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Studies on Pyridazine Compounds, XIX [1]. Mesylation of 5-Aminopyrazoles and Related Compounds**

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Summary. Acylation of 5-amino-1-substituted pyrazoles gave – depending on the substituents in position 3 and agents used – mono-, di- and triacylated products, respectively.

Keywords. Aminopyrazoles; Mesylation; Addition of N-acylpyridinium salt.

Untersuchungen an Pyridazinen, 19. Mitt.: Mesylierung von 5-Aminopyrazolen und verwandten Verbindungen

Zusammenfassung. Acylierung von 5-amino-1-substituierten Pyrazolen lieferte in Abhängigkeit von den Substituenten in Position 3 und den verwendeten Reagenzien mono-, di- und trisubstituierte Produkte.

Introduction

It is well-known that a number of aminopyrazoles can be N-monoacylated [2–4]. In a previous investigation we reported that mesylation of hydroxypyrazoles can lead to O-mesylated products, and to diacylated ones [5] due to an addition of the N-acylpyridinium salt into the position 4.

In a continuing search for useful pyrazoles of valuable biological activities, especially to gain methanesulfonamides with antiinflammatory activity, we now report on mesylations of aminopyrazoles containing a pyridazinyl or phenyl group in position 1.

Results and Discussion

The aminopyrazoles **1 a–d** were converted with mesyl chloride in pyridine at room temperature – not to the expected monomesylated derivatives – but to two kinds of compounds substituted differently: the N,N-dimesylated ones **2 a–d** and the so-called trimesylated **3 a, c** due to an addition of an N-mesylpyridinium salt into the position 4.

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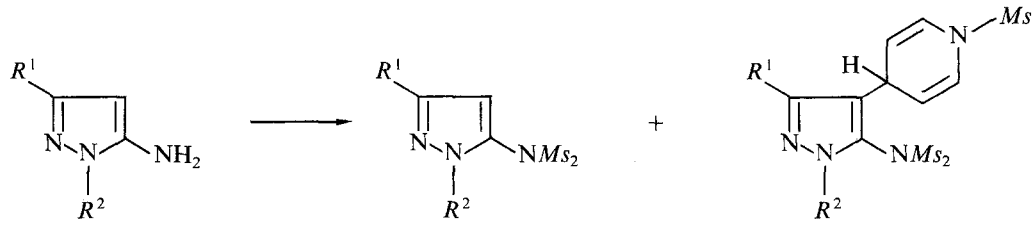


1a–d **2a–d** **3a,c**

a	$R^1 = Me$	R^2 = 6-chloro-3-pyridazinyl
b	*Ph*	6-chloro-3-pyridazinyl
c	*Me*	phenyl
d	*Ph*	phenyl

The structures of **2** and **3** were established on basis of their spectral data:

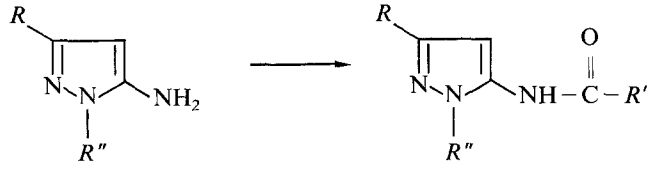
The ^{1}H-NMR spectra showed two equivalent mesyl groups, i.e. the N,N′ (pyrazole 2)-dimesylation can be ruled out; on the other hand, they showed the pyrazolyl H-4 protons at 6.9–7 ppm in **2a**, **c** and ~ 7.8 ppm in **2b**, **d**, respectively.

In the case of **3** the singlet of the pyrazole H-4 proton disappeared and the characteristic (AA′, MM′, X spin system) multiplets of the 1,4-dihydropyridine moiety were found at ~ 4.2, 4.9 and 6.65 ppm (1 : 2 : 2 intensity) and were assigned to the protons in positions 4′, 3′ and 2′, respectively.

The substituent of the pyrazole ring plays an important role in the reaction: in the presence of a bulky phenyl groups in position 3 (**2b, d**) there is no possibility for the formation of the addition product due to steric hindrance.

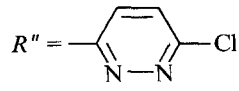
In attempting to establish some features of this interesting mesylation of 5-aminopyrazoles, acetylations of pyrazoles of this type were investigated and on the other hand the mesylation of other *α*-amino-heterocycles was performed.

Acylation of aminopyrazoles **1a, b** with trifluoracetic anhydride or acetylchloride in pyridine at room temperature gave the N-monoacylated products **4a–c**, but only **4c** was obtained under reflux in acetic anhydride; 5-amino-3,4-diphenylisoxazole, however, can be N,N-diacetylated under the same conditions [6].



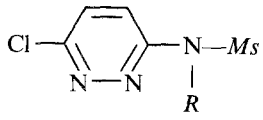
1a $R = Me$
b *Ph*

	R	*R′*
4a	*Me*	CF_3
b	*Ph*	CF_3
c	*Me*	*Me*

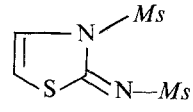


The characteristic amid band appears in the IR (KBr) at 1730 cm^{-1} and the NH-signal in the ^{1}H-NMR at 12.3 ppm (in **4c** $\nu_{C=O}$ 1690 cm^{-1}, δ_{NH} 11.1 ppm in $CDCl_3$).

For the study of the mesylation of other "*α*-amino-N-heterocycles" capable of tautomerism (e.g. 3-amino-6-chloro-pyridazine, 2-aminothiazole and 5-amino-3-methylthio-1*H*-1,2,4-triazole) have been selected because of the special tautomeric and electronic features of these compounds. 3-Amino-6-chloropyridazine gave the N,N-dimesylated derivative **5a**. The protomeric equilibrium and the ambient reactivity of 2-aminothiazole [7] favoured the N,N′-dimesylation (**6**), whereas the triazole derivative – due to the decreased basicity of the *exo*-amino group, and in agreement with our finding by the acylation of triazoles of this type [8] – yielded only the monomesylated derivative **7**:



5a $R = Ms$
b H



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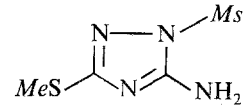

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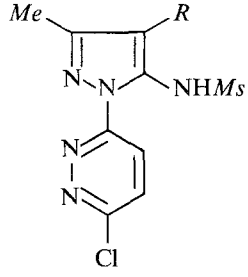
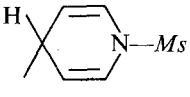
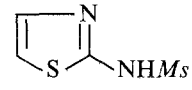
This synthetic method as described above cannot be used for the preparation of monomesylated compounds.

In order to gain these products, we have developed a reversed and selective method for demesylation either by *PPA*, by aqueous sodium hydrocarbonate solution or by sodium methoxide/methanol. **5b**, **8a**, **b** and **9** could be obtained with this procedure:



8a $R = H$
b $= H$





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In all cases the ^{1}H-NMR spectra showed a methanesulfonic acid (primary) amide moiety.

These reactions revealed that the monomesylated derivatives are stable compounds – but under the reaction conditions, due to the dissociable strong acidic mesyl NH-proton in contrast to the acetyl NH-proton – they can also be acylated again.

On the basis of this assumption we could transform **8a, b** into **2a** and **3a**.

From this study it seems obvious that the mesylation of α-amino heterocycles leads to differently acylated products depending on the electronic and steric structure of the substrates; on the other hand the addition of an acyl pyridinium salt to a highly electrophilic carbon atom of a heterocycle, e.g. pyrazole, results in very stable compounds (this addition could be found so far only in the case of indole [9, 10]).

Experimental

M.p.'s are uncorrected. IR spectra were recorded on a Jeol 60 spectrometer by using KBr pellets. ^{1}H-NMR spectra were measured on a Varian EM 390 spectrometer with *TMS* as the internal standard. Electron impact mass spectra (MS) were determined with a Varian MAT SM 1.

Mesylation of α-amino-N-heterocycles

To a stirred mixture of 5 mmol of the amino-compound in 5 ml pyridine 7.5 mmol of mesylchloride were added at 10°C for 30 min, then after 24 h again 7.5 mmol of mesylchloride. The reaction mixture was then stirred at room temperature for 6 h. The addition of ice cold 10% HCl caused the deposition of the product as colorless crystals. The fractionated crystallization from ethanol led to the pure compounds.

1-(6-Chloro-3-pyridazinyl)-3-methyl-5-(N,N-dimethylsulfonyl)pyrazolamine (**2a**)

M.p.: 216–218°C. $C_{10}H_{12}ClN_5O_4S_2$. Calcd.: C 32.83, H 3.31, S 17.53. Found: C 32.81, H 3.42, S 17.46. IR (KBr): 1370 and 1170 (SO_2) cm^{-1}. ^{1}H-NMR (*DMSO-d*$_6$): δ 7.00 (4-CH-pyrazole, s), 3.62 (s, 6H, mesyl) ppm. MS (M^+): 365 (365.83).

1-(6-Chloro-3-pyridazinyl)-3-phenyl-5-(N,N-dimethylsulfonyl)pyrazolamine (**2b**)

M.p.: 207–208°C. $C_{15}H_{14}ClN_5O_4S_2$. Calcd.: C 42.10, H 3.30, S 14.97. Found: C 42.07, H 3.41, S 14.79. IR (KBr): 1590 and 1490 (aryl), 1370 and 1160 (SO_2) cm^{-1}. ^{1}H-NMR (*DMSO-d*$_6$): δ 7.78 (4-CH-pyrazole, s), 3.78 (s, 6H, mesyl) ppm. MS (M^+): 428 (427.89).

3-Methyl-1-phenyl-5-(N,N-dimethylsulfonyl)pyrazolamine (**2c**)

M.p.: 140–142°C. $C_{12}H_{15}N_3O_4S_2$. Calcd.: C 43.75, H 4.59, S 19.47. Found: C 43.69, H 4.64, S 19.42. IR (KBr): 1590 and 1490 (aryl), 1360 and 1160 (SO_2) cm^{-1}. ^{1}H-NMR (*DMSO-d*$_6$): δ 6.91 (4-CH-pyrazole, s) ppm. 3.22 (s, 6H, mesyl). MS (M^+): 329 (329.40).

1,3-Diphenyl-5-(N,N-dimethylsulfonyl)pyrazolamine (**2d**)

M.p.: 151–152°C. $C_{17}H_{17}N_3O_4S_2$. Calcd.: C 52.17, H 4.38, S 16.39. Found: C 52.15, H 4.43, S 16.31. IR (KBr): 1590 and 1495 (aryl), 1360 and 1160 (SO_2) cm^{-1}. ^{1}H-NMR (*DMSO-d*$_6$): δ 7.4–8.1 (m, 11H, *Ar*H + 4-CH-pyrazole), 3.32 (s, 6H, mesyl) ppm. MS (M^+): 391 (391.34).

1-(6-Chloro-3-pyridazinyl)-3-methyl-4-(1-methylsulfonyl-1,4-dihydro-4-pyridyl)-5-(N,N-dimethylsulfonyl)pyrazolamine (**3a**)

M.p.: 253–254°C. $C_{16}H_{19}ClN_6O_6S_3$. Calcd.: C 36.74, H 3.66, S 18.39. Found C 36.70, H 3.72, S 18.35. IR (KBr): 1380 and 1170 (SO_2) cm^{-1}. ^{1}H-NMR (*DMSO-d*$_6$): δ 6.72 (d, 2H, 2',6'-CH), 4.96 (dd,

2 H, 3′,5′-CH), 4.26 (m, 1 H, 4′-CH), 3.65 (s, 6 H, mesyl), 3.30 (s, 3 H, mesyl) ppm. MS (M^+): 523 (523.02).

3-Methyl-4-(1-methylsulfonyl-1,4-dihydro-4-pyridyl)-1-phenyl-5-(N,N-dimethylsulfonyl)pyrazolamine (**3c**)

M.p.: 215–217°C. $C_{18}H_{22}N_4O_6S_3$. Calcd.: C 44.43, H 4.56, S 19.77. Found: C 44.37, H 4.61, S 19.72. IR (KBr): 1 590 and 1 500 (aryl), 1 365 and 1 160 (SO_2) cm^{-1}. ^{1}H-NMR (*DMSO-d*$_6$): δ 6.65 (d, 2 H, 2′,6′-CH), 4.90 (dd, 2 H, 3′,5′-CH), 4.16 (m, 1 H, 4′-CH), 3.22 (s, 9 H, mesyl) ppm. MS (M^+): 486 (486.58).

6-Chloro-3-(N,N-dimethylsulfonyl)pyridazinamine (**5a**)

M.p.: 243–244°C. $C_6H_8ClN_3O_4S_2$. Calcd.: C 25.22, H 2.83, S 22.44. Found: C 25.18, H 2.91, S 22.57. IR (KBr): 1 360 and 1 260 (SO_2) cm^{-1}. ^{1}H-NMR (*DMSO-d*$_6$): δ 3.72 (s, 6 H, mesyl) ppm. MS (M^+): 285 (285.74).

3-Methylsulyfonyl-2-(N-methylsulfonyl)tiazolimine (**6**)

M.p.: 201–202°C. $C_5H_8N_2O_4S_3$. Calcd.: C 23.43, H 3.15, S 37.53. Found: C 23.40, H 3.19, S 37.47. IR (KBr): 1 365 and 1 180 (SO_2) cm^{-1}. ^{1}H-NMR (*DMSO-d*$_6$): δ 3.77 (s, 3 H, endo-mesyl), 3.08 (s, 3 H, exo-mesyl) ppm. MS (M^+): 256 (256.37).

1-Methylsulfonyl-3-methylthio-5-(1H-1,2,4-triazolamine) (**7**)

M.p.: 147–148°C. $C_4H_8N_4O_4S_2$. Calcd.: C 19.99, H 3.36, S 26.69. Found: C 19.91, H 3.44, S 26.62. IR (KBr): 3 450 and 3 300 (NH_2), 1 360 and 1 180 (SO_2) cm^{-1}. ^{1}H-NMR (*DMSO-d*$_6$): δ 3.47 (s, 3 H, mesyl), 2.47 (s, 3 H, *Me*S) ppm. MS (M^+): 240 (240.27).

1-(6-Chloro-3-pyridazinyl)-3-methyl-5-(N-acetyl)pyrazolamine (**4c**)

To the stirred mixture of 1.05 g (5 mmol) of **1a** and 5 ml of pyridine in 5 ml of dioxane was added a solution of 0.86 g (11 mmol) acetylchloride in 5 ml of dioxane at 0° for 20 min. The reaction mixture was then stirred at 0–5°C for 40 min then at room temperature for 5 h, then poured into cold 10% HCl yielding **4c**. M.p.: 179–181°C. $C_{10}H_{10}ClN_5O$. Calcd.: C 47.72, H 4.01. Found: C 47.69, H 4.09. IR (KBr): 3 200 (NH), 1 690 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ (4-CH-pyrazole, s), 2.22 and 2.25 (2 × s, 2 × 3 H, methyl) ppm. MS (M^+): 251 (251.68).

Reaction with trifluoracetic anhydride

To a stirred mixture of 5 mmol of the amino-compound, 2.1 g (10 mmol) trifluoracetic anhydride and 0.39 g (5 mmol) of pyridine was added 5 ml of pyridine at 10 °C for 30 min, then it was stirred at room temperature for 6 h. The reaction mixture was then poured into cold 10% HCl to precipitate the product, which could be recrystallized from ethanol.

1-(6-Chloro-3-pyridazinyl)-3-methyl-5-(N-trifluoroacetyl)pyrazolamine (**4a**)

M.p.: 170–172°C. $C_{10}H_7ClF_3N_5O$. Calcd.: C 39.17, H 2.30. Found: C 39.15, H 2.38. IR (KBr): 3 170 (NH) and 1 730 (C=O) cm^{-1}. ^{1}H-NMR (*DMSO-d*$_6$): δ 6.66 (4-CH-pyrazole, s) ppm. MS (M^+): 305 (305.64).

1-(6-Chloro-3-pyridazinyl)-3-phenyl-5-(N-trifluoracetyl)pyrazolamine (**4b**)

M.p.: 248–250°C. $C_{15}H_9ClF_3N_5O$. Calcd.: C 48.99, H 2.47, F 15.77. Found: C 48.94, H 2.52, F 15.65. IR (KBr): 3170 (NH) and 1730 (C=O) cm^{-1}. ^{1}H-NMR (*DMSO-d_6*): δ 7.30 (4-CH-pyrazole, s) ppm. MS (M^+): 367 (367.72).

Demesylation

a) *By PPA* (**5b**, **8a**, **b** *and* **9**). A solution of 1 g of the dimesylated compounds in 5 ml polyphosphoric acid was stirred at 120°C for 40 min. The reaction mixture was then poured onto cracked ice, diluted with water to precipitate the products.

b) *By sodium methoxide* (**8a**, **b**). A mixture of 1 mmol of **2a** (or **3a**), 3 mmol of sodium methoxide in 25 ml of methanol was stirred at 10°C for 3 h. The reaction mixture was then neutralized by 10% aq. acetic acid and diluted with water to deposit the product.

c) *By aqueous sodium hydrocarbonate solution (6%)* (**8a**). A mixture of 0.5 g of **2a** in 10 ml of 6% $NaHCO_3$ solution was stirred at 90°C for 5 to 8 h. The work-up is the same as mentioned above (method b).

6-Chloro-3-(N-methylsulfonyl)pyridazinamine (**5b**)

M.p.: 145–146°C. $C_5H_6ClN_3O_2S$. Calcd.: C 28.92, H 2.91. Found: C 28.94, H 2.98. IR (KBr): 2500–3100 (NH, br), 1350 and 1150 (SO_2) cm^{-1}. ^{1}H-NMR ($CDCl_3$ + *DMSO-d_6*): δ 3.33 (s, 3H, mesyl) ppm. MS (M^+): 207 (207.65).

1-(6-Chloro-3-pyridazinyl)-3-methyl-5-(N-methylsulfonyl)pyrazolamine (**8a**)

M.p.: 184–185°C. $C_9H_{10}ClN_5O_2S$. Calcd.: C 37.57, H 3.50, S 11.14. Found: C 37.58, H 3.58, S 11.06. IR (KBr): 2800–3200 (NH, br) cm^{-1}. ^{1}H-NMR (*DMSO-d_6*): δ 6.16 (4-CH-pyrazole, s), 3.10 (s, 3H, mesyl) ppm. MS (M^+): 287 (287.73).

1-(6-Chloro-3-pyridazinyl)-3-methyl-4-(1-methylsulfonyl-1,4-dihydro-4-pyridyl)-5-(N-methylsulfonyl)pyrazolamine (**8b**)

M.p.: 211–213°C. $C_{15}H_{15}ClN_6O_4S_2$. Calcd.: C 40.68, H 3.41, S 14.48. Found: C 40.62, H 3.48, S 14.41. IR (KBr): 3250 (NH) cm^{-1}. ^{1}H-NMR (*DMSO-d_6*): δ 6.55 (dd, 2H, 2′,6′-CH), 4.83 (dd, 2H, 3′,5′-CH), 4.28 (m, 1H, 4′-CH), 3.21 and 2.95 (2 × s, 2 × 3H, mesyl) ppm. MS (M^+): 442 (442.90).

2-(N-Methylsulyfonyl)thiazolamine (**9**)

M.p.: 221–223°C (219.5–221°C [11], 220–222°C [12]).$C_4H_6N_2O_2S_2$. Calcd.: C 26.95, H 3.39, S 35.98. Found: C 26.87, H 3.44, S 35.82. IR (KBr): 2700–3200 (NH, br). ^{1}H-NMR (*DMSO-d_6*): δ 2.90 (s, 3H, mesyl). MS (M^+): 178 (178.25).

Acknowledgment

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