 (3H, m, Ph), 7,62 (2H, m, Ph), 12,02 (1H, NH)	3499, 3395, 1646, 1632, 1594	69,2
VIa	$C_{13}H_6ClF_3N_2O_2$	204...206	7,35 (5H, m, Ph), 12,44 (1H, NH)	3200...3060, 1798, 1634	64,3
VIb	$C_{13}H_6BrF_3N_2O_2$	187...190	7,55 (5H, m, Ph), 9,31 (1H, NH)	3210...3135, 1800, 1628	65,6
VII	$C_{15}H_{12}F_3N_2O_3$	208...210	1,19 (3H, t, CH_3), 4,05 (2H, q, CH_2), 6,68 (1H, s, 5-H), 7,49 (3H, m, Ph), 7,82 (2H, m, Ph), 8,64 (1H, s, NH), 12,42 (1H, NH)	3235, 2999, 1706, 1672, 1634	69,0
VIIIa	$C_{14}H_9F_3N_2O_2$	154...155	3,53 (3H, CH_3), 7,40 (3H, m, Ph), 7,71 (1H, s, 6-H), 7,89 (2H, m, Ph)	1788, 1634, 1616	85,7
VIIIb	$C_{15}H_{11}F_3N_2O_2$	104...106	1,40 (3H, t, CH3), 4,06 (2H, q, CH_2), 7,48 (3H, m, Ph), 7,77 (1H, s, 6-H), 7,97 (2H, m, Ph)	1814, 1634, 1614	74,4
VIIIc	$C_{16}H_{13}F_3N_2O_2$	116...118	1,02 (3H, t, CH_3), 1,80 (2H, m, CH_2), 3,91 (2H, t, CH_2), 7,44 (3H, m, Ph), 7,75 (1H, s, 6-H), 7,93 (2H, m, Ph)	1800, 1634, 1616	80,0
VIIId	$C_{17}H_{15}F_3N_2O_2$	95...97	0,97 (3H, t, CH_3), 1,11...2,00 (4H, m, $(CH_2)_2$), 3,93 (2H, t, CH_2), 7,46 (3H, m, Ph), 7,75 (1H, s, 6-H), 7,93 (2H, m, Ph)	1786, 1630, 1616	72,3
VIIIe	$C_{18}H_{17}F_3N_2O_2$	92...94	0,93 (3H, t, CH_3), 1,11...2,00 (6H, m, $(CH_2)_3$), 3,94 (2H, t, CH_2), 7,46 (3H, m, Ph), 7,77 (1H, s, 6-H), 7,95 (2H, m, Ph)	1782, 1632, 1614	69,4
VIIIf	$C_{18}H_{17}F_3N_2O_2$	108...110	0,97 (6H, d, $2CH_3$), 1,65 (3H, m, CH_2, CH), 3,93 (2H, m, CH_2), 7,44 (3H, m, Ph), 7,75 (1H, s, 6-H), 7,93 (2H, m, Ph)	1784, 1628, 1614	69,4
VIIIg	$C_{16}H_{11}F_3N_2O_2$	126...128	4,62 (2H, d, CH_2), 4,93...5,44 (2H, m, CH_2), 5,69...6,20 (1H, m, CH), 7,49 (3H, m, Ph), 7,77 (1H, s, 6-H), 8,00 (2H, m, Ph)	1794, 1670, 1654, 1630, 1610	80,0
VIIIh	$C_{20}H_{13}F_3N_2O_2$	137...139	5,24 (2H, s, CH_2), 7,24 (5H, m, Ph), 7,44 (3H, m, Ph), 7,75 (1H, s, 6-H), 7,97 (2H, m, Ph)	1790, 1632, 1612	57,7
VIIIi	$C_{16}H_{11}F_3N_2O_2$	140...142	3,76 (3H, s, CH_3), 4,71 (2H, s, CH_2), 7,40 (3H, m, Ph), 7,70 (1H, s, 6-H), 7,91 (2H, m, Ph)	1786, 1760, 1634, 1622	77,6

*Spectra of compounds IVa, V, VIa and VII were obtained with DMSO-D_6 solutions, IVb in CD_3OD, and VIIIa-i in $CDCl_3$.

General Method for the Preparation of N-Substituted 7-Trifluoromethyl-5-phenyl-2-oxooxazolo[5,4-*b*]pyridines (VIII a-i). The requisite organic halide (3.1 mmole) was added dropwise with stirring to a solution of the hydrated potassium salt IV (0.5 g, 1.41 mmole) in DMF (10 cm^3) and the mixture was heated on a water bath for 1 h. The mixture was cooled, poured into water and hydrochloric acid added to adjust the pH to 6-7. Compound VIII a was crystallized from 80% dioxane, VIIIb-i from 80% ethanol.

1-Allyl-7-trifluoromethyl-5-phenyl-2-oxo-oxazolo[5,4-*b*]pyridine (VIIIg, $C_{16}H_{11}F_3N_2O_2$) was also prepared from a solution of the hydrated potassium salt IV (0.3 g, 0.84 mmole) in ethanol (10 cm^3) and a solution of allyl bromide (0.16 cm^3, 1.9 mmole) in ethanol (5 cm^3). The mixture was heated on a water bath for 1 h. Yield 0.2 g (74.1 %). The product did not depress the melting point of with a sample of VIIIg prepared in DMF by the general method.

1-Methyl- (VIIIa) and 1-Isopentyl-7-trifluoromethyl-5-phenyl-2-oxooxazolo[5,4-*b*]pyridine (VIIIf) were prepared analogously from the anhydrous potassium salt (IV) in dry DMF in yields of 92.8 and 78.8% respectively. The yield of compound VIIIa from absolute ethanol solution was 71.4%.

REFERENCES

1. A. Binz, C. Rath and E. Mibkhat. Annalen, **475**, 139 (1929).
2. Ch. Flouzat, M. Blanchet, and G. Guillamet, Tetrahedr. Lett., **33**, 4571 (1992).
3. M. C. Viaud, P. Jamoneau, Ch. Flouzat, J.-G.Bizot-Espiard, B. Pfeiffer, P. Renard, D. H. Caignard, G. Adam, and G. Guillaumet, J. Med. Chem., **38**, 1278 (1995).
4. É. Gudrinietse, M. Yure, P. Pastors, A. Karkliniya, and É. Palitis, Khim. Geterotsikl. Soedin., No. 2, 271 (1995).
5. W. H. Daly and D. Poche, Tetrahedr. Lett., **29**, 5859 (1988).
6. K. Rufenacht, H. Kristinsson, and G. Mattern, Helv. Chim. Acta, **59**, 1593 (1976).