# Efficient Syntheses of ω-Chloro-, ω-Imido- and ω-Aminoalkyl-1,2,4-triazoles from *N*-Acyl-formamidinium Salts or *N*-Acylformamides and Hydrazines

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Received July 8, 1991

ω-Halo and ω-amidoalkylcyanides **1** are transformed to ω-functionalized *N*-acylformamidinium salts **4** or formamide **6a** by HCl catalyzed addition of chloromethylene iminium salts, derived from formamides **2** and POCl$_3$. Advantageously, β-halo-propionyl-formamidinium salts **4** can also be obtained from acrylonitrile. Regiospecific and chemoselective cyclization of *N*-acylformamidinium salts **4** or formamide **6a** to ω-functionalized 5-alkyl-1,2,4-triazoles **9** is possible by reaction with hydrazines **5**, *via* intermediate *N*-acylamidrazones **8** or azines **7** which must be isolated and cyclized separately in a number of cases. 5-Phthalimidoalkyl-1,2,4-triazoles **9** are cleaved to 5-(aminoalkyl)-1,2,4-triazoles **10**.

**Effiziente Synthese von ω-Chlor-, ω-Imido- und ω-Aminoalkyl-1,2,4-triazolen aus *N*-Acyl-formamidiniumsalzen oder *N*-Acylformamiden und Hydrazinen**

Funktionalisierte *N*-Acylformamidiniumsalze **4** oder das *N*-Phthalimidoacylformamid **6a** werden aus ω-Halogen- oder ω-Amidoalkylcyaniden **1** durch HCl-katalysierte Addition von Chlormethyleniminiumsalzen hergestellt. β-Halogen-propionyl-formamidiniumsalze **4** sind vorteihafterweise auch ausgehend von Acrylnitril und Chlormethyleniminiumsalzen zugänglich. Die *N*-Acylformamidiniumsalze **4** bzw. das Acylformamid **6a** lassen sich regiospezifisch und chemoselektiv durch Reaktion mit Hydrazinen **5** in ω-funktionalisierte 5-Alkyl-1,2,4-triazole **9** überführen. Als Intermediate werden *N*-Acylamidrazone **8** oder Azine **7** durchlaufen, die in einigen Fällen isoliert und getrennt cyclisiert werden müssen. Die synthetisierten 5-Phthalimidoalkyl-1,2,4-triazole **9** werden zu 5-Aminoalkyl-1,2,4-triazolen **10** gespalten.

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ω-Functionalized 5-alkyl-1,2,4-triazoles such as 5-(2-aminoethyl)-1,2,4-triazole have gained pharmaceutical interest as histamine analogues. Known ring closure reactions leading to ω-aminoalkyl, ω-phthalimidoalkyl, and ω-chloralkyl-1,2,4-triazoles are:

1. Cyclisation of 1-(ω-phthalimidoalkanoyl)thiosemicarbazides (*e.g. ref.*[1])
2. Reaction of functionalized α-aminoacetimidoester with formylhydrazine (*e.g.* ref.[2])
3. Condensation of *N*-(1,2-dichlorovinyl)benzimidoylchloride with arylhydrazines (*e.g.* ref.[3])
4. Reaction of diethyl-α-chloroacetylamino-malonate with aryl-diazonium salts (*e.g. ref.*[4])
5. Reaction of α-chloroalkanoylchlorides with amidrazones (*e.g. ref.*[5])

These syntheses have only a limited range of application. Therefore, we tried to synthesize ω-chloro, ω-phthalimido and ω-aminoalkyl-1,2,4-triazoles **9** by reaction of *N*-acylformamidines or *N*-acylformamides as C-N-C-synthons with hydrazines as N-N-building block. This method was very useful in the synthesis of 5-aryl and 1,5-diaryl-1,2,4-triazoles[6].

The ω-functionalized *N*-acyl-formamidinium salts **4** and -formamide **6a** (Table 1) necessary as educts for the preparation of the ω-functionalized 5-alkyl-1,2,4-triazoles **9** can be conveniently obtained[7] by addition of adducts of *N,N*-disubstituted formamides **2** and POCl$_3$ (chloromethylene iminium salts) to corresponding ω-functionalized nitriles **1** (chloroacetonitrile, phthalimidoacetonitrile or phthalimidopropionitrile) *via* intermediate 2-aza-3-chloro-2-propeniminium salts **3**[20]. This addition requires mild conditions and catalysis by gaseous HCl. Otherwise no reaction takes place or other products, *e.g.* azapentamethinium salts[8] by bisiminoformylation, are obtained. In some cases the success of the reaction also depends on the substituents R$^1$ at the N atom of **2** that is on its electron density in the chloromethylene iminium salts[9]. *E.g.* the adducts of DMF or *N*-formyl-pyrrolidine **1** (NR$^1_2$ = pyrrolidino) with POCl$_3$ in reaction with chloroacetonitrile give the corresponding *N*-chloroacetyl-formamidinium salts **4** while the stronger electrophilic *N*-formylmorpholine gives 2-aza-3,4-dichloro-pentamethinium salts by bisiminoformylation even in the presence of HCl and at low temp. (0°C).

β-Phthalimido-propionitrile **1** (X = phthalimido, n = 2) smoothly reacts in the same way. But during working up mixtures of *N*-(β-phthalimido-propionyl)-amidinium salts **4** and formamide **6a** are obtained. Therefore, these reaction mixtures are further hydrolyzed by ice water in order to obtain *N*-(β-phthalimido-propionyl)formamide **6a** (X = phthalimido, n = 2) solely in high yield.

*N*-(β-Halopropionyl)formamidinium salts **4** (X = Cl, Br; n = 2) can be prepared starting from *N,N*-disubstituted formamide **2**/POCl$_3$ adducts in two different ways (Method A), *i.e.* using β-halopropionitrile **1** (X = halo, n = 2) or, more conveniently, acrylonitrile as substrate. In the latter procedure two additions take place, that is addition of hydrohalide to the C=C double bond and addition of the **2**/POCl$_3$ adduct to the C≡N triple bond. Again 2-aza-3-chloro-propeniminium salts **3** (n = 2, X = Cl, Br) are assumed as intermediates. With the exception of not well described *N,N*-dimethyl-*N'*-(β-chloropropionyl)-formamidinium salts **4** (X = Cl, n = 2, R$^1$ = CH$_3$) which were claimed[10] as intermediates in the synthesis of phosphorus containing insecticides starting from β-chloropropionamide and *N,N*-dimethylformamiddimethylacetal all ω-functionalized acylformamidini-

Arch. Pharm. (Weinheim) 325, 519-529 (1992) 0365-6233/92/080-0519 $ 3.50 + .25/0

**Table 1:** Functionalized *N*-Acyl-formamidinium Perchlorates **4** and *N*-Acyl-formamide **6a**

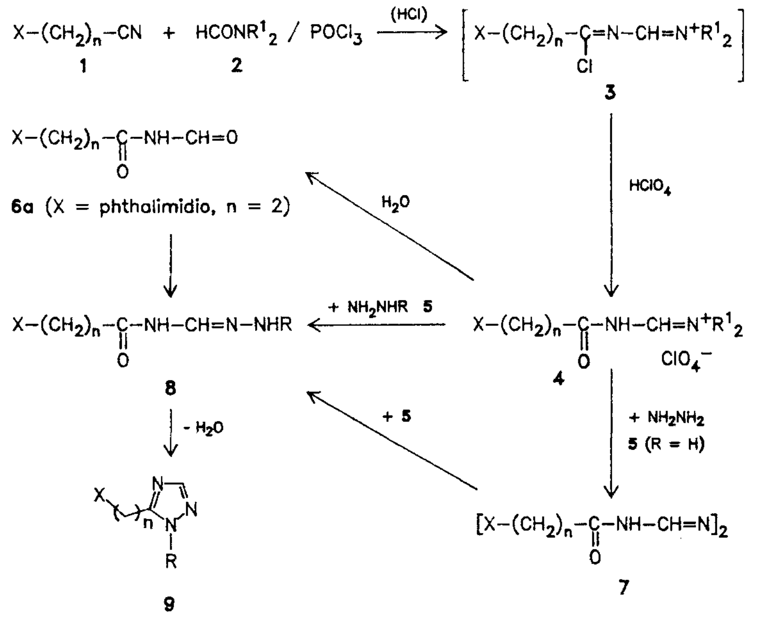
| | X | n | $R_2^1$ | yield [%]/ Method | m.p. a) [° C] | molecular formula elemental analysis Calcd. Found | C | H | Hal | N |
|---|---|---|---|---|---|---|---|---|---|---|
| 4a | Cl | 1 | $(CH_3)_2$ | 46/A | 169-172 | $C_5H_{10}Cl_2N_2O_5$ (249.1) | | | | |
| | | | | | | | 24.1 | 4.05 | 28.5 | 11.2 |
| | | | | | | | 24.2 | 4.17 | 28.4 | 11.4 |
| 4b | Cl | 1 | $(CH_2)_4$ | 42/A | 184-187 | $C_7H_{12}Cl_2N_2O_5$ (275.1) | | | | |
| | | | | | | | 30.6 | 4.40 | 25.8 | 10.2 |
| | | | | | | | 30.3 | 4.56 | 26.1 | 10.1 |
| 4c | Cl | 2 | $(CH_3)_2$ | 71/A b)<br>66/A c) | 135-137 | $C_6H_{12}Cl_2N_2O_5$ (263.1) | | | | |
| | | | | | | | 27.4 | 4.60 | 26.9 | 10.6 |
| | | | | | | | 27.4 | 5.06 | 26.9 | 10.6 |
| 4d | Cl | 2 | $(CH_2)_4$ | 62/A b) | 131-133 | $C_8H_{14}Cl_2N_2O_5$ (289.1) | | | | |
| | | | | | | | 33.2 | 4.88 | | 9.7 |
| | | | | | | | 33.2 | 5.04 | | 9.8 |
| 4e | Cl | 2 | $(CH_2)_5$ | 59/A b) | 139-141 | $C_9H_{16}Cl_2N_2O_5$ (303.1) | | | | |
| | | | | | | | 35.7 | 4.66 | | 9.2 |
| | | | | | | | 36.0 | 5.24 | | 9.5 |
| 4f | Cl | 2 | $(CH_2)_2O(CH_2)_2$ | 81/A b) | 155-157 | $C_8H_{14}Cl_2N_2O_6$ (305.1) | | | | |
| | | | | | | | 31.5 | 4.62 | | 9.2 |
| | | | | | | | 31.0 | 4.43 | | 9.4 |
| 4g | Br | 2 | $(CH_2)_2O(CH_2)_2$ | 77/A b) | 195-197 | $C_8H_{14}BrClN_2O_6$ (349.6) | | | | |
| | | | | | | | 27.5 | 4.04 | | 8.0 |
| | | | | | | | 28.0 | 4.62 | | 8.6 |
| 4h | $N(CH_2CH_3)_2$ | 2 | $(CH_2)_4$ | 27/A | 138-140 | $C_{12}H_{24}ClN_3O_5$ (325.8) | | | | |
| | | | | | | | 44.2 | 7.42 | | 12.9 |
| | | | | | | | 44.8 | 6.90 | | 12.7 |
| 4i | succinimido | 2 | $(CH_3)_2$ | 31/B | 158-160 | $C_{10}H_{16}ClN_3O_7$ (311.7) | | | | |
| | | | | | | | 36.9 | 4.95 | 10.9 | 12.9 |
| | | | | | | | 36.8 | 4.79 | 11.2 | 12.6 |
| 6a | phthalimido | 2 | --- | 90 | 178-182 | $C_{12}H_{10}N_2O_4$ (246.2) | | | | |
| | | | | | | | 58.5 | 4.09 | | 11.4 |
| | | | | | | | 58.8 | 3.89 | | 11.3 |

a) recrystallized from acetic acid.- b) prepared from acrylonitrile.- c) prepared from β-substituted propionitrile.

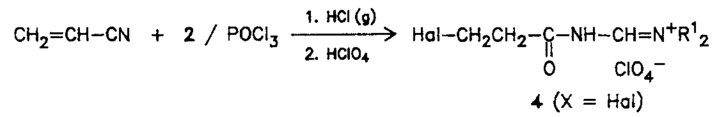
um salts **4** and the formamide **6a** are new. They form crystalline solids, which are stable enough to be stored for months in a refrigerator. *N*-(β-Bromopropionyl)-formamidinium salt **4g** (X = Br, n = 2), however, is more sensitive.

In order to synthesize ω-functionalized 5-alkyl-1,2,4-triazoles **9** the *N*-acyl-formamidinium salts **4** or formamides **6a** are reacted with hydrazines **5**[9,11,12]. Depending on substituents in the educts these reactions either lead directly to the isolation of ω-functionalized 5-alkyl-1,2,4-triazoles **9** (Methods F,H) (n = 2, X = succinimido, R = 4-nitrophenyl or n = 2, X = chloro, R = methyl) (Table 5) or acyl-formamidrazones **8** (Table 3) are obtained. As far as the substituent R is not too strongly electron withdrawing, the amidrazones **8** can further be cyclized in high yields to the corresponding triazoles **9** by heating in polyphosphoric acid (Method E). Heating of β-chloro-propionyl-formamidrazone **8e** (X = Cl, n = 2) in acetic anhydride did not cyclize but, after hydrolytic working up, led to 1-acetyl-2-(4-nitro-phenyl)hydrazine.

As a peculiarity azines **7** are formed, when ω-chloroacyl-formamidinium salts **4** (X = Cl) are reacted with hydrazine hydrate **5** (R = H). Obviously the unsubstituted amino group of the expected primary amidrazone **8** (X = Cl, R = H) is nucleophilic enough to attack another molecular of the educt **4**. Surprisingly, it is possible to transform these azines **7** to the desired 1-unsubstituted 5-(ω-chloroalkyl)-1,2,4-triazoles **9** (X = Cl, R = H) by treating with additional hydrazine hydrate (Method G). Probably this reaction also runs *via* intermediate chloroacyl-amidrazones **8** (X = Cl, R = H) which, however, were not isolated. This supposition is supported bythe fact, that reaction of the azine 7b (X = Cl, n = 2) with 4-nitrophenylhydrazine 5 (R = $C_6H_4$-$NO_2$ (p)) gives rise to the



Scheme 1



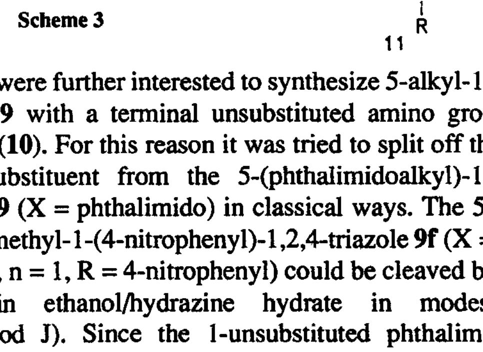
$$CH_2{=}CH{-}CN + 2 / POCl_3 \xrightarrow[2.\ HClO_4]{1.\ HCl\ (g)} Hal{-}CH_2CH_2{-}\underset{\overset{\|}{O}}{C}{-}NH{-}CH{=}N^+R^1_2\ ClO_4^-$$

4 (X = Hal)

Scheme 2

formation of 3-(β-chloropropionyl)-1-(4-nitrophe-nyl)formamidrazone **8e** (X = Cl, n = 2, R = 4-nitrophenyl) in 48% yield.

Since in the phthalimidopropionyl-substituted series (X = phthalimido) the *N*-acyl-formamide **6a** was available rather than the pure formamidinium salt **4** (X = phthalimido, n = 2), the former was employed in reactions with hydrazines **5**. Smooth formation of 5-(ω-phthalimidoalkyl)-1,2,4-triazoles **9** (X = phthalimido) are achieved in acetic acid medium. It is worth mentioning, that reaction with thiosemicarbazide gives the same 1-unsubstituted triazole **9m** (X = phthalimido, n = 2, R = H) like hydrazine hydrate. Obviously thiocyanic acid is split off in the former case. The synthesis of a corresponding triazoles fails if the *N*-(β-phthalimidopropionyl)formamide **6a** is reacted with methylhydrazine **5** (R = $CH_3$). In a fragmentation-like reaction β-phthalimidopropionitrile is formed[13)]. For most reactions of acylformamidinium salts **4** or formamide **6a** mentioned above the high chemo and regioselectivity is remarkable, leaving the functional group X (halo or phthalimido) unaffected on one hand and giving rise to the isolation of only the 5-substituted 1,2,4-triazoles **9** rather than the regioisomeric 3-substituted 1,2,4-triazoles on the other hand. This fact demonstrates the high reactivity of the *N*-acylformamidinium and *N*-acylformamide moiety of **4** and **7**, respectively, which allows to run the reactions with hydrazines under such mild conditions (10 min at room temp.) that the substituent X survives. On the other hand it is well known that halo or phthalimido groups in α- or β-position of a carbonyl or cyano group can react with hydrazines at elevated temp. (for an example see ref.[14)]). An alternative way to 5-phthalimidoalkyl-1,2,4-triazoles **9** (X = phthalimido) is found in reaction of corresponding chloroalkyl-1,2,4-triazole **9** (X = Cl) with phthalimide (Method I).



Scheme 3

We were further interested to synthesize 5-alkyl-1,2,4-triazoles **9** with a terminal unsubstituted amino group (X = $NH_2$) (**10**). For this reason it was tried to split off the phthaloyl-substituent from the 5-(phthalimidoalkyl)-1,2,4-triazoles **9** (X = phthalimido) in classical ways. The 5-phthalimidomethyl-1-(4-nitrophenyl)-1,2,4-triazole **9f** (X = phthalimido, n = 1, R = 4-nitrophenyl) could be cleaved by refluxing in ethanol/hydrazine hydrate in modest yield (Method J). Since the 1-unsubstituted phthalimidoalkyl-1,2,4-triazoles **9** (X = phthalimido, n = 2, R ≠ H) have demonstrated a certain resistance to hydrazinolysis during their synthesis from **6a** and hydrazine, hydrolytic conditions were

**Table 2:** Spectroscopic Data of Functionalized *N*-Acylformamidinium Perchlorates **4** and *N*-Acyl-formamide **6a**

| Nr. | $^1$H-NMR [D$_6$]DMSO: | MS (70 eV):*m/z* (%) |
|---|---|---|
| 4a[a)] | 3.60[s, 3 H, NCH$_3$], 3.79[s, 3 H, NCH$_3$], 4.81[s, 2 H, CH$_2$], 9.05 [s, 1 H, CH] 12.12 [s, 1 H, NH] | 99 (42), 93 (17), 49 (22), 44 (100) 42 (27) |
| 4b | | 174 (1.5) [M$^{+\cdot}$- HClO$_4$], 126 (10), 125 (100), 71 (2.5) |
| 4c[b)] | 3.03 [t, J = 7 Hz, 2 H, COCH$_2$], 3.20 [s, 3 H, NCH$_3$], 3.36 [s, 3 H, NCH$_3$], 3.75 [t, J= 7 Hz, 2 H, CCH$_2$Cl], 8.75 [s, 1 H, CH], 11.25 [br, NH] | 99 (100), 45 (49), 44 (57), 43 (23), 42 (26), 38 (21), 36 (58) |
| 4d | 1.93 [m, 4 H, CCH$_2$CH$_2$C], 3.05 [t, J = 6 Hz,2 H, ClCH$_2$C$\underline{H}_2$], 3.58 [m, 4 H, CH$_2$NCH$_2$], 3.75 [t, J = 6 Hz, 2 H, CH$_2$Cl], 8.92 [s, 1 H, CH], 11.8 [br, NH] | |
| 4e | 1.59 [m, 6 H, CH$_2$C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$CH$_2$], 3.0 [t, J = 6 Hz, 2 H, C$\underline{H}_2$CH$_2$Cl], 3.70 [m, 6 H, CH$_2$NCH$_2$, CH$_2$Cl], 8.70 [s, 1 H, CH], 8.89 [s, CH], 11.10 [Br, NH] | |
| 4h[c)] | 1.16 [t, J = 7 Hz, 6 H, 2 CH$_3$ ], 1.88 [m, 4 H, CCH$_2$CH$_2$C], 3.40 [m, 12 H, 4 NCH$_2$, NCH$_2$CH$_2$], 8.87 [s, 1 H, CH], 9.00 [s, 1 H, CH], 11.40 [m, 1 H, NH] | |
| 4i[d)] | 2.87 [s, 4 H, COCH$_2$CH$_2$CO] 3.11 [t, J = 6 Hz, 2 H, CH$_2$CO], 3.54 [s, 3 H, NCH$_3$], 3.72 [s, 3 H, NCH$_3$], 3.91 [t, J = 6 Hz, 2 H, CH$_2$N], 9.02 [s, 1 H, CH] | 212 (4) [M$^{+\cdot}$-HClO$_4$], 100(9), 99 (100), 56 (10), 55 (24), 44 (31) 43 (10), 42 (20) |
| 6a | 2.91 [t, J = 8 Hz, 2 H, CH$_2$CO], 4.02 [t, J = 8 Hz, 2 H, NCH$_2$], 8.0 [s, 4 H, C$_6$H$_4$], 9.11 [m, 1 H, CHN], 11. 35 [br, NH] | 246 (6) [M$^{+\cdot}$], 200 (18), 174 (100), 160 (69), 129 (17), 104 (26), 77 (27), 76 (39) |

[1)] UV (CH$_3$CN): λ max (lg ε) = 229 nm (4.18).- [2)] UV (CH$_3$CN): λ max (lg ε) = 226 (4.23).- IR (KBr): ν = 1770 cm$^{-1}$ (C=O).- [3)] IR (KBr): ν = 1755 cm$^{-1}$ (C=O).- [4)] UV (CH$_3$CN): λ max (lg ε) = 228 nm (4.23).

chosen to cleave the phthalimido group. Boiling in 20% aqueous HCl or HBr gives high yields of 5-(β-aminoethyl)-1,2,4-triazole hydrohalides **10**·HHal or dihydrohalides **10**·2HHal (Method K). Curiously liberation of the unprotonated 5-(β-aminoethyl)-1,2,4-triazoles **10** by treating the salts **10**·HHal with triethylamine in acetonitrile or ethanol or with aqueous NaOH was not satisfying. In case of the 5-(β-aminoethyl)-1,2,4-triazole hydrochlorides **10p**·HCl and **10m**·HCl (n = 2, R = 4-nitrophenyl or H, respectively) treatment with aqueous NaOH gives rise to the formation of a mixture of the anticipated aminoethyl-triazole **10p** or **10m** and the corresponding 5-methyl-1,2,4-triazole **11** (R = 5-nitrophenyl or H respectively). The formation of the products **11** can be explained by a retro-*Mannich* reaction[15)]. Most of the ω-functionalized 5-alkyl-1,2,4-triazoles **9** and **10** described above except 5-chloromethyl **9a**[16)], 5-(β-chloroethyl) **9g**[17)], 5-(β-phthalimidoethyl) **9m**[17)] and 5-(β-aminoethyl-1,2,4-triazole **10m**[17)], are new. These known compounds were synthesized either starting from ethyl-1,2,4-triazole-3-carboxylate by reduction and chlorination[16)] or by multi-step synthesis including desulfurization of a corresponding 3-mercapto-1,2,4-triazole in the last step[17)]. The reported melting point of 5-(β-aminoethyl)-1,2,4-triazole dihydrochloride **10m**· 2HCl[17)] is in contrast to the value found by us. Since we could prove the structure of the compound **10m**·2HCl obtained starting from the phthalimidopropionylformamide **6a** (X = phthalimido, n = 2) *via* the corresponding phthalimidoethyl-1,2,4-triazole **9m** by modern spectroscopic methods as well as by subsequent reactions[9)] either the previously reported melting point or that proposed structure are wrong.

The structure of the new triazoles **9** and **10** is confirmed by elemental analysis and by spectroscopic methods. The signal of H-3 of the 1,2,4-triazole ring appears in the typical range of 7.7-8.35 ppm, excluding isomeric ω-

**Table 3:** *N*-Acyl-formamidrazones **8** and Azines **7**

| | X | n | R | yield [%]/ Method | m.p. [° C] | molecular formula elemental analysis Calc. Found | C | H | Cl | N |
|---|---|---|---|---|---|---|---|---|---|---|
| 8a[a)] | Cl | 1 | $C_6H_5$ | 81/C | 94-96<br>($CHCl_3$) | $C_9H_{10}ClN_3O$ (211.5) | | | | |
| 8b | Cl | 1 | $4\text{-}NO_2C_6H_4$ | 84/D | 213-215<br>(iso-propanol) | $C_9H_9ClN_4O_3$ (256.7) | | | | |
| | | | | | | Calc. | 42.1 | 3.53 | 13.8 | 21.8 |
| | | | | | | Found | 41.9 | 3.80 | 14.2 | 21.5 |
| 8c | Cl | 2 | $C_6H_5$ | 81/C | 119-121<br>($CHCl_3$) | $C_{10}H_{12}ClN_3O$ (225.7) | | | | |
| | | | | | | Calc. | 53.2 | 5.36 | 15.7 | 18.6 |
| | | | | | | Found | 53.2 | 5.59 | 16.0 | 18.7 |
| 8d | Cl | 2 | $4\text{-}FC_6H_4$ | 43/D | 114-117<br>(toluene) | $C_{10}H_{11}ClFN_3O$ (243.7) | | | | |
| | | | | | | Calc. | 49.3 | 4.52 | 14.6 | 17.3 |
| | | | | | | Found | 49.0 | 4.51 | 15.0 | 17.6 |
| 8e | Cl | 2 | $4\text{-}NO_2C_6H_4$ | 70/D | 193-195<br>(iso-propanol) | $C_{10}H_{11}ClN_4O_3$ (270.7) | | | | |
| | | | | | | Calc. | 44.4 | 4.10 | 13.1 | 20.7 |
| | | | | | | Found | 44.7 | 4.21 | 13.2 | 20.3 |
| 8f | Cl | 2 | $2,4\text{-}(NO_2)_2$ $C_6H_3$ | 71/D | 216-218<br>(n-butanol) | $C_{10}H_{10}ClN_5O_5$ ( 315.7) | | | | |
| | | | | | | Calc. | 38.1 | 3.19 | 11.2 | 22.2 |
| | | | | | | Found | 38.3 | 3.20 | 11.4 | 22.0 |
| 8g | Cl | 2 | $COCH_2CH_3$ | 98/C | 186-188<br>(n-butanol) | $C_7H_{12}ClN_3O_2$ ( 205.6) | | | | |
| | | | | | | Calc. | 40.9 | 5.88 | 17.2 | 20.4 |
| | | | | | | Found | 40.6 | 5.78 | 17.2 | 20.7 |
| 8h | Cl | 2 | $4\text{-}CH_3C_6H_4CO$ | 86/C | 212-214<br>($CH_3COOH$) | $C_{12}H_{14}ClN_3O_2$ (267.7) | | | | |
| | | | | | | Calc. | 53.8 | 5.27 | 13.2 | 15.7 |
| | | | | | | Found | 54.0 | 5.35 | 13.3 | 15.9 |
| 8i | succinimido | 2 | $C_6H_5$ | 71/C | 196-198<br>(n-butanol) | $C_{14}H_{16}N_4O_3$ ( 288.3) | | | | |
| | | | | | | Calc. | 58.3 | 5.59 | | 19.4 |
| | | | | | | Found | 58.1 | 5.35 | | 19.4 |
| 8j | succinimido | 2 | $4\text{-}NO_2C_6H_4$ | 77/D | 227-230<br>(iso-propanol) | $C_{14}H_{15}N_5O_5$ (333.3) | | | | |
| | | | | | | Calc. | 50.4 | 4.54 | | 21.0 |
| | | | | | | Found | 50.4 | 4.70 | | 21.3 |
| 7a | Cl | 1 | --- | 50 | 194-196<br>(DMF) | $C_6H_8Cl_2N_4O_2$ (239.1) | | | | |
| | | | | | | Calc. | 30.1 | 3.37 | 29.7 | 23.4 |
| | | | | | | Found | 29.9 | 3.70 | 29.6 | 23.6 |
| 7b | Cl | 2 | --- | 93 | 184-186<br>(DMF) | $C_8H_{12}Cl_2N_4O_2$ (267.1) | | | | |
| | | | | | | Calc. | 36.0 | 4.53 | 26.5 | 21.0 |
| | | | | | | Found | 36.0 | 4.50 | 26.0 | 20.8 |

a) decomposition on standing

functionalized 3-alkyl-1,2,4-triazoles with the methine proton in position 5, whose chemical shift is expected between 8.5-9.5 ppm[6)]. In case of 5-(β-aminoethyl)-1,2,4-triazoles **10** (n = 2) the two $CH_2$ signals are isochronic. This phenomenon is also observed in the aminoethyl-imidazole series[18,19)].

Spectroscopic data of precursors **4** and **6** (Table 2) as well as of intermediates **7** and **8** (Table 4) are also in agreement with the given structures. In some *N*-(β-halopropionyl)-formamidinium salts **4** (X = halo, n = 2) two signals are found for the formamidine-methine proton. While the NH-signal disappears on the addition of $D_2O$ the two signals of the amidine CH proton are uneffected. Thus NH-CH-coupling is excluded and the phenomenon might probably be caused by *E/Z* isomerism.

In addition to the molecular ion of amidrazones **8** $M^+$ of triazoles **9** is found in their mass-spectra demonstrating cyclization also under MS-conditions. Interestingly the 2,4-dinitro-substituted formamidrazone **8f** (X = Cl, n = 2, R = 2,4-dinitrophenyl), which resists preparative cyclization to the corresponding 1-(2,4-dinitrophenyl)-5-(β-chloroethyl)-1,2,4-triazole **9** (R = 2,4-dinitrophenyl; X = Cl, n = 2) does not show a corresponding peak in the MS either. According to $^1H$-NMR and $^{13}C$-NMR-investigations succinido-substituted formamidrazones **8** (X = succinimido, n = 2) appear in equilibria of two different isomers (about 1:1 in $[D_6]$DMSO). Rising the temp. to 150°C causes a slight shift of the equilibrium (about 2:3) and coalescence of the two NH signals in the $^1H$-NMR spectrum. Therefore, the phenomenon may probably be caused by restricted rotation around the amide C-N-bond. The existence of a tautomeric equilibrium of amidrazone **8** and a corresponding imidoylhydrazine can be excluded, since both sets of $^1H$-NMR signals correspond with amidrazone structures **8**. In case of azines **7**, however, appearance of tautomeric equilibria can be concluded from $^1$H-NMR spectra (Table 4).

The synthesis of ω-functionalized 5-alkyl-1,2,4-triazoles **9** and **10** allows to prepare new representatives of this pharmacologically interesting class of compounds in a convenient way, without facing the problem of separation of regioisomeres. Furthermore it is possible to synthesize some known ω-functionalized 5-alkyl-1,2,4-triazoles in a more efficient manner. Before our experiments 5-(β-aminoethyl)-1,2,4-triazole **10m**[17] or 5-(β-chloroethyl)-1,2,4-triazole **9g**[1] were available in a four-step or three-step procedure, respectively, starting from thiosemicarbazide and β-phthalimido- or β-ethoxy-propionylchloride in a total yield of not more than 17 or 8%, respectively. The new synthesis of these compounds starting from β-phthalimido-propionitrile or acrylonitrile affords total yield 38% (2 steps) or 28% (3 steps), respectively.

## Experimental Part

*ω-Functionalized N-Acyl-formamidinium Perchlorates* (**4**)

*Method* A

32 g (0.21 mol) POCl$_3$ are added dropwise under stirring and cooling (temp. below 25°C) to 0.2 mol *N,N*-disubstituted formamide **2**. Then 0.2 mol of nitrile **1** or acrylonitrile are added and the mixture is cooled to 0-5°C and is saturated with dry HCl gas for 3 h. The mixture is allowed to stand overnight at ambient temp. and is then poured into a solution of 12 ml 70% HClO$_4$ in 250 ml glacial acetic acid with stirring. After dilution with excess diethylether a yellow oil spearates, which crystallizes after a short time. The solid is filtered by suction and recrystallized.

*Method* B

Analogous to method A, however the nitrile **1** is dissolved in 100 ml chloroform and after cooling to 0-5°C the mixture is allowed to reach a temp. of maximum 20°C.

*N-(β-Phthalimidopropionyl)-formamide* (**6a**) *(n = 2, X = phthalimido)*

32 g (0.21 mol) POCl$_3$ are added dropwise under stirring and cooling (temp. < 25°C) to 14.6 g (0.2 mol) DMF. After the addition of a solution of 40 g 0.2 mol β-phthalimidopropionitrile in 100 ml chloroform the mixture is cooled to 0-5°C and is saturated with dry HCl gas while the temp. is kept < 20°C. After standing overnight at room temp. chloroform is evaporated and the residue is poured into 1 l of ice water. The precipitate is filtered by suction and recrystallized.

*ω-Functionalized N-Acyl-formamidrazones* (**8**)

*Method* C

0.01 Mol *N*-acyl-formamidinium perchlorate **4** are added to a mixture of 0.01 mol of the corresponding hydrazine **5** and 20 ml water. The resulting mixture is stirred for 10 min. The resulting precipitate is filtered by suction and recrystallized.

*Method* D

A mixture of 0.01 mol *N*-acyl-formamidinium perchlorate **4** and 20 ml ethanol is combined with 0.01 mol of substituted hydrazine **5**. After refluxing for 5 min (product **8** may already separate) the cold mixture is diluted with some water. The precipitate is filtered by suction and recrystallized.

*Azines* (**7**)

0.36 g (0.005 mol) 70% hydrazine hydrate are added to a mixture of 0.01 mol *N*-acyl-formamidinium perchlorate **4** and 20 ml acetonitrile. After 15 min stirring at room temp. the colorless precipitate is filtered by suction and recrystallized from DMF.

*ω-Functionalized 5-Alkyl-1,2,4-triazoles* **9**

*Method* E

0.01 mol *N*-Acyl-formamidrazone **8** are heated with the same volume of polyphosphoric acid (Table 3) and then cooled to room temp. The mixture is neutralized with dil. NaOH. Solid products are filtered by suction and recrystallized. If products resist crystallizing they are separated from the mixture by extraction with chloroform.

*Method* F

0.01 mol *N*-acylformamidinium perchlorate **4** or N-(β-phthalimido-propionyl)-formamide **6a** are added to a solution of the hydrazine **5** (or the corresponding hydrochloride and 1 g triethylamine) in 20 ml ethanol or 20 ml glacial acetic acid. The mixture is refluxed (Table 5). After cooling to room temp. it is diluted with water. If no product precipitates from the diluted acetic acid solution, the mixture is neutralized with K$_2$CO$_3$. The product is filtered by suction and recrystallized.

*Method* G

A mixture of 0.01 mol azine **7**, 30 ml acetonitrile and 0.71 g (0.01 mol) 70% hydrazine hydrate **5** (R = H) is refluxed until educts have dissolved. NH$_4$Cl formed is filtered from the hot reaction mixture. The filtrate is evaporated. The remainder slowly crystallizes (seeding is advisable). The crystals are recrystallized from toluene.

*Method* H

0.01 mol methylhydrazine are added dropwise under stirring to a solution of 0.01 mol *N*-acyl-formamidinium perchlorate **4** in 20 ml acetonitrile. After 2 min refluxing the cold solution is diluted with 25 ml ice water and alkalized (pH 8-9) by NaHCO$_3$-solution. The solution is extracted four times with about 15 ml chloroform. The combined extracts are washed with water and evaporated. The remaining triazole can be transformed in the corresponding picrate by treatment with ethanolic picric acid.

*Method* I

A solution of 1.47 g (0.01 mol) phthalimid, 1.38 g (0.01 mol) K$_2$CO$_3$, and 0.01 mol of the corresponding *5-chloroalkyl-1,2,4-triazole* **9** *(X = Cl)* in 25 ml DMF is heated to 160-180°C for 3 h. After cooling to room temp. water is added. The product is filtered by suction and recrystallized.

*5-Aminomethyl-1-(4-nitrophenyl)-1,2,4-triazol* (**10f**)

*Method* J

A mixture of 3.49 g (0.01 mol) 1-(4-nitrophenyl)-5-phthalimidomethyl-1,2,4-triazole (**9a**), 20 ml ethanol, and 0.71 g (0.01 mol) 70% hydrazine hydrate **5** (R = H) is refluxed for 3 h. After cooling the phthalazine is filtered by suction. The filtrate is evaporated *in vacuo*. The remainder is twice dissolved in ethanol, filtered and evaporated. The product is recrystallized from iso-propanol.

*5-(β-Aminoethyl)-1,2,4-triazole dihydrohalogenides* **10m, n, p**·2HHal

*Method* K

A mixture of 0.01 mol 5-(β-phthalimidoethyl)-1,2,4-triazole **9** (X = phthalimido) and 30 ml 20% HCl or 36 ml 20% HBr is refluxed for 8 h. Phthalic acid precipitating on cooling is removed by suction. The filtrate is concentrated *in vacuo*. The remaining material is dissolved in 50 ml methanol and shortly heated to boiling after addition of char coal. The product is precipitated by diluting of the cold filtrate with diethylether.

**Table 4:** Spectroscopic Data of Functionalized *N*-Acylformamidrazones **8** and Azines **7**

| Nr. | $^1$H-NMR [$D_6$]DMSO: | MS (70 eV):m/z (%) |
|---|---|---|
| 8b[a)] | 4.16 [s, 2 H, $CH_2$], 6.79 [d, J = 9 Hz, 2 H, $C_6H_4$], 8.00 [d, J = 9 Hz, 2 H, $C_6H_4$], 8.29 [d, J = 10 Hz, 1 H, NCHN], 10.69 [s, 1 H, NH], 11.02 [d, J = 10 Hz, 1 H, $N\underline{H}CH$] | 256 (7) [$M^{+\cdot}$], 23 (48), 207 (45), 163 (100), 136 (61), 90 (34) |
| 8c[b)] | 2.69 [t, J = 6 Hz, 2 H, $CH_2CO$], 3.75 [t, J = 6 Hz, 2 H, $CH_2Cl$], 6.77 [m, 5 H, $C_6H_5$], 8.20 [d, J = 9 Hz, 1 H, CHN], 9.40 [s, 1 H, NH], 10.56 [d, J = 9 Hz, 1 H, $N\underline{H}CH$] | |
| 8d | 2.78 [t, J = 6 Hz, 2 H, $CH_2CO$], 3.80 [t, J = 6 Hz, 2 H, $CH_2Cl$], 6.90 [d, J = 7 Hz, 4 H, $C_6H_4$], 7.10 [d, J = 10 Hz, 1 H, CHN], 8.73 [s, 1 H, NH], 10.20 [d, J = 10 Hz, 1 H, $N\underline{H}CH$] | 243 (4) [$M^{+\cdot}$], 190 (37), 136 (29), 109 (100), 86 (87), 72 (29), 58 (26) |
| 8e | 2.71 [t, J = 9 Hz, 2 H, $CH_2CO$], 3.75 [t, J = 9 Hz, 2 H, $CH_2Cl$], 6.76 [d, J = 9 Hz, 2H, 2 CCHC], 8.00 [d, J = 9 Hz, 2 H, 2 CCHC], 8.31 [d, J = 11 Hz, 1 H, CHN], 10.64 [s, 1 H, NH], 10.82 [d, J = 11 Hz, 1 H, NH] | 270 (24) [$M^{+\cdot}$], 217 (33), 207 (24), 180 (100), 136 (35), 90 (41), 63 (61) |
| 8f | 2.76 [t, J = 6 Hz, 2 H, $CH_2CO$], 3.76 [t, J = 6 Hz, 2 H, $CH_2Cl$], 7.53 [d, J = 10 Hz, 1 H, CHN], 8.21 [d, J = 10 Hz, 1 H, NH], 8.70 [d, J = 3 Hz, 1 H, $C_6H_3$], 8.97 [t, J = 9 Hz, 1 H, $C_6H_3$], 11.02 [d, J = 9 Hz, 1 H, NH], 11.40 [s, 1 H, NH] | 315 (52) [$M^{+\cdot}$], 279 (14), 225 (100), 181 (20), 152 (18), 91 (27), 65 (38) |
| 8g[c)] | 1.27 [t, J = 7 Hz, 3 H, $CH_3$], 2.36 [q, J = 7 Hz, 2 H, $CCH_2CO$], 3.02 [t, J = 6 Hz, 2 H, $CH_2CON$], 4.06 [t, J = 6 Hz, 2 H, $CH_2Cl$], 8.55 [t, J = 9 Hz, 0.5 H, CH], 8.77 [t, J = 9 Hz, 0.5 H, CH], 10.86 [d, J = 8 Hz, 0.5 H, NH], 11.10 [d, J = 8 Hz, 0.5 Hz, NH], 11.20 [br, NH] | 205 (8) [$M^{+\cdot}$], 169 (4), 149 (14), 133 (8), 115 (13), 113 (8), 90 (15), 86 (24), 59 (81), 57 (100) |
| 8h | 2.27 [s, 3 H, $CH_3$], 2.70 [t, J = 6 Hz, 2 H, $CH_2CO$], 3.74 [t, J = 6 Hz, 2 H, $CH_2Cl$], 7.17 [d, J = 8 Hz, 2 H, $C_6H_4$], 7.69 [d. J = 8 Hz, 2 H, $C_6H_4$], 8.70 [t, J = 9 Hz, 1 H, CHN], 11.05 [d, J = 9 Hz, NH], 11.23 [s, 1 H, NH] | 267 (1) [$M^{+\cdot}$], 160 (38), 119 (100), 91 (30), 72 (21) |
| 8i[d)] | 2.50 [s, 6 H, 3 $CH_2CO$], 3.49, m, 2 H, $CH_2N$], 6.37 - 7.19 (m, 5.5 H, $C_6H_5$, CHN], 8.06 [d, J = 10 Hz, 0.5 H, CHN], 8.64 [s, 0.5 H, NH], 9.30 [s, 0.5 H, NH], 9.96 [d, J = 10 Hz, NH], 10.42 [d, 0.5 H, J = 10 Hz, NH] | 288 (5) [$M^{+\cdot}$], 270 (100), 228 (12), 172 (63), 61 (93), 55 (78) |
| 8j[e)] | 2.56 [s, 6 H, 3 $CH_2CO$], 3.57 [m, 2 H, $CH_2N$], 6.79 [d, J = 9 Hz, 1 H, $C_6H_4$6.97 [d, J = 9 Hz, 1 H, $C_6H_4$], 7.29 [t, J = 10 Hz, 0.5 H, CHN], 8.01 [d, J = 9 Hz, 1 H, $C_6H_4$], 8.05 [d, J = 9 Hz, 1 H, $C_6H_4$], 8.29 [t, J = 10 Hz, 0.5 H, CHN], 9.79 [s, 0.5 H, NH], 10.25 [d, J = 10 Hz, 0.5 H, NH], 10.66 [s, 0.5 H, NH], 10.81 [d, J = 10 Hz, 0.5 H, NH] | 315 (100) [$M^{+\cdot}$], 333 (3), 217 (99), 136 (39), 90 (37), 84 (31), 55 (68) |

**Table 4:** Cont.

| | | |
|---|---|---|
| 7a | 4.15 [s, 0.6 H, $CH_2Cl$], 4.26 [s, 1.4 H, $CH_2Cl$], 4.66 [s, 2 H, $CH_2Cl$], 8.39 [s, 1 H, CH], 8.83 [s, 0.5 H, CH], 8.95 [s, 0.5 H, CH], 11.37 [br, NH] | 239 (7) [$M^{+\cdot}$], 203 (19), 189 (42), 119 (25), 113 (43), 93 (19), 86 (54), 77 (76), 51 (28), 49 (89), 44 (100) |
| 7b[f] | 2.70 [t, J = 6 Hz, 2 H, $CH_2CO$], 3.68 [t, J = 6 Hz, 2 H, $CH_2Cl$], 7.60 [d, J = 10 Hz, 0.6 H, CH], 8.35 [d, J = 10 Hz, 1.4 H, CH]. 10.97 [d, J = 10 Hz, NH] | 267 (10) [$M^{+\cdot}$], 212 (12), 211 (100), 156 (24), 129 (15), 102 (18), 77 (16), 63 (13), 51 (16), 49 (19) |

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[a] IR (KBr): ν = 1710 $cm^{-1}$ (C=O), 3300 (NH), 3350 (NH); [b] IR (KBr): ν = 1675 $cm^{-1}$ (C=O), 3240 (NH), 3340 (NH). UV ($CH_3CN$): $\lambda_{max}$ (lg ε) = 249sh nm (3.74), 289 (4.18); [c] IR (KBr): ν = 1650 $cm^{-1}$ (C=O), 1680 (CO), 3190 (NH), 3240 (NH). UV ($CH_3OH$): $\lambda_{max}$ (lg ε) = 264 nm (4.31) [d] IR (KBr): ν = 1700 $cm^{-1}$ (C=O), 1770 (C=O), 3300 (NH). UV ($CH_3OH$): $\lambda_{max}$ (lg ε) = 242 nm (3.90), 291 (4.23), 310sh (4.16), 420 (2.23); [e] $^{13}$C-NMR ((D6))DMSO): δ =20.82 ($CH_2N$), 28.0 ($CO\underline{C}H_2\underline{C}H_2CO$), 30.0/33.14 ($CH_2CONH$), 110/111.1 (o-$C_6H_4NO_2$, 126/126.2 (m-$C_6H_4NO_2$), 127.7 (ipso-$C_6H_4NO_2$), 136.7 (p-$C_6H_4NO_2$), 150.9 (NH-CH=N), 168.6/169.2 ($CH_2\underline{C}ONH$), 177.4 ($\underline{C}OCH_2CH_2CH_2\underline{C}O$). [f] IR (KBr): ν = 1685 $cm^{-1}$ (C=O), 3280 (NH). UV ($CH_3CN$): $\lambda_{max}$ = 266nm (sparingly soluble)

**Table 5:** 1,2,4-Triazoles **9** and **10**

| | X | n | R | yield [%]/ Method | m.p. [°C] | molecular formula elemental analysis Calc. C H Cl N Found |
|---|---|---|---|---|---|---|
| 9a | Cl | 1 | H | 10/G | 98-103[a)]<br>(toluene) | |
| 9b | Cl | 1 | $C_6H_5$ | 52/E[b)] | 101-103[c)]<br>(iso-propanol) | $C_{15}H_{11}ClN_6O_7$ (422.7)[c)]<br>42.6 2.62 8.4 19.9<br>42.8 2.80 8.7 20.1 |
| 9c | Cl | 1 | 4-$CH_3OC_6H_4$ | 44/F[d)] | 67-69<br>(cyclohexane) | $C_{10}H_{10}ClN_3O$ (223.7)<br>53.7 4.51 15.9 18.7<br>4.55 16.1 18.4 |
| 9d | Cl | 1 | 4-$FC_6H_4$ | 71/F[e)] | 85-86<br>(cyclohexane) | $C_9H_7ClFN_3$ (211.6)<br>51.1 3.33 16.8 19.8<br>51.3 3.45 17.0 19.6 |
| 9e | Cl | 1 | 4-$NO_2C_6H_4$ | 87/E[f)] | 113-114<br>(iso-propanol) | $C_9H_7ClN_4O_2$ (238.6)<br>45.3 2.96 14.9 23.5<br>45.3 3.20 14.9 23.0 |
| 9f | phthalimido | 1 | 4-$NO_2C_6H_4$ | 77/I | 214-217<br>(n-butanol) | $C_{17}H_{11}N_5O_4$ (349.3)<br>58.5 3.17 20.0<br>58.8 3.27 20.0 |
| 9g | Cl | 2 | H | 30/G | 65-70[g)]<br>(toluene) | $C_4H_6ClN_3$ (131.6)<br>36.5 4.60 27.0 31.9<br>36.5 4.39 27.2 32.3 |
| 9h | Cl | 2 | $CH_3$ | 70/H | 165-167[c)]<br>(ethanol) | $C_{11}H_{11}ClN_6O_7$ (374.7)[c)]<br>35.3 2.96 9.5 22.4<br>35.8 3.03 9.5 22.7 |
| 9i | Cl | 2 | $C_6H_5$ | 50/E[h)] | 131[c)]<br>(ethanol) | $C_{16}H_{13}ClN_6O_7$ (436.8)[c)]<br>44.0 3.00 8.1 19.2<br>44.3 3.43 8.1 19.5 |
| 9j | Cl | 2 | 4-F-$C_6H_4$ | 42/E[i)] | 125-127[c)]<br>(ethanol) | $C_{16}H_{12}ClFN_6O_7$ (454.8)[c)]<br>42.2 2.64 7.8 18.5<br>42.0 2.53 7.9 18.2 |

**Table 5:** Cont.

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 9k | Cl | 2 | 4-$NO_2C_6H_4$ | 71/E[j)] | 121-123<br>(iso-propanol) | $C_{10}H_9ClN_4O_2$ (252.7) | | | | |
| | | | | | | | 47.5 | 3.59 | 14.0 | 22.2 |
| | | | | | | | 47.6 | 3.80 | 13.9 | 22.4 |
| 9l | succinimido | 2 | 4-$NO_2C_6H_4$ | 65/F[k)] | 200-202<br>(ethanol) | $C_{14}H_{13}N_5O_4$ (315.3) | | | | |
| | | | | | | | 53.3 | 4.16 | | 22.2 |
| | | | | | | | 53.6 | 4.36 | | 21.9 |
| 9m | phthalimido | 2 | H | 65/F[l)] | 211-213[m)]<br>($CH_3COOH$) | $C_{12}H_{10}N_4O_2$ (242.2) | | | | |
| | | | | | | | 59.5 | 4.16 | | 23.1 |
| | | | | | | | 59.7 | 3.98 | | 22.9 |
| 9n | phthalimido | 2 | $C_6H_5$ | 74/F[n)] | 125-128<br>(iso-propanol) | $C_{18}H_{14}N_4O_2$ (318.3) | | | | |
| | | | | | | | 67.9 | 4.43 | | 17.6 |
| | | | | | | | 68.2 | 4.65 | | 17.6 |
| 9o | phthalimido | 2 | 4-$CH_3OC_6H_4$ | 75/F[o)] | 124-128<br>(cyclohexane) | $C_{19}H_{16}N_4O_3$ (348.4) | | | | |
| | | | | | | | 65.5 | 4.63 | | 16.1 |
| | | | | | | | 65.5 | 4.79 | | 16.3 |
| 9p | phthalimido | 2 | 4-$NO_2C_6H_4$ | 66/F[n)]<br>67/I | 205-207<br>($CH_3COOH$) | $C_{18}H_{13}N_5O_4$ (363.3) | | | | |
| | | | | | | | 59.5 | 3.61 | | 19.3 |
| | | | | | | | 59.4 | 3.47 | | 19.4 |
| 10f | --- | 1 | 4-$NO_2C_6H_4$ | 57/J | 136-138.5<br>(iso-propanol) | $C_9H_9N_5O$ (203.2) | | | | |
| | | | | | | | 49.3 | 4.10 | | 32.0 |
| | | | | | | | 49.3 | 3.95 | | 31.7 |
| 10m | --- | 2 | H | 65/K[p)] | 180-185[q)]<br>($CH_3OH$/<br>diethylether) | $C_4H_{10}Cl_2N_4$ (185.1)[r)] | | | | |
| | | | | | | | 26.0 | 5.45 | 38.3 | 30.3 |
| | | | | | | | 25.9 | 5.40 | 38.4 | 30.3 |
| 10n | --- | 2 | $C_6H_5$ | 82/K[p)] | 118-123[r)]<br>($CH_3OH$/<br>diethylether) | $C_{10}H_{12}N_4$ (188.2)[r)] | | | | |
| 10p | --- | 2 | 4-$NO_2C_6H_4$ | 38/K[s)] | 190-195[t)]<br>($CH_3OH$/<br>diethylether) | $C_{10}H_{13}Br_2N_5O_2$ (395.1)[t)] | | | | |
| | | | | | | | 30.4 | 3.32 | 40.5 | 17.7 |
| | | | | | | | 30.3 | 3.57 | 40.8 | 17.2 |

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[a)] corresponding hydrochloride: m.p. 115-116°C[16)]; [b)] 8 h at 60°C; [c)] picrate; [d)] using **4**, **5**·HCl, acetic acid and triethylamine, 5 min reflux; [e)] using **4**, **5**·HCl, ethanol and triethylamine, 5 min reflux; [f)] 15 min at 130°C; [g)] hydrochloride: m.p. 116-118°C (ref.[17)] m.p. 120°C); [h)] 24 h at 60°C; [i)] 1 h at 130°C; [j)] 15 min at 130°C; [k)] using **4**, **5** and acetic acid, 1 h reflux; [l)] 20 min reflux; [m)] ref.[17)] m.p. 215°C; [n)] using **6a**, **5** and acetic acid, 1 h reflux; [o)] using **6a**, **5**·HCl and acetic acid, 1 h reflux; [p)] hydrochloric acid; [q)] dihydrochloride, ref.[17)] m.p. 215°C; [r)] dihydrochloride; [s)] hydrobromic acid; [t)] dihydrobromide.

**Table 6:** Spectroscopic Data of 1,2,4-Triazoles **9** and **10**

| Nr. | $^1$H-NMR [$D_6$]DMSO: | MS (70 eV): m/z (%) |
|---|---|---|
| 9a | 4.65 [s, 2 H, $CH_2$], 8.35 [s, 1H, CH] | 117 (32) [$M^{+\cdot}$], 82 (100), 55 (29), 42 (14), 28 (70) |
| 9b[a)] | 5.09 [s, 2 H, $CH_2$], 7.76 [s, 5 H, $C_6H_5$], 8.41 [s, 1 H, H], 8.81 [s, 2 H, $C_6H_2$], 8.96 [s, 1 H, NH] | 193 (53) [$M^{+\cdot}$ - picric acid], 158 (16), 118 (58), 91 (100), 64 (22) |
| 9c | 3.75 [s, 3 H, $CH_3$], 4.76 [s, 2 H, $CH_2$], 7.04 [d, J = 9 Hz, 2 H, $C_6H_4$], 7.47 [d, J = 9 Hz, 2 H, $C_6H_4$], 8.04 [s, 1 H, CH] | 225 (16) [$M^{+\cdot}$], 223 (28), 148 (19), 121 (100), 106 (17), 80 (26), 78 (17), 64 (15), 63 (12), 52 (17) |
| 9d[b)] | 4.85 [s, 2 H, $CH_2$], 7.39 [p, J = 9 Hz, 2 H, $C_6H_4$], 7.62 [q, J = 5 Hz, 2 H, $C_6H_4$], 8.15 [s, 1 H, CH] | 211 (42) [$M^{+\cdot}$], 176 (8), 149 (7), 136 (42), 109 (100) |

**Table 6:** Cont.

| | | |
|---|---|---|
| 9e | 4.97 [s, 2 H, $CH_2$], 7.87 [d, J = 8 Hz, 2 H, $C_6H_4$], 8.22 [s, 1 H, CH], 8.45 [d, J = 8 Hz, 2 H, $C_6H_4$] | 238 (59) [$M^{+\cdot}$], 163 (100), 136 (55), 90 (45), 76 (24), 64 (20), 63 (55), 50 (28) |
| 9f | 5.06 [s, 2 H, $CH_2$], 7.80 [s, 4 H, o-$C_6H_4$], 7.92 [d, J = 9 Hz, 2 H, p-$C_6H_4$], 8.06 [s, 1 H, CH], 8.34 [d, J = 9 Hz, 2 H, p-$C_6H_4$] | 350 (20) [$M^{+\cdot}$], 349 (100), 303 (10), 302 (12), 202 (9), 160 (33), 156 (5), 136 (51), 104 (64), 90 (44), 76 (37), 63 (39) |
| 9g[c)] | 3.08 [t, J = 6 Hz, 2 H, $CH_2CN$], 3.88 [t, J = 6 Hz, 2 H, $CH_2Cl$], 8.12 [s, 1 H, CH], 13.75 [br, NH] | 131 (3) [$M^{+\cdot}$], 96 (100), 82 (12), 68 (3), 55 (15), 42 (18), 39 (26) |
| 9h[d)] | 3.10 [t, J = 7 Hz, 2 H, $CH_2CN$], 3.77 [s, 3 H, $CH_3$], 3.80 [t, J = 7 Hz, 2 H, $CH_2Cl$], 7.70 [s, 1 H, CH] | 145 (8) [$M^{+\cdot}$], 110 (100), 96 (15), 90 (5), 83 (10), 56 (33) |
| 9i | [c)]3.13 [t, J = 7 Hz, 2 H, $CH_2CN$], 3.81 [t, J = 7 Hz, 2H, $CH_2Cl$], 7.37 [m, 5H, $C_6H_5$], 7.88 [s, 1H, CH] | |
| 9j | [a)]3.50 [t, J = 7 Hz, 2 H, $CH_2CN$], 4.18 [t, J = 7 Hz, 2 H, $CH_2Cl$], 6.06 [s, NH], 7.71 [m, 4 H, $C_6H_4$], 8.44 [s, 1 H, CH], 8.84 [s, 2 H, $C_6H_2$] | 225 (14) [$M^{+\cdot}$], 190 (32), 136 (25), 109 (100) |
| 9k | 3.28 [t, J = 7 Hz, 2 H, $CH_2CN$], 3.92 [t, J = 7 Hz, 2 H, $CH_2Cl$], 7.81 [d, J = 9 Hz, 2 H, $C_6H_4$], 8.22 [d, J = 9 Hz, 2 H, $C_6H_4$], 8.15 [s, 1 H, CH] | 252 (10) [$M^{+\cdot}$], 217 (100), 163 (50), 136 (94), 90 (50), 63 (31) |
| 9l | 2.46 [m, 4 H, 2 $CH_2$], 3.0 [t, J = 7 Hz, 2 H, $CH_2CN$], 3.60 [t, J = 7 Hz, 2 H, $CH_2N$], 7.75 [d, J = 9 Hz, 2 H, $C_6H_4$], 8.02 [s, 1 H, CH], 8.27 [d, J = 9 Hz, 2 H, $C_6H_4$], | 315 (3) [$M^{+\cdot}$], 288 (8), 217 (54), 136 (33), 90 (42), 84 (31), 63 (52), 56 (37), 55 (82), 30 (100) |
| 9m | 2.95 [t, J = 8 Hz, 2 H, $CH_2CN$], 3.78 [t, J = 8 Hz, 2 H, $CH_2N$], 7.74 [s, 4 H, $C_6H_4$], 8.03 [s, 1 H, CH], 11.15 [s, 1 H, NH] | 242 (40) [$M^{+\cdot}$], 160 (100), 133 (13), 105 (12), 104 (13), 96 (18) 95 (30), 77 (22) |
| 9n | 3.14 [t, J = 8 Hz, 2 H, $CH_2CN$], 3.82 [t, J = 8 Hz, 2 H, $CH_2N$], 6.12 [s, 5 H, $C_6H_5$], 7.72 [s, 4 H, $C_6H_4$], 7.95 [s, 1H, CH] | 318 (68) [$M^{+\cdot}$], 236 (13), 227 (65), 160 (98), 91 (100), 77 (9) |
| 9o | 3.01 [t, J = 7 Hz, 2 H, $CH_2CN$], 3.66 [s, 3 H, $CH_3$], 3.74 [t, J = 7 Hz, 2 H, $CH_2N$], 6.85 [d, J = 9 Hz, 2 H, p-$C_6H_4$], 7.30 [d, J = 9 Hz, 2 H, p-$C_6H_4$], 7.69 (s, 4 H, o-$C_6H_4$], 7.86 [s, 1 H, CH] | 348 (81 [$M^{+\cdot}$], 265 (50), 202 (61), 160 (92), 121 (100), 77 (50) |
| 9p | 3.27 [t, J = 8 Hz, 2 H, $CH_2CN$], 3.82 [t, J = 8 Hz, 2 H, $CH_2N$], 7.69 [s, 4 H, o-$C_6H_4$], 7.81 [d, J = 5 Hz, 2 H, p-$C_6H_4$], 8.10 [d, J = 5 Hz, 2 H, p-$C_6H_4$], 8.25 [s, 1 H, CH] | 363 (42) [$M^{+\cdot}$], 346 (13), 281 (33), 217 (20), 160 (100), 136 (7), 133 (10), 105 (13), 104 (13) |
| 10f | 2.50 [m, 2 H, $NH_2$], 3.95 [s, 2 H, $CH_2$], 7.93 [d, J = 9 Hz, 2 H, $C_6H_4$], 8.09 [s, 1 H, CH], 8.33 [d, J = 9 Hz, 2 H, $C_6H_4$] | 219 (100) [$M^{+\cdot}$], 191 (18), 172 (16), 145 (22), 136 (24), 90 (38), 63 (46), 30 (76) |

**Table 6:** Cont.

| | | |
|---|---|---|
| 10m[e][f] | 3.55 [s, 4 H, $CH_2CH_2$], 6.26 [br, 3 H, $NH_3$], 9.57 [s, 1 H, CH], 11.3 [br, 2 H, NH] | 112 (2) [$M^{+\cdot}$ - 2 HCl], 83 (51), 43 (10), 42 (15), 38 (12), 36 (31), 30 (100) |
| 10n[e] | 3.14 [s, 4 H, $CH_2CH_2$], 6.92 [s, 3 H, $NH_3$], 7.55 [s, 5 H, $C_6H_5$], 7.98 [br, 2 H, NH], 8.26 [s, 1 H, CH] | 188 (1) [$M^{+\cdot}$ - 2 HCl], 159 (15), 158 (13), 91 (8), 82 (95), 80 (100), 64 (5) |
| 10p[g] | 3.21 [s, 4 H, $CH_2CH_2$], 6.78 [s, 3 H, $NH_3$], 7.84 [d, J = 9 Hz, 2 H, $C_6H_4$], 7.98 [br, 2 H, NH], 8.20 [s, 1 H, CH], 8.35 [d, J = 9 Hz, 2 H, $C_6H_4$] | 233 (2) [$M^{+\cdot}$ - 2 HBr], 204 (16), 203 (8), 90 (8), 82 (12), 80 (14), 63 (13), 50 (7), 39 (9), 30 (100) |

[a] picrate; [b] UV ($CH_3CN$): λ max (lg ε) = 228 nm (3.89); [c] hydrochloride: $^1$H-NMR (DMSO-$d_6$): δ (ppm) = 3.74 [t, *J* = 7 Hz, 2H, $CH_2CN$], 4.40 [t, *J* = 7 Hz, 2H, $CH_2Cl$], 9.76 [s, 1H, CH], 13.06 [s, 1H, NH]; [d] in $CDCl_3$; [e] dihydrochloride; [f] $^1$H-NMR ($D_2O$): δ (ppm) = 3.80 [t, J = 5 Hz, 4H, $CH_2CH_2$], 9.88 [s, 1H, CH].- $^1$H-NMR ($CF_3COOH$): δ (ppm) = 3.40 [m, 4H, $CH_2CH_2$], 5.60 [s, 0.5 H, NH], 6.26 [s, 0.5 H, NH], 6.94 [s, 4H, NH], 9.09 [s, 1H, CH].- IR (KBr): ν = 1620 $cm^{-1}$ (C=N), 2600-3200 (NH).- $^{13}$C-NMR ($D_2O$): δ (ppm) = 23.8 ($CH_2NH_2$), 37.1 ($\underline{C}H_2CH_2NH_2$), 143.6 (N=CH-N), 154.0 (N=$\underline{C}$-$CH_2$); [g] dihydrobromide

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