Synthesis of Trifluoromethylisoxazoloazines

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When reacted with mixtures of phosphorus pentoxide, aniline, and triethylamine hydrochloride, 5-acetamidoisoxazoles (*2* and *3*) gave isoxazolo[5,4-*d*]pyrimidines (*4* and *7*, respectively). The same reagent and cyclohexanone were used to prepare the isoxazoloquinoline *8*.

It has been reported that some 3-trifluoromethylisoxazole derivatives have antimicrobial activity.[1] Several patents claim the potential applications of the isoxazoloazines.[2] For example, substituted isoxazolo[5,4-*b*]pyridines[3] and [5,4-*d*]pyrimidines[4] are effective as antiasthmatics and fungicides, respectively. In this connection, it was of particular interest to synthesize isoxazolopyridines and pyrimidines with a trifluoromethyl group. For this purpose, reactions of appropriately substituted isoxazoles with the newly developed reagent mixtures of phosphorus pentoxide and amines[5–7] seemed to be an easy way. However, this type of reagents requires extremely vigorous reaction conditions with temperatures around 200 °C and performance of the reactions in salt mixtures of phosphate and substituted ammonium ions. Although isoxazoles could be expected to be too sensitive for these reaction conditions, it is nevertheless shown in this paper that mixtures of phosphorus pentoxide and amines are useful reagents for preparation of isoxazoloazines.

The acetamido derivative *2* prepared by acetylation of the corresponding amino compound *1a* was reacted with a mixture of aniline, phosphorus pentoxide, and triethylamine hydrochloride to give the isoxazolo[5,4-*d*]pyrimidin-4(5*H*)-one *4*. Deacetylation of *2* was detected as a side reaction, as shown by isolating *N,N'*-diphenylacetamidine (*5*).

By reaction of *2* with the corresponding reagent prepared from pyrrolidine hydrochloride, formation of *6* showed that both the ester and the acetamido group can undergo reactions with phosphorus pentoxide/amine reagents. Compound *6* was very stable in the reagent mixture and could be recovered when treated with the reagent mixture. An expected ring closure reaction with formation of 4,6-bis(pyrrolidino)-3-trifluoromethylisoxazolo[5,4-*b*]pyridine could not be detected. The diacetyl derivative *3* prepared in low yield from *1b* was reacted to give a 4-anilinoisoxazolo[5,4-*d*]pyrimidine *7* as the main product. Finally, to demonstrate that the phosphorus pentoxide/amine reagents are tools with many applications for the preparation of condensed isoxazoles, the aminooxazole derivative *1a* was reacted with cyclohexanone to give the otherwise difficultly accessible 4-anilinoisoxazolo[5,4-*b*]quinoline *8*.

Experimental

Preparation of isoxazole 2. Triethylamine (3.00 g, 30.00 mmol) dissolved in toluene (10 ml) was added dropwise to a solution of *1a*[8] (2.00 g, 9.5 mmol) and acetyl chloride (2.40 g, 30.6 mmol) in toluene (20 ml). After stirring at 20 °C for 17 h, the mixture was washed with water, dried over $MgSO_4$, and evaporated to leave an oily residue. The oil was dissolved in 50 ml water/ethanol (1:1), the mixture refluxed for 1 h and evaporated to leave a residue which was recrystallized from hexane/chloroform to give 1.56 g (65 %) of *2*; m.p. 79–80 °C.

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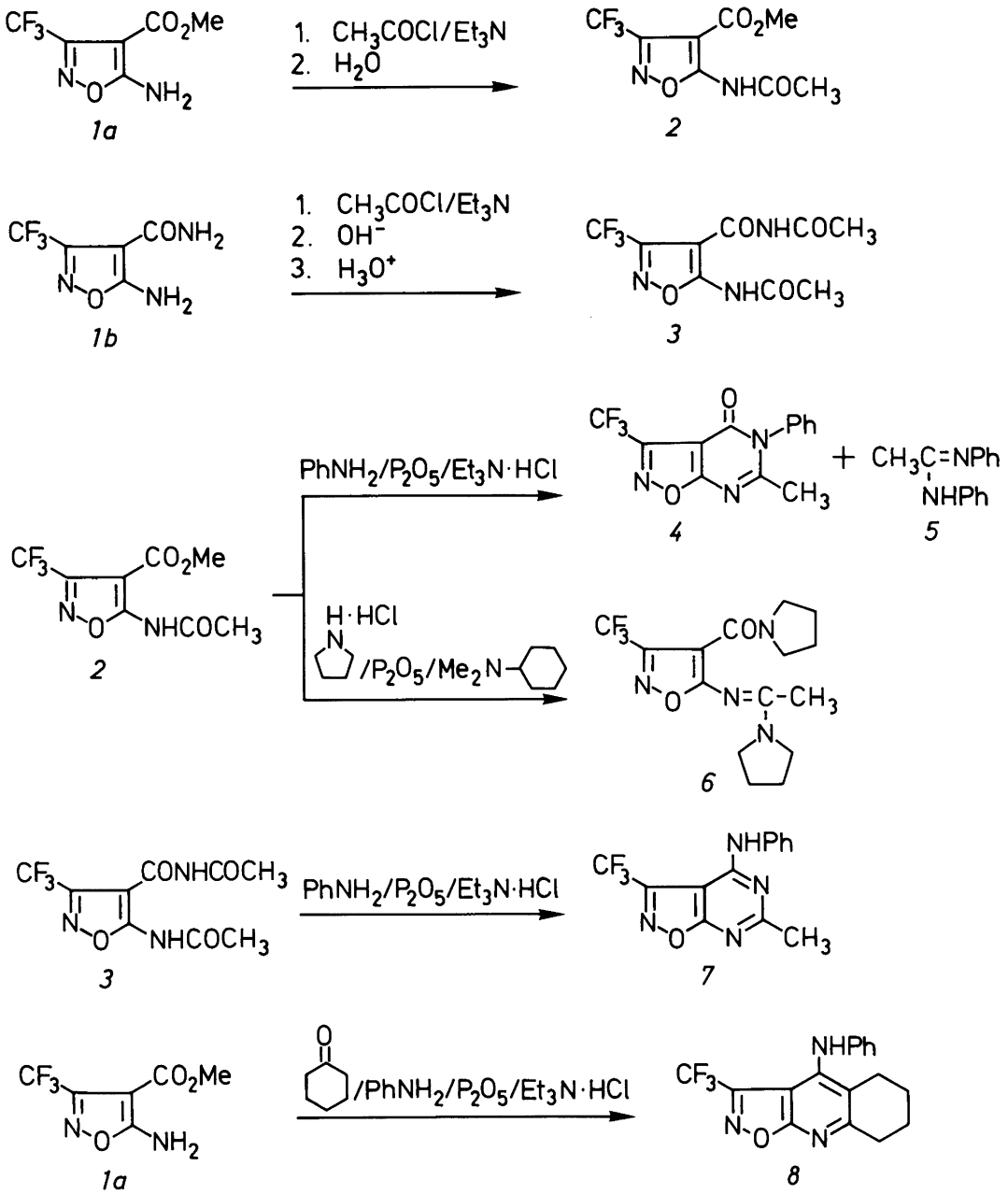

Preparation of isoxazole 3. Triethylamine (7.20 g, 71.3 mmol) was added dropwise to a solution of *1b*[8] (2.80 g, 14.4 mmol) and acetyl chloride (5.6 g, 71.3 mmol) in 30 ml of diethyl ether and the mixture stirred at 20 °C for 10 h. After addition of water, the mixture was extracted with diethyl ether and the combined extracts washed with 5 % aqueous $NaHCO_3$, dried over $MgSO_4$, and evaporated to leave 2.54 g of a residue. The residue obtained was stirred with 20 ml of 5 % aqueous

Na_2CO_3 at room temperature for 12 h and the solid formed collected and washed with diethyl ether. The solid was dissolved in water and the solution acidified with 5% aqueous HCl. The mixture was evaporated and the residue extracted with acetone. The extracts were dried over $MgSO_4$ and evaporated to give 0.37 g (9%) of *3* which was further purified by recrystallization from acetone/hexane; m.p. 207.5–208 °C (dec.).

*Preparation of isoxazolo[5,4-*d*]pyrimidinone* 4. A mixture of phosphorus pentoxide (2.25 g, 15.8 mmol), triethylamine hydrochloride (2.18 g, 15.9 mmol), and aniline (1.48 g, 15.9 mmol) was heated on a silicone oil bath at 150 °C for about 15 min until a homogeneous mass was obtained. One g (4.0 mmol) of *2* was added and the mixture stirred at 150 °C for 6.5 h. After cooling to 110 °C, 25 ml of water was poured into the mixture and stirring continued at 100 °C for about 30 min. The mixture was allowed to cool to room temperature and the hydrolyzed mixture adjusted to pH 5 with 2M NaOH. The precipitate was filtered off, dried, and recrystallized from cyclohexane/ethanol to give 0.55 g (47%) of *4*; m.p. 154–155 °C. The filtrate was adjusted to pH 9–10 with 2M NaOH and the solid formed collected on a filter, dried, and recrystallized from cyclohexane to afford 0.20 g (24%) of the acetamidine *5*; m.p. 129–131 °C (lit.,[9] 131–132 °C).

Reaction of 2 *with pyrrolidine in the presence of phosphorus pentoxide.* A mixture of phosphorus pentoxide (1.92 g, 13.5 mmol), pyrrolidine hydrochloride (1.45 g, 13.5 mmol), and cyclohexyldimethylamine (3.43 g, 27.0 mmol) was heated at 210 °C for 15 min and 0.85 g (3.4 mmol) of *2* added. The mixture was stirred at 210 °C for an additional 30 min and, after cooling to 140 °C, adjusted to pH 11 with 2M NaOH. The mixture was extracted with diethyl ether and the extracts dried over K_2CO_3 and evaporated to leave a residue which was recrystallized from petroleum ether/diethyl ether to give a solid *6* (0.53 g, 46%) which was purified by recrystallization from petroleum ethe/ethanol; m.p. 126.5–127 °C.

In a similar manner, *6* was treated with phosphorus pentoxide, pyrrolidine hydrochloride, and cyclohexyldimethylamine at 210 °C for 4.5 h. However, *6* was recovered unchanged.

*Preparation of the isoxazolo[5,4-*d*]pyrimidine* 7. A mixture of phosphorus pentoxide (710 mg, 5.0 mmol), triethylamine hydrochloride (690 mg, 5.0 mmol), and aniline (470 mg, 5.0 mmol) was heated at 180 °C for 30 min and 280 mg (1.0 mmol) of *3* added. The mixture was stirred at 180 °C for 1 h, allowed to cool to 100 °C, and adjusted to pH 10 with 2M NaOH. The mixture was extracted with diethyl ether, the combined extracts dried over $MgSO_4$ and evaporated to leave

Table 1. Preparation of *2, 3, 4, 6, 7,* and *8.*

Compound	Yield/%	M.p./°C (Solvent)	Molecular formula (molecular weight)	Analysis Calc./Found C	H	N	Peak matching Calc./Found
2	65	79–80 (Hexane-chloroform)	$C_8H_7F_3N_2O_4$ (252.15)	38.11 37.92	2.80 2.66	11.11 11.09	
3	9	207.5–208 (dec.) (Acetone-hexane)	$C_9H_6F_3N_3O_4$ (279.18)	38.72 38.73	2.89 2.87	15.05 15.33	
4	47	154–155 (Cyclohexane-ethanol)	$C_{13}H_8F_3N_3O_2$ (295.22)	52.89 52.86	2.73 2.71	14.23 13.96	
6	46	126.5–127 (Petroleum ether-ethanol)	$C_{15}H_{19}F_3N_4O_2$ (344.34)	52.32 52.53	5.56 5.59	16.27 16.43	344.1460 344.1459
7	30	118.5–119 (Hexane)	$C_{13}H_9F_3N_4O$ (294.24)	53.07 53.19	3.08 3.07	19.04 19.22	294.0728 294.0744
8	45	109–109.5 (Cyclohexane)	$C_{17}H_{14}F_3N_3O$ (333.32)	61.26 61.86	4.23 4.26	12.61 12.40	333.1089 333.1091

Table 2. Spectroscopic data of *2, 3, 4, 6, 7,* and *8.*

Compound	IR(KBr) ν/cm^{-1}	^{1}H NMR($CDCl_3$/TMS)/ppm	MS *m/z* [%]
2	3270, 1713, 1603 1280, 1193, 1163	2.39 (s, 3H), 3.92 (s, 3H) 9.7 (br.s., 1H)	
3	3260, 3210, 1735, 1700 1535, 1180, 1155	2.17 (s, 3H), 2.28 (s, 3H) 10.6 (br.s, 1H), 11.7 (br.s, 1H)[a]	
4	1730, 1555, 1205 1170, 1155	2.36 (s, 3H), 7.2–7.8 (m, 5H)	295 (M^+, 100, 294(39), 280(28) 118(65, 77(56)
6	1640, 1605, 1560 1430, 1170, 1145	1.8–2.1 (m, 8H), 2.20 (s, 3H) 2.6 (t, 8H)	344 (M^+, 48), 343(23), 316(22) 274(70), 206(58), 139(97) 114(20), 70(100)
7	3460, 1620, 1610, 1595 1580, 1210, 1135	2.73 (s, 3H), 7.1–7.8 (m, 6H)	294 (M^+, 98), 293(100), 252(17) 224(8), 184(5), 157(16) 118(8), 103(10), 77(41)
8	3410, 1605, 1580, 1505 1190, 1160, 1150	1.5–1.9 (m, 4H), 2.3 (t, 2H) 3.1 (t, 2H), 6.3 (br.s, 1H) 6.8–7.4 (m, 5H)	333 (M^+, 100), 305(10), 264(24) 256(10), 77(12)

[a]Measured in $CDCl_3$/DMSO-d_6.

a residue which was passed through a short column (silica, dichloromethane) to give 120 mg of a mixture of *7* and *4* in the ratio of 74/26 (30 %/11 %) according to ^{1}H NMR analysis. The products were separated by column chromatography (silica, diethyl ether/benzene, 1:2). The isoxazolopyrimidine *7* was further purified by recrystallization from hexane; m.p. 118.5–119 °C. The spectral data of thus separated *4* were similar to those obtained above.

Preparation of the tetrahydroisoxazolo[5,4-b]quinoline 8. Phosphorus pentoxide (8.52 g, 60.0 mmol), triethylamine hydrochloride (8.25 g, 60.0 mmol), and aniline (5.58 g, 60.0 mmol) were mixed and then heated at 220 °C until a clear homogeneous solution was obtained which was allowed to cool to below 150 °C. Cyclohexanone (1.76 g, 18.0 mmol) was added dropwise followed by *1a* (2.10 g, 10.0 mmol). The mixture was again heated at 220 °C with stirring for 30 min. After cooling to 120 °C, 200 ml of 2M NaOH were added and stirring continued for a further 30 min at room temperature. The mixture was extracted with dichloromethane and the extracts washed with saturated K_2CO_3, dried over K_2CO_3, and evaporated under reduced pressure to leave a solid. The solid was chromatographed on silica with dichloromethane to give 1.51 g (45 %) of *8*; m.p. 109–109.5 °C (recrystallized from cyclohexane).

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