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Remarkable stereoselectivity switch in synthesis of carbonyl substituted N^2-arylamidrazones with low lipophilicity

Petra Frohberg *, Ingo Schulze, Christian Donner, Fabian Krauth

Institute of Pharmacy, Martin-Luther-University Halle-Wittenberg, Wolfgang-Langenbeck-Str. 4, 06120 Halle, Germany

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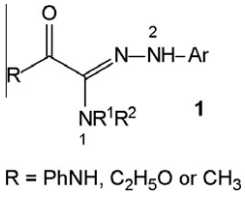
ABSTRACT

Reaction of carbonyl substituted hydrazonoyl chlorides with amines usually leads to *Z*-configured amidrazone derivatives via nucleophilic substitution of the chlorine atom. Surprisingly, *N,N*-dimethylcarboxamide substituted hydrazonoyl chlorides yielded *E*-amidrazones when dialkylamines were used as nucleophilic reagent. The lipophilicities of the obtained amidrazones were found to be drastically reduced compared to their corresponding carboxanilides.

N^2-Arylamidrazones **1** (Fig. 1) provide a highly variable source for the synthesis of nitrogen containing heterocycles.[1] Moreover, they exhibit a great variety of biological activities, among which are corticotropin releasing factor receptor antagonists, insecticides, or sphingosine-1-phosphate receptor 3 (S1P3) antagonists as well.[2] A general application of amidrazones in heterocyclic chemistry is achieved by inserting a carbonyl substituent at the α-position of the amidrazone moiety.[3] Compounds **1** containing ester, anilido, or keto groups have already been synthesized and characterized.

Recently, we reported the synthesis of (*Z*)-oxanilo-N^1-dialkyl-N^2-arylamidrazones (**1** with R = PhNH, R^1R^2 = dialkyl).[4] We observed that during the preparation procedure including recrystallization, these compounds undergo an isomerization to the *E*-isomer. This isomerization process could yield compounds with altered biological activities. The high lipophilicity of these compounds (Table 1) limits their evaluation in biological assays.[5]



R = PhNH, C_2H_5O or CH_3

Figure 1. General structure of α-carbonyl substituted amidrazones. Numbering is according to IUPAC nomenclature.

Table 1
Correlation of the substitution pattern and the lipophilicity of oxanilo-N^2-arylamidrazones **1a–e**: estimated log*P* values ($\log P_{calc}$) and retardation factors (R_f values) are given

	R	R^1/R^2	Ar	$\log P_{calc}$[a]	R_f value[b]
1a	PhNH	H/H	Ph	2.3	0.50
1b	PhNH	H/CH_3	Ph	2.6	0.56
1c	PhNH	$(CH_2)_5$	Ph	3.3	0.66
1d	PhNH	$(CH_2)_5$	4-Cl-C_6H_4	4.4	0.67
1e	PhNH	$(CH_2)_2O(CH_2)_2$	4-Cl-C_6H_4	2.8	0.53

[a] Log*P* values were estimated with ACD ChemSketch 12.01 freeware.
[b] R_f values were determined using thin layer chromatography with silica gel sheets and solvent system heptane/ethyl acetate (1:1, v/v).

Based on these findings we aimed to synthesize more polar compounds containing an amide structure in order to investigate spectroscopic properties of *E*/*Z*-amidrazones. In this Letter, we report a stereoselectivity switch in the preparation of *N,N*-dimethylcarboxamido-N^2-arylamidrazones from hydrazonoyl chlorides depending on the nature of the N^1 substitution.

Access to hydrazonoyl chlorides could be realized via a Japp–Klingemann cleavage.[6] β-Chlorinated dicarbonyl compounds, such as 2-chloro-3-oxobutanoic acid derivatives couple with diazotized anilines and concomitant acetic acid cleavage. Nevertheless, this versatile reaction is limited to compounds containing ester, anilido, or keto structures so far. We aimed to synthesize hydrazonoyl

* Corresponding author.
E-mail address: petra.frohberg@pharmazie.uni-halle.de (P. Frohberg).

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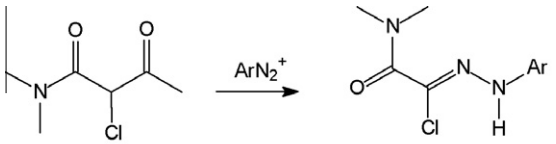


Scheme 1. Synthesis of hydrazonoyl chlorides **2**.

Table 2
Substitution patterns, melting points (mp, °C), and yields (%) of hydrazonoyl chlorides $(CH_3)_2NCOC(Cl)=NNHAr$ **2**

	Ar	Mp	Yield
(*Z*)-**2a**	Ph	107–109 (Ethanol)	32
(*Z*)-**2b**	4-CH_3-C_6H_4	104–106 (Methanol)	58
(*Z*)-**2c**	4-Cl-C_6H_4	125–130 (Methanol)	40
(*Z*)-**2d**	4-F-C_6H_4	78–80 (Methanol)	54

chlorides **2** by reaction of 2-chloro-3-oxo-*N*,*N*-dimethylbutanamide with diazotized anilines (Scheme 1).

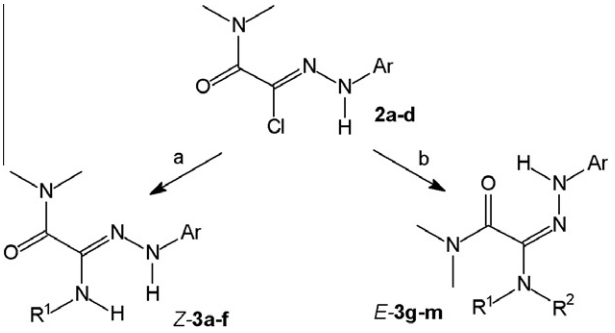
Yet, the compounds of interest could not be isolated from the reaction mixture by filtration because they did not precipitate. Also, after bringing the reaction mixture to room temperature decomposition of the desired products was observed. When keeping the aqueous reaction mixture at 5–10 °C overnight, compounds **2a–d** (Table 2) were successfully isolated.

According to hydrazonoyl chlorides described in the literature, which exist in the *Z*-form,[7] the obtained compounds **2a–d** were detected as *Z*-isomers by NMR experiments. In particular, the chemical shift of the C=NNH signal in the ^{1}H NMR spectra recorded in DMSO-d_6 was found in the prescribed region of 9–10 ppm. In ^{13}C NMR spectra the signal of the C=N moiety was observed at approx. 115 ppm.

Reaction of hydrazonoyl chlorides with ammonia in dioxane or methanol solution yielded *Z*-configured amidrazones **3a–c** (Scheme 2, Table 3).

The reaction conditions have to be carefully chosen using an excess of ammonia. Otherwise, particularly if triethylamine is used as a proton acceptor, formation of dimer **4** is preferred, which decomposes during heating or recrystallization to give the triazole derivatives **5** (Scheme 3).

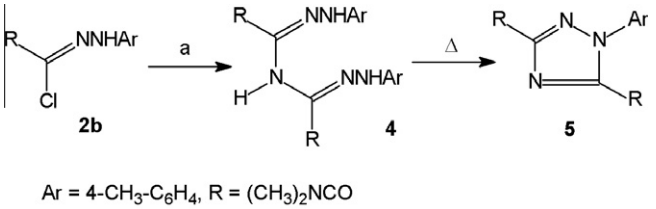
Treating hydrazonoyl chlorides **2** with monosubstituted amines, that is, methylamine or aniline, afforded mostly *Z*-amidrazones **3d–f** (Scheme 2, Table 3), but the *E*-isomer was detected



Scheme 2. Synthesis of amidrazones **3**. Reagents and conditions: (a) R^1 = H: 2.5 equiv NH_3, dioxane; R^1 = CH_3: 2.0 equiv CH_3NH_2, dioxane; R^1 = Ph: 1.0 equiv $PhNH_2$, 1.0 equiv NEt_3, dioxane; (b) 2.0 equiv R^1R^2NH, dioxane.

in the product mixture as well. These compounds were isolated as mixed crystals of the *Z*- and *E*-isomers, with the *E*-isomer between 20% and 30%. Surprisingly, disubstituted amines such as pyrrolidine, piperidine, and morpholine, respectively, gave exclusively *E*-amidrazones **3g–m** (Scheme 2, Table 3).

The formation of *E*/*Z*-isomers was monitored by ^{1}H NMR in DMSO-d_6 due to the very slow isomerization in solution in the range of days. Isomers were assigned using NOE NMR experiments. For **3b**, irradiation at the frequency of the NH_2 protons causes an NOE to the hydrazone proton =NNH. In contrast, the NOE spectrum of **3h** displays an NOE signal for the amide CH_3 protons, when irradiating at the frequency of the amidrazone N^1 methylene protons. In addition, the ^{13}C NMR signal corresponding to the C=N group changes depending on the configuration of this group[4] resulting in a ca. 10 ppm downfield shift for the *E*-isomer (Table 3).



Scheme 3. Side reaction observed during synthesis of **3b**: Reagents and conditions: (a) 1.0 equiv ammonia, 1.0 equiv NEt_3, dioxane, rt.

Table 3
Substitution patterns, melting points (mp, °C), yields (%), and characteristics (^{13}C NMR signals of C=N (ppm), logP_{calc} and R_f values) of prepared amidrazones $(CH_3)_2NCOC(NR^1R^2)=NNHAr$ **3a–m**

	R^1/R^2	Ar	Mp	Yield	^{13}C NMR signal of C=N[a]	LogP_{calc}[b]	R_f value[c]
(*Z*)-**3a**	H/H	Ph	132–134 (Heptane/ethyl acetate)	27	138.3	0.50	0.19
(*Z*)-**3b**	H/H	4-CH_3-C_6H_4	126–129 (Heptane/ethyl acetate)	31	137.8	0.96	0.20
(*Z*)-**3c**	H/H	4-Cl-C_6H_4	155–158 (Methanol)	38	139.4	1.49	0.17
(*E*,*Z*)-**3d**	H/CH_3	4-CH_3-C_6H_4	166–172 (Water)	46	143.5 (153.3)[d]	1.29	0.05
(*E*,*Z*)-**3e**	H/CH_3	4-Cl-C_6H_4	175–178 (Methanol)	58	144.7 (153.9)[d]	1.82	0.04
(*E*,*Z*)-**3f**	H/Ph	4-Cl-C_6H_4	140–147 (Chloroform)	67	135.1 (146.0)[d]	3.58	0.35
(*E*)-**3g**	$(CH_2)_4$	4-Cl-C_6H_4	141–143 (Methanol)	71	153.5	1.99	0.11
(*E*)-**3h**	$(CH_2)_5$	Ph	110–115	53	153.0	1.56	0.29
(*E*)-**3i**	$(CH_2)_5$	4-CH_3-C_6H_4	125–127 (Methanol)	48	153.4	2.02	0.29
(*E*)-**3j**	$(CH_2)_5$	4-Cl-C_6H_4	149–151 (Methanol)	86	154.0	2.55	0.31
(*E*)-**3k**	$(CH_2)_5$	4-F-C_6H_4	102–105 (Methanol)	78	156.6	2.01	0.26
(*E*)-**3l**	$(CH_2)_2O(CH_2)_2$	Ph	148–149	33	150.7	0.02	0.13
(*E*)-**3m**	$(CH_2)_2O(CH_2)_2$	4-Cl-C_6H_4	160–162 (Methanol)	55	151.2	1.01	0.14

[a] 100 MHz, solvent DMSO-d_6.
[b] Values were estimated with ACD ChemSketch 12.01 freeware.
[c] R_f values were determined using thin layer chromatography with silica gel sheets and solvent system heptane/ethyl acetate (1:1, v/v).
[d] Signal of *E*-isomer.

Log *P* values were estimated with ACD software, yet, the configuration is not considered in this calculation program. The lipophilicity of amidrazones with the *N,N*-dimethylcarboxamide structure **3** (Table 3) was found to be drastically reduced by ca. two log units compared to the corresponding carboxanilide derivatives **1** (Table 1).

Calculated log *P* values were compared with R_f values from thin layer chromatography using a solvent system of heptane/ethyl acetate 1:1 (v/v). Likewise, R_f values for **3** were found to be only half of these of amidrazones **1** (compare Tables 1 and 3).

In summary, we present a promising strategy to synthesize amidrazones stereoselectively, which will be beneficial to study their physical and biophysical properties, in more detail.

Supplementary data

Supplementary data (experimental procedures and characterization data such as ^{1}H, ^{13}C NMR, MS, microanalyses data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.06.032.

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