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# Derivatives of arylhydrazonic acids. Part 2: A facile approach to novel 4,5-dihydro-1*H*-1,2,4-triazoles via cyclization of amidrazones☆

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**Abstract**—Starting from arylhydrazonoyl chlorides, the amide arylhydrazones (amidrazones) were obtained by nucleophilic substitution of the chloride function with ammonia, amines or anilines. Treatment of amidrazones with alkyl ketones under acidic catalysis led generally to 4,5-dihydro-1*H*-1,2,4-triazoles. In addition, with aldehydes 1*H*-1,2,4-triazoles or aryl condensed 4,5-dihydro-1*H*-1,3,4-triazepines were formed depending on substitution pattern of amidrazone moiety. The structures of the new products have been established by $^{1}H$ and $^{13}C$ NMR studies. 

## 1. Introduction

In the recent past, derivatives of 4,5-dihydro-1*H*-1,2,4-triazoles have been worthy of an increased note as a result of their ability to form stable carbenes, which are applied as ligand in organometallic and inorganic chemistry as well as in organic catalysis.[2] Furthermore, Neugebauer and Fischer could isolate stable 2,5-dihydro-1,2,4-triazol-2-yl radicals, which have been prepared by dehydrogenation of 4,5-dihydro-1*H*-1,2,4-triazoles.[3] The stability of these radicals has made NMR and ESR studies and the application in controlled radical polymerization processes possible.[3,4]

Various known 4,5-dihydro-1*H*-1,2,4-triazoles were synthesized via 1,3-dipolar cycloaddition of nitrilimines with dipolarophiles, but the substitution pattern is limited by availability of nitrilimines and of appropriate reactive dipolarophiles. Recently, the synthesis of 5-disubstituted 3-acetyl-4,5-dihydro-1*H*-1,2,4-triazoles has been described, which were yielded by reaction of ketoximes with hydrazonoyl chlorides.[5] However, this synthetic pathway excludes the formation of 4-substituted derivatives. Alternatively, 1,3,4-trisubstituted 4,5-dihydro-1*H*-1,2,4-triazoles can be prepared using amidrazones as intermediates.[6] No reports are found in literature concerning cyclization reaction of α-carbonyl substituted amidrazones **I** to highly substituted dihydrotriazoles **II** (Fig. 1).

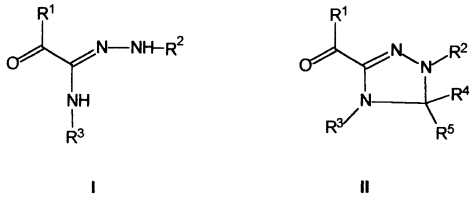


**Figure 1.**

A wide range of various substituents of heterocylic systems gains importance to construct combinatorial libraries for medicinal chemistry program. Cyclic and open-chain derivatives of amidrazones are known to exhibit inhibitory activity against enzymes of arachidonic acid cascade which is responsible for the formation of biological active metabolites.[7] These substances are considered as potent mediators of inflammatory and allergic reactions in human.[8] Our interest in amidrazones **1**, their properties and stability prompt us to investigate their reactivity.

In this paper, we describe the synthesis of 5,5-dialkyl-1-aryl-4,5-dihydro-1*H*-1,2,4-triazole-3-carboxanilides **2** besides 1*H*-1,2,4-triazoles **3** and aryl condensed 4,5-dihydro-1*H*-1,3,4-triazepines **4** (for review on 1,3,4-triazepines, see Ref. 9) by cyclization of amidrazones **1** with monocarbonyl compounds (Fig. 2).

☆ See Ref. 1 for Part 1.

*Keywords*: amidrazones; heterocycles; structural assignment; triazoles; benzotriazepines.

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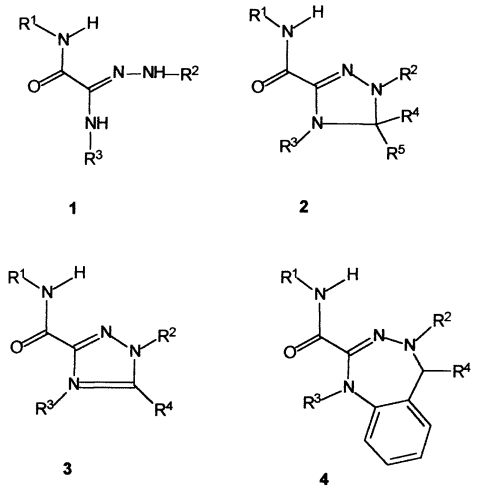



**Figure 2.**

## 2. Results and discussion

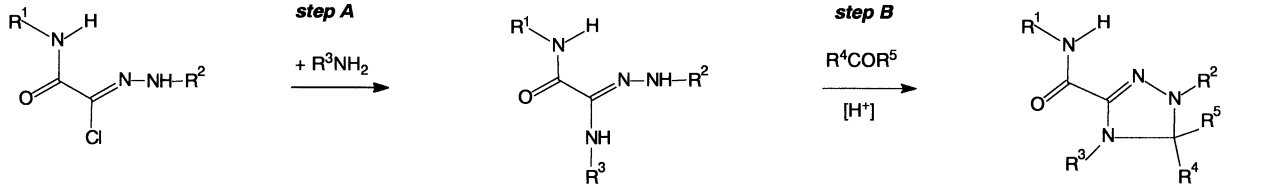
### 2.1. Synthesis

Oxaniloamide arylhydrazones **1** were prepared according to known procedures,[10] see Scheme 1 (step A). Nucleophilic substitution of recently reported oxaniloarylhydrazonoyl chlorides **5**[1] was carried out with ammonia, amines or anilines in dioxane and was promoted by an additional equimolar amount of base, ammonia or the corresponding aliphatic amine, respectively. At a temperature between 40 and 45°C, the reaction was complete usually within less than 12 h. The ammonia was applied as a methanolic solution to suppress side reactions, which occurred in the presence of water. However, anilines as nucleophiles (synthesis of amidrazones **1m**, **1p** and **1q**) required an additional equimolar amount of triethylamine as proton acceptor. Yields varied between 70 and 80%.

It is known that amidrazones cyclisize with monocarbonyl compounds to give 4,5-dihydro-1*H*-1,2,4-triazoles as well as 1,2,4-triazoles.[11] The condensation of amidrazones with aldehydes and ketones can yield 4,5-dihydro-1*H*-1,2,4-triazoles.[12] However, this method is limited by the fact that the product obtained from $N^1$- or $N^2$-unsubstituted amidrazones is often the open-chain hydrazone rather than the tautomeric dihydrotriazole.[13]

The not as yet described 5,5-dialkyl-1-aryl-4,5-dihydro-1*H*-1,2,4-triazole-3-carboxanilides **2** were obtained from **1** and alkyl ketones, which served themselves as solvent for the reaction (Scheme 1, step B). Yields varied between 20 and 60%. Acidic conditions needed for cyclization were achieved by addition of catalyzing amounts of *p*-toluene sulfonic acid. Attempts to increase the yields using other acids for catalyzing (e.g. diluted or concentrated acetic acid or hydrochloric acid, respectively) were unsuccessful and led not only to the desired dihydrotriazoles but also to a lot of byproducts in the reaction mixture. The ring closure mostly occurred within 30 min. However, in some cases, the reaction required about five or more hours. Controlling reaction progress by TLC was necessary to find out the completion of the synthesis.

In addition to the affording 4,5-dihydro-1*H*-1,2,4-triazole-3-carboxanilide **2i**, a further product was formed by treating **1p** with acetone. Using TLC and comparing to the obtained derivatives of triazepines **4** described below, it is conceivable, that this product was the related 4,5-dihydro-1*H*-1,3,4-benzotriazepine (analogous compound **4**). Nevertheless, it was not isolable.




**5a-n**

| | $R^1$ | $R^2$ |
|---|---|---|
| **5a** | Ph | Ph |
| **5b** | Ph | 2-F-$C_6H_4$ |
| **5c** | Ph | 3-F-$C_6H_4$ |
| **5d** | Ph | 4-$CH_3$-$C_6H_4$ |
| **5e** | Ph | 4-Cl-$C_6H_4$ |
| **5f** | Ph | 4-F-$C_6H_4$ |
| **5g** | 2-Cl-$C_6H_4$ | Ph |
| **5h** | 2-Cl-$C_6H_4$ | 2-Cl-$C_6H_4$ |
| **5i** | 2-Cl-$C_6H_4$ | 2-CN-$C_6H_4$ |
| **5j** | 2-Cl-$C_6H_4$ | 3-Cl-$C_6H_4$ |
| **5k** | 3-Cl-$C_6H_4$ | 2-Cl-$C_6H_4$ |
| **5l** | 3-Cl-$C_6H_4$ | 3-Cl-$C_6H_4$ |
| **5m** | 4-Cl-$C_6H_4$ | 3-Cl-$C_6H_4$ |
| **5n** | 4-F-$C_6H_4$ | 3-$COCH_3$-$C_6H_4$ |

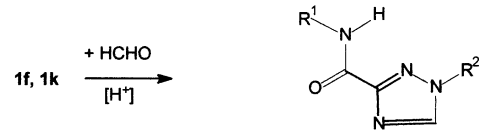
**1a-q**

| | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| **1a** | Ph | Ph | H |
| **1b** | Ph | 2-F-$C_6H_4$ | H |
| **1c** | Ph | 3-F-$C_6H_4$ | H |
| **1d** | Ph | 4-F-$C_6H_4$ | H |
| **1e** | 2-Cl-$C_6H_4$ | Ph | H |
| **1f** | 2-Cl-$C_6H_4$ | 2-Cl-$C_6H_4$ | H |
| **1g** | 2-Cl-$C_6H_4$ | 2-CN-$C_6H_4$ | H |
| **1h** | 2-Cl-$C_6H_4$ | 3-Cl-$C_6H_4$ | H |
| **1i** | 3-Cl-$C_6H_4$ | 3-Cl-$C_6H_4$ | H |
| **1j** | 4-Cl-$C_6H_4$ | 3-Cl-$C_6H_4$ | H |
| **1k** | 4-F-$C_6H_4$ | 3-$COCH_3$-$C_6H_4$ | H |
| **1l** | Ph | Ph | Me |
| **1m** | Ph | Ph | Ph |
| **1n** | Ph | 4-$CH_3$-$C_6H_4$ | Me |
| **1o** | Ph | 4-Cl-$C_6H_4$ | Me |
| **1p** | 2-Cl-$C_6H_4$ | Ph | 4-Cl-$C_6H_4$ |
| **1q** | 3-Cl-$C_6H_4$ | 2-Cl-$C_6H_4$ | 2-naphthyl |

**2a-g, 2i-m: $R^4$ = $R^5$ = Me**
**2h: $R^4$ = Me, $R^5$ = Et**

| | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| **2a** | Ph | Ph | H |
| **2b** | Ph | Ph | Me |
| **2c** | Ph | 3-F-$C_6H_4$ | H |
| **2d** | Ph | 4-$CH_3$-$C_6H_4$ | Me |
| **2e** | Ph | 4-Cl-$C_6H_4$ | Me |
| **2f** | Ph | 4-F-$C_6H_4$ | H |
| **2g** | 2-Cl-$C_6H_4$ | Ph | H |
| **2h** | 2-Cl-$C_6H_4$ | Ph | H |
| **2i** | 2-Cl-$C_6H_4$ | Ph | 4-Cl-$C_6H_4$ |
| **2j** | 2-Cl-$C_6H_4$ | 3-Cl-$C_6H_4$ | H |
| **2k** | 3-Cl-$C_6H_4$ | 3-Cl-$C_6H_4$ | H |
| **2l** | 4-Cl-$C_6H_4$ | 3-Cl-$C_6H_4$ | H |
| **2m** | 4-F-$C_6H_4$ | 3-$COCH_3$-$C_6H_4$ | H |

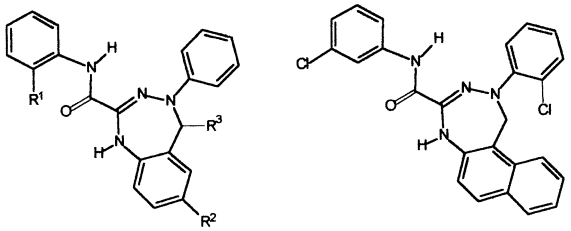
**Scheme 1.**




**3a-b**

| | $R^1$ | $R^2$ |
|---|---|---|
| **3a** | 2-Cl-$C_6H_4$ | 2-Cl-$C_6H_4$ |
| **3b** | 4-F-$C_6H_4$ | 3-$COCH_3$-$C_6H_4$ |

**Scheme 2.**



**4a**: $R^1$, $R^2$ = Cl, $R^3$ = H
**4b**: $R^1$, $R^2$ = H, $R^3$ = Ph

**4c**

**Scheme 3.**

Amidrazones **1b**, **1f**, **1g** and **1q** were recovered unchanged under the described conditions (Section 4). Only a trace of the 4,5-dihydrotriazole was detected by TLC in the reaction mixtures because of the characteristic fluorescence. We assume that *ortho* substitution of the arylhydrazone moiety could result in a steric hindrance and a decreased reactivity.

5,5-Dialkyl-1-aryl-4,5-dihydro-1*H*-1,2,4-triazole-3-carboxanilides **2** commonly form yellow colored crystals and are soluble in alcohols with appearance of an intensive green–yellow fluorescence. The stability of these compounds is much higher than that of the corresponding open-chain derivatives **1**. No decomposition was discovered during keeping the solid products at room temperature for some months.

Under strong acidic conditions, the ring closure is reversible which becomes visible by loss of fluorescence. It has been proved by NMR experiments that in DMSO-$d_6$ dihydrotriazoles **2** slowly decompose into the corresponding amidrazones **1** in the presence of trifluoroacetic acid.

No reaction could be observed between amidrazones **1** and alkyl aryl as well as diaryl substituted ketones, which is attributed to lower carbonyl reactivity of aryl ketones. However, the replacement by substituted α,α-dichloromethane should yield the cyclization.[3]

The treatment of amidrazones **1** (provided that $R^3$=H, e.g. **1f** or **1k**) with formaldehyde instead of ketones in refluxing ethanol led under acidic catalysis to 1-aryl-1*H*-1,2,4-triazole-3-carboxanilides **3** (Scheme 2). The corresponding dihydrotriazoles **2** were observed as intermediates and detected in the reaction mixture by TLC. However, they underwent a rapid oxidation to 1*H*-1,2,4-triazoles **3**.[14] Unlike the reaction with ketones, orthosubstituted $N^2$-arylamidrazones (e.g. **1f**) gave a successful cyclization with formaldehyde as well.

On the other hand, the addition of formaldehyde or benzaldehyde to **1m**, **1p** or **1q** ($R^3$=aryl, reaction conditions like that shown in Scheme 2) furnished aryl condensed dihydrotriazepines **4**, see Scheme 3. The preparation of similar 4-aryl-4,5-dihydro-1*H*-1,3,4-benzo[*e*]triazepines and the assignment of its structure have previously been reported.[15,16] By analogy with the referred reaction, 2-chlorooxanilo-*N*-(4-chlorophenyl)amide phenylhydrazone (**1p**) and formaldehyde gave **4a**; oxanilo-*N*-phenylamide phenylhydrazone (**1m**) and benzaldehyde yielded

**Table 1.** Essential spectroscopic data of amidrazones **1**

| | $^1$H NMR spectroscopic data (DMSO-$d_6$) $\delta$ (ppm) | | | | $^{13}$C NMR spectroscopic data (DMSO-$d_6$) $\delta$ (ppm) | | | IR spectroscopic data (potassium bromide) $\nu$ ($cm^{-1}$) | |
|---|---|---|---|---|---|---|---|---|---|
| | NN*H* (s, 1H) | N$H_2$/N*H* | CON*H* (s, 1H) | Ar-*H* | *C*=O (1C) | *C*=N (1C) | Ar-*C* | C=O | NH |
| **1b** | 8.25 | 6.44 (s, 2H) | 9.80 | 6.7–7.8 (9H) | 160.2 | 138.0 | 115.6–150.9 (12C) | 1654 | 3357, 3441 |
| **1c** | 8.80 | 6.12 (s, 2H) | 9.83 | 6.4–7.8 (9H) | 160.1 | 136.7 | 104.2–164.9 (12C) | 1648 | 3440, 3361 |
| **1d** | 8.54 | 6.01 (s, 2H) | 9.75 | 7.0–7.8 (9H) | 159.9 | 138.1 | 113.4–158.0 (12C) | 1646 | 3431, 3358 |
| **1e** | 8.79 | 6.21 (s, 2H) | 9.96 | 6.7–8.3 (9H) | 159.4 | 134.3 | 112.0–145.6 (12C) | 1675 | 3368 |
| **1f** | 8.02 | 6.71 (s, 2H) | 9.96 | 6.8–8.2 (8H) | 159.6 | 137.7 | 114.6–142.0 (12C) | 1691 | 3418, 3329 |
| **1g**[a] | 9.13 | 6.55 (s, 2H) | 9.71 | 6.8–8.0 (8H) | 159.6 | 137.7 | 114.9–147.6 (12C) | 1701, 1672 | 3460, 3356 |
| **1h** | 8.99 | 6.25 (s, 2H) | 9.97 | 6.7–8.2 (8H) | 159.5 | 136.2 | 111.0–147.3 (12C) | 1678 | 3324 |
| **1i** | 8.81 | 6.13 (s, 2H) | 10.01 | 6.7–7.9 (8H) | 160.4 | 136.7 | 111.3–147.4 (12C) | 1677 | 3355 |
| **1j** | 8.79 | 6.12 (s, 2H) | 9.99 | 6.7–7.8 (8H) | 160.0 | 137.1 | 111.1–147.2 (12C) | 1675 | 3359 |
| **1k**[b] | 8.83 | 6.10 (s, 2H) | 9.92 | 7.1–7.8 (8H) | 160.2 | 137.8 | 111.9–159.7 (12C) | 1667 | 3339, 3437 |
| **1l**[c] | 8.51 | 5.73 (q, 1H) | 9.94 | 6.7–8.0 (10H) | 160.6 | 140.4 | 113.9–146.3 (12C) | 1683 | 3331 |
| **1m** | 9.25 | 8.02 (s, 1H) | 10.07 | 6.7–7.8 (15H) | 160.8 | 132.4 | 114.1–145.5 (18C) | 1685 | 3351 |
| **1n**[d] | 8.37 | 5.66 (q, 1H) | 9.91 | 7.0–7.7 (9H) | 160.3 | 139.7 | 112.7–143.8 (12C) | 1679 | 3403, 3336, 3284 |
| **1o**[e] | 8.64 | 5.82 (q, 1H) | 9.98 | 7.0–7.8 (9H) | 162.2 | 142.7 | 115.2–147.0 (12C) | 1682 | 3350 |
| **1p** | 9.53 | 8.27 (s, 1H) | 9.81 | 6.6–8.2 (13H) | 160.1 | 130.1 | 113.7–144.4 (18C) | 1672 | 3335 |
| **1q** | 8.96 | 8.04 (s, 1H) | 10.44 | 6.8–7.9 (15H) | 160.8 | 133.9 | 112.0–140.2 (22C) | 1678 | 3345, 3307 |

[a] Additional signals: 119.3 (1C, *C*≡N).
[b] Additional signals: 2.49 (s, 1H, C$H_3$), 198.5 (1C, *C*=O), 26.8 (1C, *C*$H_3$).
[c] Additional signals: 2.93 (d, 3H, C$H_3$), 30.3 (1C, *C*$H_3$).
[d] Additional signals: 2.19 (s, 3H, C$H_3$), 2.91 (d, 3H, C$H_3$), 20.3 (1C, *C*$H_3$), 30.3 (1C, *C*$H_3$).
[e] Additional signals: 2.92 (d, 3H, C$H_3$), 31.7 (1C, *C*$H_3$).

**Table 2.** Essential spectroscopic data of cyclic compounds **2–4**

| | $^1$H NMR spectroscopic data (DMSO-d$_6$) $\delta$ (ppm) | | | | $^{13}$C NMR spectroscopic data (DMSO-d$_6$) $\delta$ (ppm) | | | | | IR spectroscopic data (potassium bromide) $\nu$ (cm$^{-1}$) | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | N*H* (s, 1H) | CON*H* (s, 1H) | C*H*$_3$ (s) | Ar-*H* | *C*═O (1C) | *C*═N (1C) | *C*-5 (1C) | *C*H$_3$ | Ar-*C* | C═O | NH |
| **2a** | 7.34 | 10.24 | 1.57 (6H) | 6.9–8.6 (10H) | 156.7 | 144.4 | 84.2 | 26.6 (2C) | 116.7–143.9 (12C) | 1672 | 3295, 3383 |
| **2b**[a] | – | 10.15 | 1.52 (6H) | 6.9–7.7 (10H) | 157.4 | 144.2 | 87.3 | 22.1 (2C) | 117.4–143.8 (12C) | 1678 | 3331 |
| **2c** | 7.55 | 10.06 | 1.60 (6H) | 6.6–7.8 (9H) | 156.5 | 144.5 | 83.8 | 26.4 (2C) | 102.4–165.4 (12C) | 1668 | 3294 |
| **2d**[b] | – | 10.11 | 1.45 (6H) | 7.1–7.8 (9H) | 157.3 | 141.5 | 87.7 | 22.2 (2C) | 118.6–144.2 (12C) | 1679 | 3436 |
| **2e**[c] | – | 10.19 | 1.53 (6H) | 7.3–7.7 (9H) | 157.3 | 144.4 | 87.1 | 28.0 (2C) | 118.4–142.6 (12C) | 1671 | 3306 |
| **2f** | 7.30 | 10.05 | 1.47 (6H) | 7.0–7.8 (9H) | 156.7 | 144.8 | 84.7 | 26.5 (2C) | 114.9–159.6 (12C) | 1679 | 3381, 3325 |
| **2g** | 7.38 | 9.54 | 1.56 (6H) | 6.8–8.0 (9H) | 156.3 | 143.4 | 84.7 | 26.6 (2C) | 116.3–143.8 (12C) | 1679 | 3339 |
| **2h**[d] | 7.40 | 9.48 | 1.50 (3H) | 6.8–8.0 (9H) | 156.5 | 143.9 | 87.2 | 25.4 (1C) | 115.2–143.5 (12C) | 1679 | 3351 |
| **2i** | – | 9.81 | 1.51 (6H) | 7.0–7.8 (13H) | 156.0 | 142.8 | 88.7 | 25.3 (2C) | 118.2–142.5 (18C) | 1697 | 3358 |
| **2j** | 7.69 | 9.73 | 1.60 (6H) | 6.7–7.8 (8H) | 156.5 | 144.3 | 84.2 | 26.5 (2C) | 113.4–144.8 (12C) | 1697 | 3358 |
| **2k** | 7.43 | 10.26 | 1.59 (6H) | 6.8–7.9 (8H) | 156.9 | 144.5 | 84.0 | 26.4 (2C) | 113.4–144.9 (12C) | 1668 | 3327 |
| **2l** | 7.58 | 10.24 | 1.58 (6H) | 6.8–7.8 (8H) | 156.6 | 144.5 | 83.9 | 26.5 (2C) | 113.3–144.8 (12C) | 1674 | 3317 |
| **2m**[e] | 7.53 | 10.22 | 1.58 (6H) | 7.1–7.8 (8H) | 156.6 | 144.7 | 84.0 | 26.6 (2C) | 114.9–160.9 (12C) | 1676 | 3290 |
| **3a** | – | 10.07 | – | 7.2–8.0 (8H) | 156.5 | 147.2 | 130.5 | – | 124.7–134.1 (12C) | 1703 | 3346 |
| **3b**[f] | – | 10.65 | – | 7.2–8.5 (8H) | 157.1 | 144.1 | 130.5 | – | 115.2–138.4 (12C) | 1698 | 3372 |
| **4a** | 9.29 | 10.11 | – | 6.9–8.3 (12H) | 159.2 | 132.9 | 57.3 | – | 114.9–148.5 (18C) | 1685 | 3327 |
| **4b** | 8.90 | 9.78 | – | 6.9–7.7 (19H) | 159.7 | 139.2 | 69.7 | – | 116.8–149.4 (24C) | 1674 | 3328 |
| **4c** | 9.09 | 10.12 | – | 7.2–8.1 (14H) | 160.5 | 133.2 | 58.8 | – | 120.3–149.1 (22C) | 1685 | 3442, 3337 |

[a] Additional signals: 2.98 (s, 3H, C*H*$_3$), 28.1 (1C, *C*H$_3$).
[b] Additional signals: 2.24 (s, 3H, C*H*$_3$), 2.96 (s, 3H, C*H*$_3$), 28.3 (1C, *C*H$_3$), 20.4 (1C, *C*H$_3$).
[c] Additional signals: 2.98 (s, 3H, C*H*$_3$), 22.1 (1C, *C*H$_3$).
[d] Additional signals: for R$^5$: 0.85 (t, 3H, CH$_2$C*H*$_3$), 1.76 (m, 1H) and 2.17 (m, 1H, C*H*$_2$CH$_3$), 9.2 (1C, CH$_2$*C*H$_3$), 33.7 (1C, *C*H$_2$CH$_3$).
[e] Additional signals: 2.57 (s, 3H, C*H*$_3$), 26.8 (1C, C*H*$_3$), 198.1 (1C, *C*═O).
[f] Additional signals: 2.68 (s, 3H, C*H*$_3$), 9.63 (s, 1H, N═C*H*–N); 26.9 (1C, *C*H$_3$).

**4b**; 3-chlorooxanilo-*N*-naphthylamide (2-chlorophenyl)-hydrazone (**1q**) was converted with formaldehyde into **4c**. Furthermore, dihydrotriazoles, which were formed according to above described cyclization mechanism (see Scheme 1, step B), were detected in reaction mixtures by TLC as well but could not be isolated.

The structures of all compounds described herein were confirmed by analytical (Section 4) and spectroscopic methods.

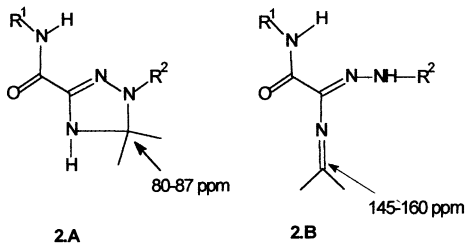
## 2.2. Establishment of structures

$^{1}H$, $^{13}C$ NMR and IR spectral data of considerable moieties of amidrazones **1** are listed in Table 1. As expected, $^{1}H$ NMR spectra of these compounds in DMSO-$d_6$ show three characteristic signals: one singlet of the CONH group at about 9–10 ppm, another singlet of the NNH group in the region of 8–9 ppm and the signal of the $NH_2$ or alkyl substituted NH group near 6 ppm or at about 8 ppm in case of aryl substituted amide moiety, respectively. We assigned the signal in the region of 8–9 ppm to the proton of the NNH moiety using $^{1}H$, $^{13}C$ long range experiments. $^{13}C$ NMR spectra exhibit two characteristic signals for the C=O and the C=N moieties at about 160 and 137 ppm. The signal of the hydrazone carbon is strongly influenced by the amide substituent of the amidrazone structure, see **1l**–**1q**. Typical bands of C=O stretching at about 1650 $cm^{-1}$ and of NH stretching in the region of 3400 $cm^{-1}$ appear in the IR spectra.

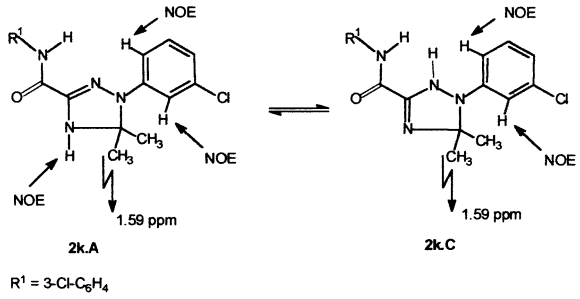
Essential $^{1}H$, $^{13}C$ NMR and IR spectroscopic data of the new synthesized heterocyclic compounds **2**–**4** are summarized in Table 2. $^{1}H$ NMR spectra of all carboxanilides displays a characteristic singlet in the range of 10 ppm. Considering the spectral establishment of amidrazones **1** and the structure of triazole derivatives **3**, the signal was assumed to be that of the anilide proton. Accordingly, the signal near 7 ppm in the spectra of dihydrotriazoles **2** and about 9 ppm in the spectra of dihydrotriazepines **4** was assigned to the heterocyclic NH moiety. NOE experiments with **2** (see below) as well as $^{1}H$, $^{13}C$ long range experiments with **4** confirmed this assignment. Comparing to $^{13}C$ NMR spectra of open-chain derivatives **1**, the chemical shift of the C=O group of heterocycles **2** and **3** is deshielded for about 3 ppm upfield and that of the C=N moiety mostly more than 7 ppm downfield. The signals of the C-5 atom of dihydrotriazoles **2** appear at about 85 ppm and around 58 ppm in case of triazepines **4**. The spectra of the triazoles **3** show the signal of the C-5 atom in the region of aromatic carbon atoms near 130 ppm. Typical bands of the C=O and NH stretch in the region of 1680–1700 and 3290–3440 $cm^{-1}$ are observed in IR spectra.

The assignment of the $^{13}C$ signal of the C=N group in both the open-chain as well as the cyclic compounds was complicated by the similar chemical shift of the aromatic C-atom in α-position to the hydrazone moiety. $^{1}H$, $^{13}C$ long range experiments were used to distinguish between both.

The reaction of $N^1$-unsubstituted amidrazones with ketones could lead not only to the cyclic product **2.A** but also to the open-chain tautomer **2.B**, see Scheme 4.




**Scheme 4.**




**Scheme 5.**

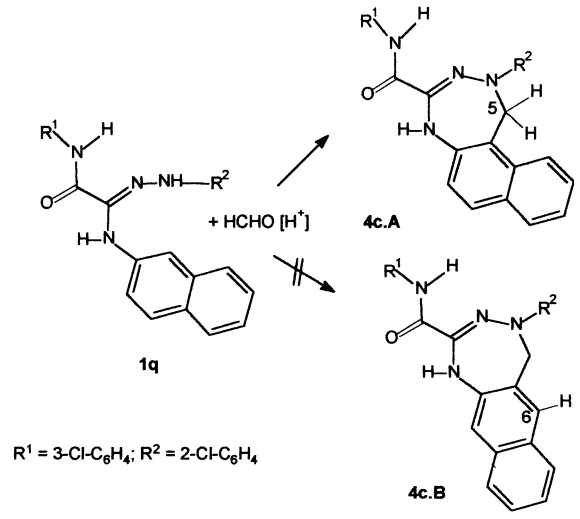
The signal in the $^{13}C$ NMR spectra of products **2** between 80 and 87 ppm (Table 2) was assigned to an aminal carbon and proves the ring closure to 4,5-dihydro-1*H*-1,2,4-triazoles consistent with literature data.[6,11] In contrast, the $^{13}C$ signal of an imine carbon atom of open-chain isomer **2.B** is expected at 145–160 ppm.[6,12]

Provided that $R^3$=H, the dihydrotriazoles **2** can exist in tautomeric form **2.A** and **2.C** as well (Scheme 5). NOE experiments with derivative **2k** (Section 4) revealed the compounds to occur in tautomer **2.A**. The irradiation in frequency of the methyl protons causes a NOE not only to the aromatic *ortho*-protons, which could accord with both tautomers but also to the cyclic NH proton, which excludes structure **2k.C**.

The acidic catalyzed reaction of amidrazone **1q** and formaldehyde could lead to product **4c.A** or the isomer **4c.B**, respectively (Scheme 6). $^{1}H$, $^{13}C$ long range experiments indicated that **4c.A** was formed. There is no coupling observed between the signal of C-5 and any proton signal. However, in case of product **4c.B** a coupling should be expected between the C-5 signal and the signal of the proton in position 6.

## 3. Conclusion

The described approach to 1,3,4,5,5-pentasubstituted 4,5-dihydro-1*H*-1,2,4-triazoles is a facile method to obtain a large scale of derivatives not only of dihydrotriazoles but also of the isolated intermediate amidrazones. The convenient cyclization of amidrazones **1** to 4,5-dihydro-1*H*-1,2,4-triazoles **2** we assume to be easy transfer to other α-carbonyl substituted amidrazones. Considering combinatorial libraries, 1,3,5-trisubstituted 1,2,4-triazoles were




**Scheme 6.**

recently obtained with difficulties by oxidative cyclization of substituted amidrazones.[17] The side reaction, which we observed by the condensation of amidrazones with formaldehyde, is a known procedure to prepare 1,2,4-triazoles from amidrazones and monocarbonyl compounds[18] and represents an alternative way to the desired trisubstituted 1,2,4-triazoles.

## 4. Experimental

### 4.1. General

Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. NMR spectra were recorded on a Gemini 2000 and Gemini 200, operating at 399.96 and 199.95 MHz for $^1$H NMR and at 100.6 and 50.3 MHz for $^{13}$C NMR spectra. TMS was used as internal standard. Chemical shifts are given in $\delta$ units and refer to the center of the signal. Mass spectra were obtained with an AMD 402 of the firm AMD INTEDRA (70 eV); IR spectra were recorded on a Spectrum BX FT-IR from the firm Perkin–Elmer. TLC was carried out with TLC aluminium sheets Silica gel 60 $F_{254}$ of the firm Merck developed in the solvent chloroform: ether (7:3, v/v) and detected with ultraviolet light (254 and 360 nm). For NMR and IR spectroscopic data, see Tables 1 and 2.

### 4.2. Arylhydrazonoyl chlorides (5a–n)

Compounds were obtained in accordance to Ref. 19 (**5a** and **5d**), Ref. 16 (**5e**) and Ref. 1 (**5b** and **5g**–**m**).

**4.2.1. *N*-(3-Fluorophenyl)-2-anilino-2-oxoethanehydrazonoyl chloride (5c).** According to Ref. 1. Compound was prepared from 3-fluoroaniline (2.2 g, 20 mmol) and 2-chloro-*N*-phenyl-3-oxobutanamide (4.2 g, 20 mmol). Crystallization from chloroform/heptane gave 2.3 g (82%) of **5c** as pale yellow needles. Mp: 168–170°C. $^1$H NMR (DMSO-$d_6$): $\delta$ 10.11 (s, 1H, N*H*), 10.45 (s, 1H, N*H*), 6.73–7.70 (m, 9H, arom. *H*). $^{13}$C NMR (DMSO-$d_6$): $\delta$ 157.4 (1C, *C*═O), 119.6 (1C, *C*═N), 101.9–145.1 (11C, arom. *C*), 163.4 (d, 1C, arom. *C*F, *J*=242 Hz). IR (potassium bromide): $\nu$ 3386, 3233 (NH), 1667 (C═O) cm$^{-1}$. MS *m*/*z*: 291 ([M]$^+$, 72), 93 (100). Anal. Calcd for $C_{14}H_{11}N_3OClF$ (291.7): C 57.65, H 3.80, N 14.40, Cl 12.15, F 6.51%. Found: C 57.82, H 3.78, N 14.30, Cl 12.06, F 6.52%.

**4.2.2. *N*-(4-Fluorophenyl)-2-anilino-2-oxoethanehydrazonoyl chloride (5f).** According to Ref. 1. Compound was prepared from 4-fluoroaniline (2.2 g, 20 mmol) and 2-chloro-*N*-phenyl-3-oxobutanamide (4.2 g, 20 mmol). Crystallization from chloroform/heptane gave 2.3 g (82%) of **5f** as pale yellow platelets. Mp: 186–188°C. $^1$H NMR (DMSO-$d_6$): $\delta$ 10.05 (s, 1H, N*H*), 10.32 (s, 1H, N*H*), 7.09–7.71 (m, 9H, arom. *H*). $^{13}$C NMR (DMSO-$d_6$): $\delta$ 157.4 (1C, *C*═O), 118.2 (1C, *C*═N), 115.5–139.6 (11C, arom. *C*), 157.8 (d, 1C, arom. *C*F, *J*=238 Hz). IR (potassium bromide): $\nu$ 3385, 3231 (NH), 1667 (C═O) cm$^{-1}$. MS *m*/*z*: 291 ([M]$^+$, 52), 93 (100). Anal. Calcd for $C_{14}H_{11}N_3OClF$ (291.7): C 57.65, H 3.80, N 14.40, Cl 12.15, F 6.51%. Found: C 57.78, H 3.90, N 14.45, Cl 12.03, F 6.38%.

**4.2.3. *N*-(3-Acetylphenyl)-2-[(4-fluorophenyl)amino]-2-oxoethanehydrazonoyl chloride (5n).** According to Ref. 1. Compound was prepared from 3-aminophenyl methyl ketone (2.6 g, 20 mmol) and 2-chloro-*N*-(4-fluorophenyl)-3-oxobutanamide (4.6 g, 20 mmol) (synthesized following Ref. 20). Crystallization from methanol gave 2.1 g (63%) of **5n** as short dark yellow needles. Mp: 232–234°C. $^1$H NMR (DMSO-$d_6$): $\delta$ 10.15 (s, 1H, N*H*), 10.32 (s, 1H, N*H*), 6.95–7.78 (m, 8H, arom. *H*), 2.56 (s, 3H, C$H_3$). $^{13}$C NMR (DMSO-$d_6$): $\delta$ 157.7 (1C, *C*═O), 119.4 (1C, *C*═N), 114.4–160.9 (11C, arom. *C*), 158.5 (d, 1C, arom. *C*F, *J*=240 Hz), 26.8 (1C, CO*C*H$_3$), 197.8 (1C, *C*OCH$_3$). IR (potassium bromide): $\nu$ 3306, 3237 (NH), 1650 (C═O) cm$^{-1}$. MS *m*/*z*: 333 ([M]$^+$, 100). Anal. Calcd for $C_{16}H_{13}N_3O_2ClF$ (333.7): C 57.58, H 3.92, N 12.59, Cl 10.62, F 5.69%. Found: C 57.70, H 4.02, N 12.51, Cl 10.59, F 5.78%.

### 4.3. Synthesis of 2-amino-*N*-aryl-2-arylhydrazonoacetamides 1a–k, general procedure (GP 1)

A solution of arylhydrazonoyl chloride **5** (20 mmol) in about 50 mL dioxane was added slowly to 40 mmol ammonia (5.7 mL of a 7N methanolic solution). After stirring at 40–45°C for 12 h the mixture was poured into 250 mL cold water. The solid was collected, thoroughly washed with water, dried and recrystallized from the given solvent.

2-Amino-*N*-phenyl-2-phenylhydrazonoacetamide **1a** was obtained starting from compound **5a** according to published procedure.[16]

**4.3.1. 2-Amino-2-[(2-fluorophenyl)hydrazono]-*N*-phenylacetamide (1b).** Compound was prepared from 2-anilino-*N*-(2-fluorophenyl)-2-oxoethanehydrazonoyl chloride **5b** (5.8 g, 20 mmol) following GP 1. Crystallization from chloroform/heptane gave 2.8 g (52%) of **1b** as yellow amorphous solid. Mp: 158–160°C. MS *m*/*z*: 272 ([M]$^+$, 100).

Anal. Calcd for $C_{14}H_{13}N_4OF$ (272.3): C 61.76, H 4.81, N 20.57, F 6.98%. Found: C 61.62, H 4.79, N 20.60, F 7.01%.

**4.3.2. 2-Amino-2-[(3-fluorophenyl)hydrazono]-*N*-phenylacetamide (1c).** Compound was prepared from 2-anilino-*N*-(3-fluorophenyl)-2-oxoethanehydrazonoyl chloride **5c** (5.8 g, 20 mmol) following GP 1. Crystallization from chloroform/heptane gave 4.0 g (74%) of **1c** as white amorphous solid. Mp: 175–178°C. MS *m/z*: 272 ([M]$^+$, 100). Anal. Calcd for $C_{14}H_{13}N_4OF$ (272.3): C 61.76, H 4.81, N 20.57, F 6.98%. Found: C 61.52, H 4.96, N 20.53, F 6.93%.

**4.3.3. 2-Amino-2-[(4-fluorophenyl)hydrazono]-*N*-phenylacetamide (1d).** Compound was prepared from 2-anilino-*N*-(4-fluorophenyl)-2-oxoethanehydrazonoyl chloride **5f** (5.8 g, 20 mmol) following GP 1. Crystallization from chloroform/heptane gave 4.2 g (77%) of **1d** as yellow amorphous solid. Mp: 151–153°C. MS *m/z*: 272 ([M]$^+$, 100). Anal. Calcd for $C_{14}H_{13}N_4OF$ (272.3): C 61.76, H 4.81, N 20.57, F 6.98%. Found: C 61.68, H 4.87, N 20.49, F 7.09%.

**4.3.4. 2-Amino-*N*-(2-chlorophenyl)-2-phenylhydrazonoacetamide (1e).** Compound was prepared from 2-[(2-chlorophenyl)amino]-2-oxo-*N*-phenylethanehydrazonoyl chloride **5g** (6.2 g, 20 mmol) following GP 1. Crystallization from methanol gave 4.2 g (72%) of **1e** as long, yellow needles. Mp: 155–156°C. MS *m/z*: 288 ([M]$^+$, 89), 91 (100). Anal. Calcd for $C_{14}H_{13}N_4OCl$ (288.7): C 58.24, H 4.54, N 19.40, Cl 12.28%. Found: C 58.19, H 4.55, N 19.48, Cl 12.26%.

**4.3.5. 2-Amino-*N*-(2-chlorophenyl)-2-[(2-chlorophenyl)hydrazono]acetamide (1f).** Compound was prepared from *N*-(2-chlorophenyl)-2-[(2-chlorophenyl)amino]-2-oxoethanehydrazonoyl chloride **5h** (6.9 g, 20 mmol) following GP 1. Crystallization from chloroform/heptane gave 4.8 g (75%) of **1f** as white needles. Mp: 172–174°C. MS *m/z*: 322 ([M]$^+$, 100). Anal. Calcd for $C_{14}H_{12}N_4OCl_2$ (323.2): C 52.03, H 3.74, N 17.33, Cl 21.94%. Found: C 51.64, H 3.69, N 16.95, Cl 21.80%.

**4.3.6. 2-Amino-*N*-(2-chlorophenyl)-2-[(2-cyanophenyl)hydrazono]acetamide (1g).** Compound was prepared from 2-[(2-chlorophenyl)amino]-*N*-(2-cyanophenyl)-2-oxoethanehydrazonoyl chloride **5i** (6.7 g, 20 mmol) following GP 1. Crystallization from ethanol/chloroform gave 4.8 g (76%) of **1g** as amorphous pale yellow solid. Mp: 222–223°C. MS *m/z*: 313 ([M]$^+$, 10), 135 (100). Anal. Calcd for $C_{15}H_{12}N_5OCl$ (313.7): C 57.43, H 3.85, N 22.32, Cl 11.30%. Found: C 57.22, H 3.71, N 21.94, Cl 11.16%.

**4.3.7. 2-Amino-*N*-(2-chlorophenyl)-2-[(3-chlorophenyl)hydrazono]acetamide (1h).** Compound was prepared from *N*-(3-chlorophenyl)-2-[(2-chlorophenyl)amino]-2-oxoethanehydrazonoyl chloride **5j** (6.9 g, 20 mmol) following GP 1. Crystallization from chloroform gave 4.1 g (63%) of **1h** as amorphous yellow solid. Mp: 192–194°C. MS *m/z*: 322 ([M]$^+$, 100). Anal. Calcd for $C_{14}H_{12}N_4OCl_2$ (323.2): C 52.03, H 3.74, N 17.33, Cl 21.94%. Found: C 52.10, H 3.71, N 17.23, Cl 21.78%.

**4.3.8. 2-Amino-*N*-(3-chlorophenyl)-2-[(3-chlorophenyl)hydrazono]acetamide (1i).** Compound was prepared from *N*-(3-chlorophenyl)-2-[(3-chlorophenyl)amino]-2-oxoethanehydrazonoyl chloride **5l** (6.9 g, 20 mmol) following GP 1. Crystallization first from chloroform, then from methanol gave 3.6 g (56%) of **1i** as white amorphous solid. Mp: 148–150°C. MS *m/z*: 322 ([M]$^+$, 100). Anal. Calcd for $C_{14}H_{12}N_4OCl_2$ (323.2): C 52.03, H 3.74, N 17.33, Cl 21.94%. Found: C 52.09, H 3.74, N 17.30, Cl 21.88%.

**4.3.9. 2-Amino-*N*-(4-chlorophenyl)-2-[(3-chlorophenyl)hydrazono]acetamide (1j).** Compound was prepared from *N*-(3-chlorophenyl)-2-[(4-chlorophenyl)amino]-2-oxoethanehydrazonoyl chloride **5m** (6.9 g, 20 mmol) following GP 1. Crystallization from chloroform/heptane gave 4.8 g (74%) of **1j** as amorphous white solid. Mp: 188–189°C. MS *m/z*: 322 ([M]$^+$, 100). Anal. Calcd for $C_{14}H_{12}N_4OCl_2$ (323.2): C 52.03, H 3.74, N 17.33, Cl 21.94%. Found: C 52.05, H 3.67, N 17.01, Cl 21.37%.

**4.3.10. 2-[(3-Acetylphenyl)hydrazono]-2-amino-*N*-(4-fluorophenyl)acetamide (1k).** Compound was prepared from *N*-(3-acetylphenyl)-2-[(4-fluorophenyl)amino]-2-oxoethanehydrazonoyl chloride **5n** (6.7 g, 20 mmol) following GP 1. Crystallization from chloroform/heptane gave 5.5 g (87%) of **1k** as yellow amorphous solid. Mp: 232–234°C. MS *m/z*: 314 ([M]$^+$, 100). Anal. Calcd for $C_{16}H_{15}N_4O_2F$ (314.3): C 61.14, H 4.81, N 17.82, F 6.04%. Found: C 60.96, H 4.86, N 17.60, F 6.22%.

### 4.4. Synthesis of *N*-substituted 2-amino-*N*-aryl-2-arylhydrazonoacetamides 1l–1q, (GP2)

A solution of arylhydrazonoyl chloride **5** (20 mmol) in about 50 mL dioxane was added dropwise to 40 mmol methylamine (20 mL of 2 M methanolic solution) or 20 mmol aniline and 20 mmol triethylamine (2.7 mL), respectively, in a few mL dioxane. After stirring at 40–45°C for at least 12 h (control of reaction progress by TLC) the solvent was evaporated and the residue was treated with cold water. The solid was collected, washed with water, dried and recrystallized from the given solvent.

**4.4.1. 2-Methylamino-*N*-phenyl-2-phenylhydrazonoacetamide (1l).** Compound was prepared from 2-anilino-2-oxo-*N*-phenylethanehydrazonoyl chloride **5a** (5.5 g, 20 mmol) and methylamine following GP 2. Crystallization from heptane gave 3.9 g (72%) of **1l** as yellow needles. Mp: 101–103°C. MS *m/z*: 268 ([M]$^+$, 100). Anal. Calcd for $C_{15}H_{16}N_4O$ (268.3): C 67.15, H 6.01, N 20.88%. Found: C 67.22, H 6.00, N 20.70%.

**4.4.2. *N*-Phenyl-2-phenylamino-2-phenylhydrazonoacetamide (1m).** Compound was prepared from 2-anilino-2-oxo-*N*-phenylethanehydrazonoyl chloride **5a** (5.5 g, 20 mmol) and aniline (1.9 g, 20 mmol) following GP 2. Crystallization from chloroform/heptane gave 3.6 g (55%) of **1m** as dark yellow needles. Mp: 166–168°C. MS *m/z*: 330 ([M]$^+$, 100). Anal. Calcd for $C_{20}H_{18}N_4O$ (330.4): C 72.71, H 5.49, N 16.96%. Found: C 72.64, H 5.55, N 16.98%.

**4.4.3. 2-Methylamino-2-[(4-methylphenyl)hydrazono]-*N*-phenylacetamide (1n).** Compound was prepared from 2-anilino-*N*-(4-methylphenyl)-2-oxoethanehydrazonoyl chloride **5d** (5.8 g, 20 mmol) and methylamine following

GP 2. Crystallization from methanol gave 3.3 g (58%) of **1n** as dark yellow crystals. Mp: 106–108°C. MS *m/z*: 282 ($[M]^+$, 100). Anal. Calcd for $C_{16}H_{18}N_4O$ (282.3): C 68.06, H 6.43, N 19.84%. Found: C 68.05, H 6.46, N 19.93%.

**4.4.4. 2-[(4-Chlorophenyl)hydrazono]-2-methylamino-*N*-phenylacetamide (1o).** Compound was prepared from 2-anilino-*N*-(4-chlorophenyl)-2-oxoethanehydrazonoyl chloride **5e** (6.2 g, 20 mmol) and methylamine following GP 2. Crystallization from methanol gave 3.8 g (62%) of **1o** as orange needles. Mp: 106–108°C. MS *m/z*: 302 ($[M]^+$, 100). Anal. Calcd for $C_{15}H_{15}N_4OCl$ (302.8): C 59.51, H 4.99, N 18.51, Cl 11.71%. Found: C 59.64, H 5.01, N 18.46, Cl 11.68%.

**4.4.5. *N*-(2-Chlorophenyl)-2-[(4-chlorophenyl)amino]-2-phenylhydrazonoacetamide (1p).** Compound was prepared from 2-[(2-chlorophenyl)amino]-2-oxo-*N*-phenylethanehydrazonoyl chloride **5g** (6.2 g, 20 mmol) and 4-chloroaniline (2.6 g, 20 mmol) following GP 2. Crystallization first from chloroform/heptane, then from 2-propanol gave 4.6 g (58%) of **1p** as yellow crystals. Mp: 210–211°C. MS *m/z*: 398 ($[M]^+$, 14), 220 (100). Anal. Calcd for $C_{20}H_{16}N_4OCl_2$ (399.3): C 60.17, H 4.04, N 14.03, Cl 17.76%. Found: C 60.14, H 4.09, N 13.74, Cl 17.32%.

**4.4.6. *N*-(3-Chlorophenyl)-2-[(2-chlorophenyl)hydrazono]-2-(2-naphthylamino)acetamide (1q).** Compound was prepared from *N*-(2-chlorophenyl)-2-[(3-chlorophenyl)-amino]-2-oxoethanehydrazonoyl chloride **5k** (6.9 g, 20 mmol) and 2-naphthylamine (2.9 g, 20 mmol) following GP 2. Crystallization first from methanol, then from chloroform/heptane gave 6.0 g (67%) of **1q** as small white needles. Mp: 198–200°C. MS *m/z*: 448 ($[M]^+$, 100). Anal. Calcd for $C_{24}H_{18}N_4OCl_2$ (449.3): C 64.16, H 4.04, N 12.47, Cl 15.78%. Found: C 63.80, H 4.05, N 12.26, Cl 15.36%.

### 4.5. Synthesis of 5,5-dialkyl-1-aryl-4,5-dihydro-1*H*-1,2,4-triazole-3-carboxamides 2a–m, general procedure (GP 3)

The appropriate 2-amino-*N*-aryl-2-arylhydrazonoacetamide **1** (10 mmol) and 0.1 g *p*-toluene sulfonic acid dissolved in approximately 50 mL of the required ketone were refluxed until the reaction was complete (controlling reaction progress by TLC). The overabundant ketone was removed by evaporation and the residue was crystallized from the given solvent.

**4.5.1. 5,5-Dimethyl-*N*,1-diphenyl-4,5-dihydro-1*H*-1,2,4-triazole-3-carboxamide (2a).** Compound was prepared from 2-amino-*N*-phenyl-2-phenylhydrazonoacetamide **1a** (2.5 g, 10 mmol) and acetone following GP 3. Crystallization from methanol gave 0.8 g (26%) of **2a** as yellow needles. Mp: 156–159°C. MS *m/z*: 294 ($[M]^+$, 19), 186 (100). Anal. Calcd for $C_{17}H_{18}N_4O$ (294.4): C 69.37, H 6.16, N 19.03%. Found: C 69.59, H 6.25, N 19.03%.

**4.5.2. 4,5,5-Trimethyl-*N*,1-diphenyl-4,5-dihydro-1*H*-1,2,4-triazole-3-carboxamide (2b).** Compound was prepared from 2-methylamino-*N*-phenyl-2-phenylhydrazonoacetamide **1l** (2.7 g, 10 mmol) and acetone following GP 3. Crystallization from methanol gave 1.3 g (43%) of **2b** as yellow crystals. Mp: 100–102°C. MS *m/z*: 308 ($[M]^+$, 11), 292 (100). Anal. Calcd for $C_{18}H_{20}N_4O$ (308.4): C 70.11, H 6.53, N 18.16%. Found: C 69.79, H 6.40, N 17.95%.

**4.5.3. 1-(3-Fluorophenyl)-5,5-dimethyl-*N*-phenyl-4,5-dihydro-1*H*-1,2,4-triazole-3-carboxamide (2c).** Compound was prepared from 2-amino-2-[(3-fluorophenyl)-hydrazono]-*N*-phenylacetamide **1c** (2.7 g, 10 mmol) and acetone following GP 3. Crystallization from methanol gave 2.3 g (73%) of **2c** as yellow platelets. Mp: 172–175°C. MS *m/z*: 312 ($[M]^+$, 18), 204 (100). Anal. Calcd for $C_{17}H_{17}N_4OF$ (312.3): C 65.37, H 5.48, N 17.93, F 6.08%. Found: C 65.27, H 5.59, N 17.91, F 6.22%.

**4.5.4. 4,5,5-Trimethyl-1-(4-methylphenyl)-*N*-phenyl-4,5-dihydro-1*H*-1,2,4-triazole-3-carboxamide (2d).** Compound was prepared from 2-methylamino-2-[(4-methylphenyl)hydrazono]-*N*-phenylacetamide **1n** (2.8 g, 10 mmol) and acetone following GP 3. Crystallization from methanol gave 2.4 g (75%) of **2d** as yellow crystals. Mp: 106–110°C. MS *m/z*: 322 ($[M]^+$, 9), 307 (100). Anal. Calcd for $C_{19}H_{22}N_4O$ (322.4): C 70.78, H 6.88, N 17.34%. Found: C 70.60, H 6.95, N 17.40%.

**4.5.5. 1-(4-Chlorophenyl)-4,5,5-trimethyl-*N*-phenyl-4,5-dihydro-1*H*-1,2,4-triazole-3-carboxamide (2e).** Compound was prepared from 2-[(4-chlorophenyl)hydrazono]-2-methylamino-*N*-phenylacetamide **1o** (3.1 g, 10 mmol) and acetone following GP 3. Crystallization from methanol gave 1.2 g (35%) of **2e** as yellow crystals. Mp: 120–122°C. MS *m/z*: 342 ($[M]^+$, 15), 327 (100). Anal. Calcd for $C_{18}H_{19}N_4OCl$ (342.8): C 63.06, H 5.59, N 16.34, Cl 10.34%. Found: C 62.99, H 5.48, N 16.30, Cl 10.30%.

**4.5.6. 1-(4-Fluorophenyl)-5,5-dimethyl-*N*-phenyl-4,5-dihydro-1*H*-1,2,4-triazole-3-carboxamide (2f).** Compound was prepared from 2-amino-2-[(4-fluorophenyl)-hydrazono]-*N*-phenylacetamide **1d** (2.7 g, 10 mmol) and acetone following GP 3. Crystallization from heptane gave 1.7 g (55%) of **2f** as yellow crystals. Mp: 119–123°C. MS *m/z*: 312 ($[M]^+$, 18), 204 (100). Anal. Calcd for $C_{17}H_{17}N_4OF$ (312.3): C 65.37, H 5.48, N 17.93, F 6.08%. Found: C 65.44, H 5.50, N 17.70, F 6.36%.

**4.5.7. *N*-(2-Chlorophenyl)-5,5-dimethyl-1-phenyl-4,5-dihydro-1*H*-1,2,4-triazole-3-carboxamide (2g).** Compound was prepared from 2-amino-*N*-(2-chlorophenyl)-2-phenylhydrazonoacetamide **1e** (2.9 g, 10 mmol) and acetone following GP 3. Crystallization from methanol gave 2.0 g (60%) of **2g** as yellow crystals. Mp: 139–141°C. MS *m/z*: 328 ($[M]^+$, 10), 186 (100). Anal. Calcd for $C_{17}H_{17}N_4OCl$ (328.8): C 62.10, H 5.21, N 17.04, Cl 10.78%. Found: C 62.34, H 5.22, N 17.26, Cl 10.97%.

**4.5.8. *N*-(2-Chlorophenyl)-5-ethyl-5-methyl-1-phenyl-4,5-dihydro-1*H*-1,2,4-triazole-3-carboxamide (2h).** Compound was prepared from 2-amino-*N*-(2-chlorophenyl)-2-phenylhydrazonoacetamide **1e** (2.9 g, 10 mmol) and ethyl methyl ketone following GP 3. Crystallization from methanol gave 1.5 g (45%) of **2h** as orange yellow crystals. Mp: 143–146°C. MS *m/z*: 342 ($[M]^+$, 9), 186 (100). Anal. Calcd for $C_{18}H_{19}N_4OCl$ (342.8): C 63.07, H 5.58, N 16.34, Cl 10.34%. Found: C 62.95, H 5.57, N 16.30, Cl 10.16%.

**4.5.9. *N*-(2-Chlorophenyl)-4-(4-chlorophenyl)-5,5-dimethyl-1-phenyl-4,5-dihydro-1*H*-1,2,4-triazole-3-carboxamide (2i).** Compound was prepared from *N*-(2-chlorophenyl)-2-[(4-chlorophenyl)amino]-2-phenylhydrazonoacetamide **1p** (4.0 g, 10 mmol) and acetone following GP 3. Crystallization from 2-propanol gave 0.6 g (14%) of **2i** as orange crystals. Mp: 148–151°C. MS *m/z*: 438 ($[M]^+$, 9), 423 (100). Anal. Calcd for $C_{23}H_{20}N_4OCl_2$ (449.3): C 62.88, H 4.59, N 12.75, Cl 16.14%. Found: C 62.71, H 4.60, N 12.70, Cl 16.03%.

**4.5.10. *N*-(2-Chlorophenyl)-1-(3-chlorophenyl)-5,5-dimethyl-4,5-dihydro-1*H*-1,2,4-triazole-3-carboxamide (2j).** Compound was prepared from 2-amino-*N*-(2-chlorophenyl)-2-[(3-chlorophenyl)hydrazono]acetamide **1h** (3.2 g, 10 mmol) and acetone following GP 3. Crystallization from methanol gave 2.6 g (71%) of **2j** as dark yellow crystals. Mp: 146–149°C. MS *m/z*: 362 ($[M]^+$, 7), 220 (100). Anal. Calcd for $C_{17}H_{16}N_4OCl_2$ (363.2): C 56.21, H 4.44, N 15.42, Cl 19.52%. Found: C 56.32, H 4.48, N 15.72, Cl 19.45%.

**4.5.11. *N*,1-Bis-(3-chlorophenyl)-5,5-dimethyl-4,5-dihydro-1*H*-1,2,4-triazole-3-carboxamide (2k).** Compound was prepared from 2-amino-*N*-(3-chlorophenyl)-2-[(3-chlorophenyl)hydrazono]acetamide **1i** (3.2 g, 10 mmol) and acetone following GP 3. Crystallization from methanol gave 1.7 g (48%) of **2k** as yellow crystals. Mp: 160–162°C. MS *m/z*: 362 ($[M]^+$, 13), 220 (100). Anal. Calcd for $C_{17}H_{16}N_4OCl_2$ (363.2): C 56.21, H 4.44, N 15.42, Cl 19.52%. Found: C 56.13, H 4.42, N 15.42, Cl 19.47%.

Data of the $^1H$ NOE experiment (DMSO-$d_6$). Frequency of irradiation: 795.07 Hz (1.59 ppm=$\delta$ $CH_3$), NOE: 3786.41 Hz (7.58 ppm=$\delta$ NH), 3711.10 Hz (7.42 ppm=$\delta$ H-Ar), 3571.28 Hz (7.14 ppm=$\delta$ H-Ar).

**4.5.12. 1-(3-Chlorophenyl)-*N*-(4-chlorophenyl)-5,5-dimethyl-4,5-dihydro-1*H*-1,2,4-triazole-3-carboxamide (2l).** Compound was prepared from 2-amino-*N*-(4-chlorophenyl)-2-[(3-chlorophenyl)hydrazono]acetamide **1j** (3.2 g, 10 mmol) and acetone following GP 3. Crystallization from methanol gave 1.3 g (36%) of **2l** as yellow crystals. Mp: 175–177°C. MS *m/z*: 362 ($[M]^+$, 9), 220 (64). Anal. Calcd for $C_{17}H_{16}N_4OCl_2$ 363.2): C 56.21, H 4.44, N 15.42, Cl 19.52%. Found: C 56.16, H 4.27, N 15.41, Cl 19.32%.

**4.5.13. 1-(3-Acetylphenyl)-*N*-(4-fluorophenyl)-5,5-dimethyl-4,5-dihydro-1*H*-1,2,4-triazole-3-carboxamide (2m).** Compound was prepared from 2-[(3-acetylphenyl)hydrazono]-2-amino-*N*-(4-fluorophenyl)acetamide **1k** (3.1 g, 10 mmol) and acetone following GP 3. Crystallization from methanol gave 1.8 g (50%) of **2m** as yellow crystals. Mp: 146–148°C. MS *m/z*: 354 ($[M]^+$, 13), 228 (100). Anal. Calcd for $C_{19}H_{19}N_4O_2F$ (354.4): C 64.40, H 5.40, N 15.81, F 5.36%. Found: C 64.23, H 5.43, N 15.73, F 5.38%.

### 4.6. Synthesis of 1-aryl-1*H*-1,2,4-triazole-3-carboxamides 3a,b and synthesis of aryl condensed 4-aryl-4,5-dihydro-1*H*-1,3,4-triazepine-2-carboxamides 4a–c, general procedure (GP 4)

The appropriate 2-amino-*N*-aryl-2-arylhydrazonoacetamides **1** (10 mmol), 1.5 mL of a 37%-solution of formaldehyde (20 mmol) or 2.1 mL benzaldehyde (20 mmol) and 0.1 g *p*-toluene sulfonic acid were refluxed in approximately 50 mL ethanol. After the given time the mixture was cooled to room temperature and the solvent was evaporated. The solid product was collected and recrystallized.

**4.6.1. *N*,1-Bis-(2-chlorophenyl)-1*H*-1,2,4-triazole-3-carboxamide (3a).** Compound was prepared from 2-amino-*N*-(2-chlorophenyl)-2-[(2-chlorophenyl)hydrazono]acetamide **1f** (3.2 g, 10 mmol) and formaldehyde following GP 4. Reaction was complete after 10 h. Recrystallization from 2-propanol gave 1.4 g (42%) of **3a** as white amorphous solid. Mp: 132–134°C. MS *m/z*: 332 ($[M]^+$, 11), 297 (100). Anal. Calcd for $C_{15}H_{10}N_4OCl_2$ (333.2): C 54.08, H 3.11, N 16.81, Cl 21.28%. Found: C 53.66, H 3.14, N 16.99, Cl 20.96%.

**4.6.2. 1-(3-Acetylphenyl)-*N*-(4-fluorophenyl)-1*H*-1,2,4-triazole-3-carboxamide (3b).** Compound was prepared from 2-[(3-acetylphenyl)hydrazono]-2-amino-*N*-(4-fluorophenyl)acetamide **1k** (3.1 g, 10 mmol) and formaldehyde following GP 4. Reaction was complete after 3 h. Recrystallization from methanol gave 1.8 g (58%) of **3b** as fine white needles. Mp: 190–192°C. MS *m/z*: 324 ($[M]^+$, 100). Anal. Calcd for $C_{17}H_{13}N_4O_2F$ (324.3): C 62.96, H 4.04, N 17.27, F 5.86%. Found: C 63.26, H 3.99, N 17.05, F 5.84%.

**4.6.3. 7-Chloro-*N*-(2-chlorophenyl)-4-phenyl-4,5-dihydro-1*H*-1,3,4-benzo[*e*]triazepine-2-carboxamide (4a).** Compound was prepared from *N*-(2-chlorophenyl)-2-[(4-chlorophenyl)amino]-2-phenylhydrazonoacetamide **1p** (4.0 g, 10 mmol) and formaldehyde following GP 4. Reaction time amounts to about 90 min. The product crystallized at cooling to room temperature. Recrystallization from methanol/chloroform gave 1.8 g (45%) of **4a** as dark orange needles. Mp: 190–192°C. MS *m/z*: 410 ($[M]^+$, 100). Anal. Calcd for $C_{21}H_{16}N_4OCl_2$ (411.3): C 61.33, H 3.92, N 13.62, Cl 17.24%. Found: C 61.04, H 4.01, N 13.61, Cl 17.37%.

**4.6.4. *N*,4,5-Triphenyl-4,5-dihydro-1*H*-1,3,4-benzo[*e*]-triazepine-2-carboxamide (4b).** Compound was prepared from *N*-phenyl-2-phenylamino-2-phenylhydrazonoacetamide **1m** (3.3 g, 10 mmol) and benzaldehyde following GP 4. Reaction time amounts to about 90 min. The product crystallized at cooling to room temperature. Recrystallization from methanol/2-isopronaol gave 1.0 g (25%) of **4b** as pale yellow needles. Mp: 186–188°C. MS *m/z*: 418 ($[M]^+$, 34), 194 (100). Anal. Calcd for $C_{27}H_{22}N_4O$ (418.5): C 77.49, H 5.30, N 13.39%. Found: C 77.45, H 5.34, N 13.34%.

**4.6.5. 4-(2-Chlorophenyl)-*N*-(3-chlorophenyl)-4,5-dihydro-1*H*-1,3,4-naphtho[*a*,*e*]triazepine-2-carboxamide (4c).** Compound was prepared from *N*-(3-chlorophenyl)-2-[(2-chlorophenyl)hydrazono]-2-(2-naphthylamino)acetamide **1q** (4.5 g, 10 mmol) within 10 h following GP 4. Recrystallization from methanol/chloroform gave 2.0 g (44%) of **4c** as fine white yellow needles. Mp: 155–156°C. MS *m/z*: 460 ($[M]^+$, 100). Anal. Calcd for $C_{25}H_{18}N_4OCl_2$ (461.4): C 65.09, H 3.93, N 12.14, Cl 15.37%. Found: C 64.76, H 3.81, N 12.12, Cl 15.25%.

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