Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 2571–2573
Tetrahedron Letters

Microwave-assisted synthesis of sterically hindered 3-(5-tetrazolyl)pyridines

Igor V. Bliznets,[a] Andrei A. Vasil'ev,[b] Sergey V. Shorshnev,[c] Aleksandr E. Stepanov[a] and Sergey M. Lukyanov[c,*]

[a]*M. V. Lomonosov Moscow State Academy of Fine Chemical Technology, Malaya Pirogovskaya 1, 119435 Moscow, Russian Federation*
[b]*N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Leninsky pr. 47, 119991 Moscow, Russian Federation*
[c]*ChemBridge Corporation, Malaya Pirogovskaya 1, 119435 Moscow, Russian Federation*

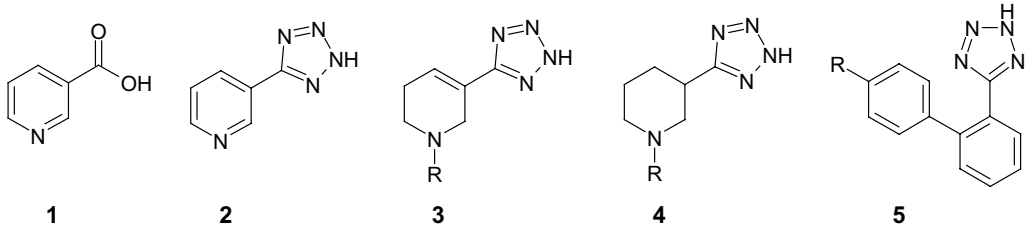
Received 9 December 2003; revised 21 January 2004; accepted 30 January 2004

Abstract—Sterically hindered 2,4-disubstituted 3-(5-tetrazolyl)pyridines were efficiently prepared from the corresponding nicotinonitriles using microwave technology.

It is known that the tetrazole ring can serve as an isosteric substitute for the carboxylic group in biologically active molecules, since they both possess comparable acidity and size.[1] The tetrazole unit, however, has proved to be superior in resisting metabolic degradation.[2] For example, such replacement in nicotinic acid **1** results in 3-(5-tetrazolyl)pyridine **2**, whose derivatives have been of particular interest to chemists[3–6] (Scheme 1). 3-(5-Tetrazolyl)pyridines, appropriately substituted in the pyridine moiety, are known as potential lipolysis inhibitors,[4] while partially or fully hydrogenated analogues **3**, **4** proved to be muscarinic agonists.[7] A related series of novel angiotensin II receptor antagonists discovered recently features a biphenyl subunit **5** with a sterically hindered *ortho*-tetrazole group[8–10] (Scheme 1).

In this context, we were interested in the preparation of some 3-(5-tetrazolyl)pyridines **6a–d** with substituents at both positions adjacent to the tetrazole unit (Scheme 2). The corresponding nitriles **7a–d** were used as starting materials for syntheses using three different reaction conditions (Scheme 3). However, only compound **6a** was obtained in moderate yield using trimethylsilyl azide and dibutyltin oxide (conditions *c*, 105 °C, 72 h). All attempts to obtain the other analogues **6b–d** under any listed conditions were not effective.

We found that the target sterically hindered 3-(5-tetrazolyl)pyridines **6** can be successfully prepared using microwave irradiation as an energy source. The application of microwave irradiation for the conversion of

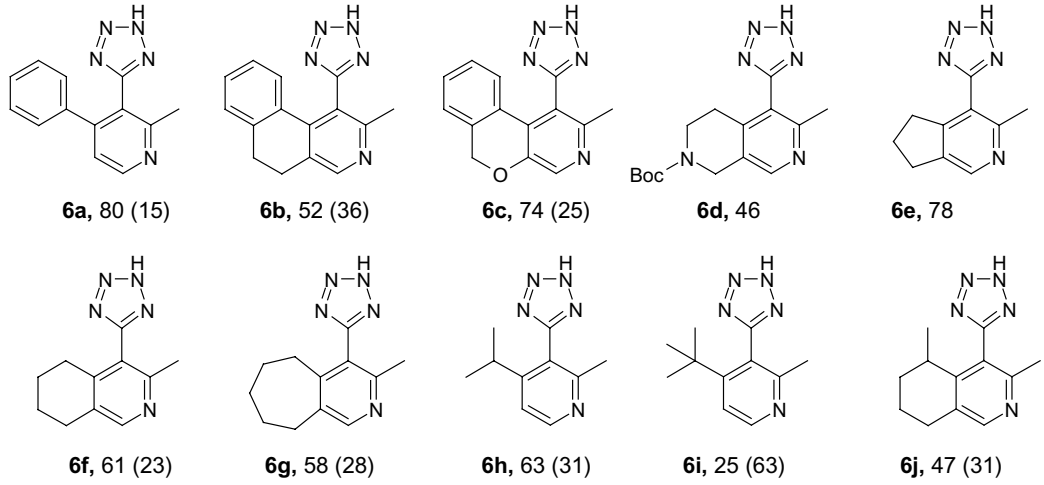


1 **2** **3** **4** **5**

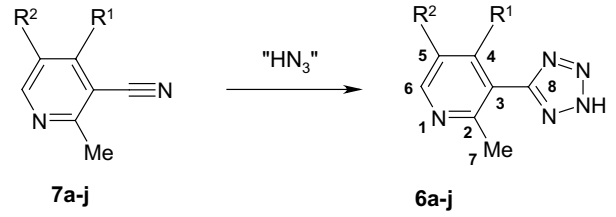
Scheme 1. Nicotinic acid **1** and its tetrazolyl derivatives **2–4** as biologically active compounds.

Keywords: Nicotinic acid; Tetrazoles; Nicotinonitriles; Microwave irradiation.
* Corresponding author. Fax: +7-095-956-49-48; e-mail: semiluk@chembridge.ru

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.01.153



Scheme 2. 3-(5-Tetrazolyl)pyridines **6a**–**j**, yields (%) and recovered starting nitriles (%, in brackets).



Scheme 3. Synthesis of 3-(5-tetrazolyl)pyridines **6a**–**j** from nicotinonitriles **7a**–**j**. 'HN_3' = (a) NaN_3, AcOH, *n*-BuOH; (b) NaN_3, $ZnBr_2$, H_2O; (c) Me_3SiN_3, Bu_2SnO, dioxane (also microwave assisted).

some model nitriles into tetrazoles was reported recently.[11] We employed the nicotinonitriles **7a**–**j** (Scheme 2) that have been described in the literature[12] with the exception of compound **7d**. All the reactions were carried out with reactor PRO-24 (Milestone Ethos SYNTH Microwave Labstation, producing continuous irradiation at 2450 MHz) under continuous internal temperature control.

To compare the behavior of nicotinonitriles **7a**–**j** having variable steric hindrance under microwave irradiation, standardized conditions had to be developed. Preliminary investigations showed that the reagent system Me_3SiN_3/Bu_2SnO was the best with respect to the reproducibility. We found that the yields of products **6a**–**j** depended considerably on the ratio of reactants, and the optimal molar ratio being 'nitrile/Bu_2SnO/Me_3SiN_3 = 1:0.3:4'. All the experiments were carried out at 140 °C for 8 h (but only 4 h for product **6d** because of partial thermal deprotection).[13] The yields of products **6a**–**j** relative to starting nitriles **7a**–**j** are presented in Scheme 2 (percentage of recovered nitriles **7** are in brackets).

The structures of the prepared compounds **6a**–**j** were confirmed by ^1H NMR, ^{13}C NMR and mass spectrometry. The mass spectra of all the 3-(5-tetrazolyl)pyridines **6a**–**j** were characterized by the fragmentation of the molecular ions to a nitrile species that is typical for 5-substituted tetrazoles,[14] that is, $[M-HN_3]^+$ and $[M-HN_2]^+$.

In conclusion, we have demonstrated that microwave irradiation may successfully assist conversion of sterically hindered nitriles into tetrazoles that would probably be difficult to achieve by other means. The role of the microwave irradiation, whether it is to provide efficient uniform heating or to provide a specific impact on some components in the activated complex, is still under discussion.

References and notes

1. Butler, R. N. *Adv. Heterocycl. Chem.* **1977**, *21*, 323–425.
2. Wittenberger, S. J. *Org. Prep. Proced. Int.* **1994**, *26*, 499–531.
3. McManus, J. M.; Herbst, R. M. *J. Org. Chem.* **1959**, *24*, 1462–1464.
4. Holland, G. F.; Pereira, J. N. *J. Med. Chem.* **1967**, *10*, 149–154.
5. Butler, R. N.; Garvin, V. C. *J. Chem. Res. (S)* **1982**, 122–123.
6. Demko, Z. P.; Sharpless, K. B. *J. Org. Chem.* **2001**, *66*, 7945–7950.
7. Moltzen, E. K.; Pedersen, H.; Bøgesø, K. P.; Meier, E.; Frederiksen, K.; Sánchez, C.; Lembøl, H. L. *J. Med. Chem.* **1994**, *37*, 4085–4099.
8. Duncia, J. V.; Pierce, M. E.; Santella, J. B., III. *J. Org. Chem.* **1991**, *56*, 2395–2400.
9. Wittenberger, S. J.; Donner, B. G. *J. Org. Chem.* **1993**, *58*, 4139–4141.
10. Russell, R. K.; Murray, W. V. *J. Org. Chem.* **1993**, *58*, 5023–5024.
11. Alterman, M.; Hallberg, A. *J. Org. Chem.* **2000**, *65*, 7984–7989.
12. Katritzky, A. R.; Denisenko, A.; Arend, M. *J. Org. Chem.* **1999**, *64*, 6076–6079.
13. *Typical procedure for* **6c**: Trimethylsilyl azide (4.61 g, 5.31 mL, 40 mmol) was added to the mixture of 2-methyl-6*H*-isochromeno[3,4-*c*]pyridine-3-carbonitrile **7c** (2.22 g, 10 mmol) and dibutyltin oxide (0.75 g, 3 mmol) in anhydrous 1,4-dioxane (10 mL). The reaction mixture was subjected to microwave irradiation in a tightly sealed

Teflon vessel (70 mL) for 8 h at 140 °C with stirring, then cooled to room temperature. The solvent was removed under reduced pressure (60 °C/15 Torr). The residue was dissolved in methanol (20 mL). Silica gel (5 g) was added to the solution, which was then evaporated to dryness. The solid residue was chromatographed using silica gel and chloroform as initial eluent then a gradient system with methanol (0–30% v/v). The fractions obtained were concentrated under reduced pressure to give the target product **6c** (1.97 g, 74%) as well as recovered nitrile **7c** (0.55 g, 25%). **6c**: mp 245–247 °C (dec). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.22 (s, 3H, Me), 5.16 (s, 2H, CH_2–O), 6.08 (d, $J = 7.8$ Hz, 1H, Ph), 6.78 (dd, $J = 7.6$ Hz, $J = 7.8$ Hz, 1H, Ph), 7.10 (d, $J = 7.6$ Hz, 1H, Ph), 7.32 (dd, $J = 7.6$ Hz, $J = 7.8$ Hz, 1H, Ph), 8.65 (s, 1H, 6-CH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 22.8 (C-7), 85.6, 114.9 (C-3), 118.2, 119.9, 122.3, 125.8, 126.1, 132.1, 137.1 (C-4), 147.3 (C-6), 153.2 (C-8), 157.0 (C-5), 158.1 (atom numbering see Scheme 3). IR (film, ν/cm^{-1}): 2990, 2460, 1990, 1630, 1595, 1440, 1390, 1310, 1250, 1160, 1100, 1020, 925, 770. MS m/z (%): 265 (5) $[M]^+$, 236 (12) $[M-HN_2]^+$, 222 (52) $[M-HN_3]^+$, 221 (100) $[M-HN_3-H]^+$, 194 (9), 181 (11), 152 (10), 139 (12), 91 (20), 77 (16), 59 (22). Anal. Calcd for $C_{14}H_{11}N_5O$ (265.28) (%): C, 63.39; H, 4.18; N, 26.40. Found (%): C, 63.25; H, 4.20; N, 26.31.

14. Butler, R. N. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 4, pp 621–678.