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Recyclization of 1-aryl-4-iminoimidazolidin-2-ones on treatment with hydrazine: synthesis of 5-arylaminomethyl-2,4-dihydro[1,2,4]triazol-3-ones

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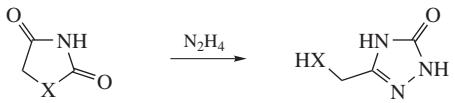
Treatment of 4-imino-*N*-arylimidazolidin-2-ones with hydrazine causes recyclization to afford 5-arylaminomethyl-2,4-dihydro[1,2,4]-triazol-3-ones.

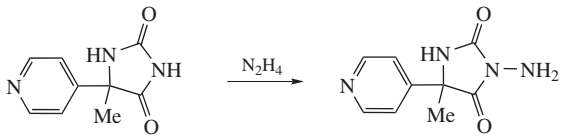
It is known[1] that the reaction of oxazolidinone **1a** and thiazolidinone **1b** with hydrazine occurs *via* recyclization of the azole moiety to give the corresponding hydroxymethyl- and mercaptomethyltriazolones **2a** and **2b**, respectively (Scheme 1).



1a,**b** **a** X = O, **b** X = S **2a**,**b**

Scheme 1

On the other hand, treatment of 5-methyl-5-(4′-pyridyl)-hydantoin **3** with hydrazine under the same conditions results in *N*-amino-substituted hydantoin **4** (Scheme 2).[2]

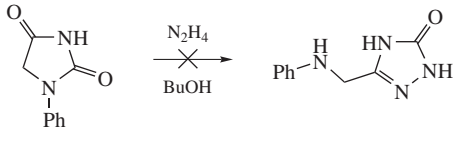


3 **4**

Scheme 2

In view of this, we studied the reactivity of *N*-phenylhydantoin **5** in the hope to synthesize analogues of compounds **2** or **4**. It is known that various substituted 1,2,4-triazolones and hydantoin derivatives have a broad scope of biological activity.[3–6]

However, our attempts to perform the recyclization of *N*-phenylhydantoin **5** on treatment with hydrazine into the corresponding *N*-arylaminomethyltriazolone **6** failed. Even after prolonged refluxing in *n*-butanol with a threefold excess of hydrazine, the reaction mixture contained much of starting compound **5** and only traces of the target product **6**. This suggests that the reactivity of hydantoin **5** is extremely low (Scheme 3).

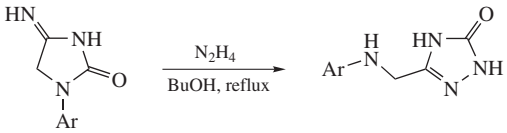


5 **6**

Scheme 3

We assumed that incorporation of an imino group possessing a higher reactivity than a carbonyl moiety into a hydantoin molecule would allow us to perform the desired recyclization. In fact, we found that the reaction of 4-imino-*N*-arylimidazolidinones **7a–f** with a threefold excess of hydrazine in boiling butanol led to recyclization products **8a–f** in high yields (Scheme 4).†

Obviously the difference in reactivity between hydantoin **5** and iminoazolidinones **7** is due to the higher reactivity of the



7a–f **8a–f**

a Ar = Ph
b Ar = 4-$MeOC_6H_4$
c Ar = 4-ClC_6H_4
d Ar = 4-FC_6H_4
e Ar = 3-ClC_6H_4
f Ar = 3-$MeOC_6H_4$

Scheme 4

† ^1H, ^{13}C, ^{15}N, ^1H-^{13}C HMBC and ^1H-^{15}N HMBC spectra were recorded with Bruker AM-300 (300 MHz) and Bruker AM-600 (600 MHz) instruments in DMSO-d_6. The melting points were measured on a Boetius heating stage and were not corrected.

The starting iminoimidazolidinones **7a–f** were obtained using reported methods.[10]

5-Arylaminomethyl-2,4-dihydro[1,2,4]triazol-3-ones **8a–f** *(general procedure)*. A mixture of iminoimidazolidinone **7a–f** (10 mmol) and hydrazine hydrate (1.5 g, 30 mmol) in 15 ml of butanol was refluxed for 16 h. The solvent was distilled off. The residue was recrystallized from acetonitrile, filtered, and washed with acetonitrile and water on the filter.

5-Phenylaminomethyl-2,4-dihydro[1,2,4]triazol-3-one **8a**. Yield 71%, mp 206–210 °C. ^1H NMR (DMSO-d_6) δ: 4.02 (d, 2H, CH_2, J 6 Hz), 5.91 (t, 1H, NH, J 6 Hz), 6.60 (m, 3H, H_{Ar}), 7.09 (m, 2H, H_{Ar}), 11.20 (s, 2H, NH). ^{13}C NMR (DMSO-d_6) δ: 39.6, 112.5, 116.6, 128.8, 146.2, 148.1, 156.3. Found (%): C, 56.61; H, 5.40; N, 29.61. Calc. for $C_9H_{10}N_4O$ (%): C, 56.83; H, 5.30; N, 29.46.

5-(4-Methoxyphenylaminomethyl)-2,4-dihydro[1,2,4]triazol-3-one **8b**. Yield 77%, mp 197–199 °C. ^1H NMR (DMSO-d_6) δ: 3.63 (s, 3H, OMe), 3.96 (d, 2H, H^6, J 5 Hz), 5.51 (t, 1H, H^7, J 5 Hz), 6.58 (d, 2H, $H^{2'}$, $H^{2''}$, J 8 Hz), 6.72 (d, 2H, $H^{3'}$, $H^{3''}$, J 8 Hz), 11.22 (s, 2H, H^2, H^5). ^{13}C NMR (DMSO-d_6) δ: 40.5 (C^6), 55.4 (OMe), 113.9 ($C^{2'}$, $C^{2''}$), 114.6 ($C^{3'}$, $C^{3''}$), 142.2 ($C^{1'}$), 146.6 (C^4), 151.5 ($C^{4'}$), 156.4 (C^1). ^{15}N NMR (DMSO-d_6) δ: –323.51 (N^7), –236.72 (N^5), –213.15 (N^2), –119.52 (N^3). Found (%): C, 54.77; H, 5.38; N, 25.57. Calc. for $C_{10}H_{12}N_4O_2$ (%): C, 54.54; H, 5.49; N, 25.44.

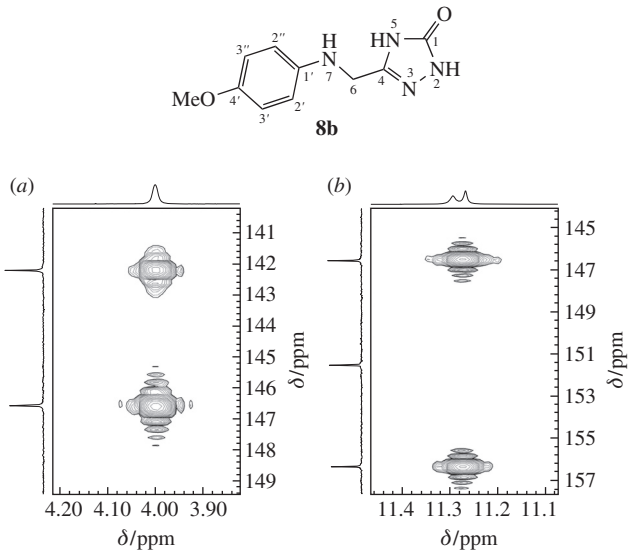


Figure 1 Fragments of the 2D ^{1}H-^{13}C HMBC spectrum (600 MHz, DMSO-d_6) of compound **8b**.

cyclic system of iminoazolidinones **7** toward hydrazine. At the present time the available experimental data do not allow us to make the conclusion explaining the difference in the reactivity between compounds **5** and **7**, which can be the subject of our further investigations.

The triazolones **8a–f** are solid crystalline compounds whose structures were confirmed by ^{1}H and ^{13}C NMR spectroscopy and elemental analyses. The ^{1}H NMR spectra of the products contain characteristic signals of methylene protons at δ 3.96–4.04 ppm and substituted amino group protons at δ 5.51–6.32 ppm. These values are in good agreement with literature data.[7]

The structure of 4-methoxyphenylaminomethyltriazolone **8b** was proved by ^{15}N NMR spectroscopy and HMBC experiments. The ^{1}H-^{13}C HMBC spectrum contains cross-peaks between the doublet of protons at C^6 (δ 3.96, J 5 Hz) and $C^{1'}$ (δ 142.21), C^4 (δ 146.57) atoms [Figure 1(*a*)]. The interactions of the hydrogen atoms at N^2 (δ 11.27) with C^4 (δ 146.57) and C^1 (δ 156.35) atoms of the triazolone moiety [Figure 1(*b*)] are also characteristic.

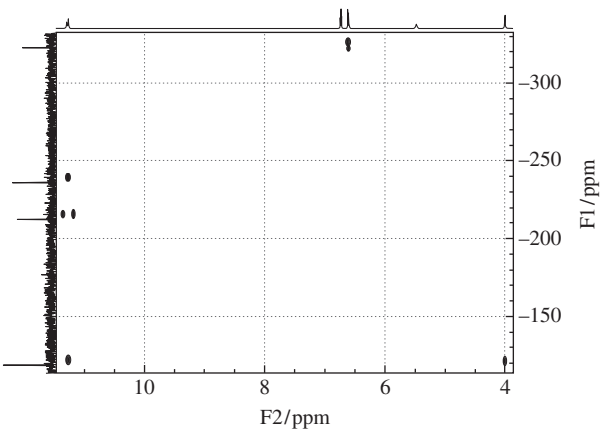


Figure 2 A fragment of the 2D ^{1}H-^{15}N HMBC spectrum (600 MHz, DMSO-d_6) of compound **8b**.

The ^{1}H-^{15}N HMBC spectrum contains cross-peaks between the doublet of protons at C^6 (δ 3.96, J 5 Hz) and the N^5 (δ –236.72), N^3 (–119.52) atoms. A correlation of the protons at $C^{2'}$, $C^{2''}$ of the aromatic moiety (δ 6.58, J 8 Hz) with the N^7 atom (δ –323.51) is also observed. Furthermore, interactions of the hydrogen atom at N^2 (δ 11.27) with the N^5 (δ –236.72), N^2 (–213.15), and N^3 (–119.52) atoms of the triazolone moiety are characteristic (Figure 2).

In conclusion, we have developed a new convenient approach to the synthesis of hitherto unknown substituted 5-arylaminomethyl-2,4-dihydro[1,2,4]triazol-3-ones **8a–f** based on the reaction of 4-imino-*N*-arylimidazolidinones **7a–f** with hydrazine. The products obtained can be of interest as antemetic agents[8] as well as in the prevention and treatment of amyotrophic lateral sclerosis.[9]

5-(4-Chlorophenylaminomethyl)-2,4-dihydro[1,2,4]triazol-3-one **8c**. Yield 73%, mp 222–225 °C. ^{1}H NMR (DMSO-d_6) δ: 4.01 (d, 2H, CH_2, J 6 Hz), 6.16 (t, 1H, NH, J 6 Hz), 6.63 (d, 2H, H_{Ar}, J 8 Hz), 7.11 (d, 2H, H_{Ar}, J 8 Hz), 11.26 (m, 2H, NH). ^{13}C NMR (DMSO-d_6) δ: 39.6, 113.9, 120.1, 128.6, 145.9, 147.1, 156.3. Found (%): C, 48.34; H, 4.14; N, 25.09. Calc. for $C_9H_9ClN_4O$ (%): C, 48.12; H, 4.04; N, 24.94.

5-(4-Fluorophenylaminomethyl)-2,4-dihydro[1,2,4]triazol-3-one **8d**. Yield 81%, mp 218–221 °C. ^{1}H NMR (DMSO-d_6) δ: 4.00 (d, 2H, CH_2, J 6 Hz), 5.89 (t, 1H, NH, J 6 Hz), 6.61 (m, 2H, H_{Ar}), 6.93 (m, 2H, H_{Ar}), 11.24 (s, 2H, NH). ^{13}C NMR (DMSO-d_6) δ: 40.1, 113.4, 115.3, 144.8, 146.1, 153.3, 156.3, 156.4. Found (%): C, 52.14; H, 4.25; N, 27.07. Calc. for $C_9H_9FN_4O$ (%): C, 51.92; H, 4.36; N, 26.91.

5-(3-Chlorophenylaminomethyl)-2,4-dihydro[1,2,4]triazol-3-one **8e**. Yield 75%, mp 231–233 °C. ^{1}H NMR (DMSO-d_6) δ: 4.04 (d, 2H, CH_2, J 5 Hz), 6.32 (t, 1H, NH, J 5 Hz), 6.61 (m, 3H, H_{Ar}), 7.09 (t, 1H, H_{Ar}, J 7 Hz), 11.29 (m, 2H, NH). ^{13}C NMR (DMSO-d_6) δ: 39.3, 111.2, 111.7, 116.0, 130.3, 133.6, 145.7, 149.6, 156.2. Found (%): C, 47.91; H, 3.91; N, 24.76. Calc. for $C_9H_9ClN_4O$ (%): C, 48.12; H, 4.04; N, 24.94.

5-(3-Methoxyphenylaminomethyl)-2,4-dihydro[1,2,4]triazol-3-one **8f**. Yield 67%, mp 204–205 °C. ^{1}H NMR (DMSO-d_6) δ: 3.66 (s, 3H, OMe), 4.00 (d, 2H, CH_2, J 6 Hz), 5.94 (t, 1H, NH, J 6 Hz), 6.20 (m, 3H, H_{Ar}), 6.98 (t, 1H, H_{Ar}, J 7 Hz), 11.26 (m, 2H, NH). ^{13}C NMR (DMSO-d_6) δ: 39.7, 54.7, 98.5, 102.1, 105.7, 129.6, 146.2, 149.5, 156.3, 160.3. Found (%): C, 54.32; H, 5.60; N, 25.61. Calc. for $C_{10}H_{12}N_4O_2$ (%): C, 54.54; H, 5.49; N, 25.44.

References

1 O. P. Shvaika, V. N. Artemov and S. N. Baranov, *Chem. Heterocycl. Compd*., 1970, **6**, 922 (*Khim. Geterotsikl. Soedin*., 1970, 991).
2 H. Varbanov, R. Buyukliev, A. Bakalova and A. Roller, *Acta Crystallogr*., 2009, **E65**, o953.
3 T. R. Rodgers, M. P. LaMontagne, A. Markovac and A. B. Ash, *J. Med. Chem.*, 1977, **20**, 591.
4 M. L. Brown, G. B. Brown and W. J. Brouillette, *J. Med. Chem*., 1997, **40**, 602.
5 M. Sanudo, M. Garcia-Valverde, S. Marcaccini and T. Torroba, *Tetrahedron*, 2012, **68**, 2621.
6 J. Sharma, S. Ahmad and M. S. Alam, *J. Chem. Pharm. Res.*, 2012, **4**, 5157.
7 M. T. Bilodeau, C. Chen, N. D. P. Cosford, B. W. Eastman, J. C. Hartnett, E. H. Hu, P. J. Manley, L. A. Neilson, L. R. Tehrani and Z. Wu, *US Patent WO 2005/100356*, 2005.
8 J. J. Hale, S. G. Mills, M. MacCoss, S. K. Shah, H. Qi, D. J. Mathre, M. A. Cascieri, S. Sadowski, C. D. Strader, D. E. MacIntyre and J. M. Metzger, *J. Med. Chem*., 1996, **39**, 1760.
9 Y. Zhang, R. Benmohamed, H. Huang, T. Chen, C. Voisine, R. I. Morimoto, D. R. Kirsch and R. B. Silverman, *J. Med. Chem*., 2013, **56**, 2665.
10 J. W. Hanifin, R. Z. Gussin, E. Cohen and P. River, *US Patent 1977/4,044,021*, 1977.

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