Tetrahedron Letters 54 (2013) 21–22

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Heterocyclization of arylmethylidene derivatives of malononitrile dimer: synthesis of 4-amino-6-aryl-2-halopyridine-3,5-dicarbonitriles

Ivan N. Bardasov *, Denis L. Mihailov, Anastasiya U. Alekseeva, Oleg V. Ershov, Oleg E. Nasakin

Ulyanov Chuvash State University, Cheboksary, Moskovsky pr. 15, Russia

ARTICLE INFO

Article history:
Received 28 July 2012
Revised 22 September 2012
Accepted 4 October 2012
Available online 26 October 2012

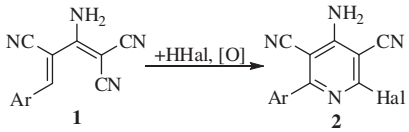
Keywords:
Heterocyclic compounds
Cyano compounds
Oxiranes
Pyridines
One-pot synthesis

ABSTRACT

The synthesis of 4-amino-6-aryl-2-halopyridine-3,5-dicarbonitriles from the reaction of arylmethylidene derivatives of malononitrile dimer with hydrohalic acid in the presence of an oxidizing agent is described.

Approaches to the synthesis of cyano-containing 4-amino-2-halopyridines can be divided into two types. The first is a multistage process that involves a phased introduction of functional substituents to the pyridine ring.[1] In these reactions there is usually a greater consumption of reagents, solvents, but only low total yields of final products. The second variant of the synthesis of cyano-containing 4-amino-2-halopyridines is the use of cascade reactions of poly- and heterofunctional compounds. The non-cyclic cyano group of the substrate, in most cases, is involved in the construction of the pyridine ring.[2] This is due to its ability to form an iminium anion during the attack of nucleophilic reagents, and the imine anion then reacts with a spatially contiguous electrophilic center of the molecule, forming an azaheterocycle. This strategy follows the principles of 'green chemistry' in organic synthesis since it allows the incorporation of most of the starting reagents into the final product and reduces the number of steps, as well as the reagents, thereby reducing the energy consumption and toxicity of the process. We have previously described convenient one-step processes for the preparation of heterocyclic compounds from non-cyclic cyano-containing precursors.[3] In this paper, we describe a new approach to 4-amino-2-halopyridines using arylmethylidene derivatives **1a–e** of malononitrile dimer as starting materials.[4] It was found that the reactions with hydrohalic acids in the presence of an oxidant formed 4-amino-6-aryl-2-chloropyridine-3,5-dicarbonitriles **2a–e**[5] in 76–89% yields and 4-amino-6-aryl-2-bromopyridine-3,5-dicarbonitriles **2f–j**[6] in 78–89% yields (Scheme 1 and Table 1).

The structures of compounds **2a–j** were confirmed by IR, ^{1}H, and ^{13}C NMR spectroscopy and by mass spectrometry. The infrared spectra contained absorption bands due to the conjugated cyano groups at 2222–2237 cm^{-1} and the amino group at 3216–



1 2

Scheme 1. Synthesis of pyridines **2a–j**.

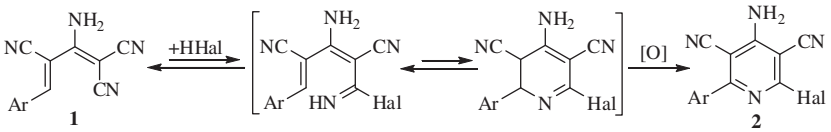
Table 1
Synthesis of 6-aryl-4-amino-2-halopyridine-3,5-dicarbonitriles **2a–j**

Substrate	Ar	Hal	Product	Yield[a] (%)				
				SeO_2	Br_2	$KMnO_4$	O_2	TCE[b]
1a	C_6H_5	Cl	**2a**	82	–	12	18	65
1b	3-ClC_6H_4	Cl	**2b**	86	–	–	–	71
1c	4-$H_3CC_6H_4$	Cl	**2c**	83	–	–	–	–
1d	4-FC_6H_4	Cl	**2d**	76	–	–	–	–
1e	2-ClC_6H_4	Cl	**2e**	89	–	–	–	–
1a	C_6H_5	Br	**2f**	83	82	–	–	–
1b	3-ClC_6H_4	Br	**2g**	–	86	–	–	–
1c	4-$H_3CC_6H_4$	Br	**2h**	–	83	–	–	–
1d	4-FC_6H_4	Br	**2i**	–	78	–	–	–
1e	2-ClC_6H_4	Br	**2j**	–	89	–	–	–

[a] Yield of the isolated product.
[b] TCE = tetracyanoethylene.

* Corresponding author. Tel.: +7 9083030163; fax: +7 8352770979.
E-mail address: bardasov.chem@mail.ru (I.N. Bardasov).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.10.015



Scheme 2. Proposed mechanism for the synthesis of pyridines **2a–j**.

3388 cm^{-1}. The ^1H NMR spectra of products **2a–j** exhibited singlets at 8.10–8.37 ppm for the amino group and resonances expected for the aryl group and other substituents. The ^{13}C NMR spectra of **2b** and **2f** exhibited signals due to the carbon atoms of the benzene ring, and the cyano groups at 113.19–114.89 ppm, and signals for the pyridine ring at 91.74–92.02 ppm (C-3, C-5) and 147.65–163.69 ppm (C-2, C-4 and C-6). The mass spectra of compounds **2a–j** displayed molecular ion peaks and other fragmentations, including peaks due to $[M-Hal]^+$ fragments.

The reaction apparently involves nucleophilic addition of the halide to the electrophilic carbon atom of the cyano group in the first stage Scheme 2. Subsequent cyclization of the imine on to the spatially contiguous electrophilic carbon atom leads to formation of the dihydropyridine ring. Aromatization under the action of an oxidizing agent completes the reaction.

In the absence of an oxidant, even after many days of heating at reflux, only the parent compounds **1a–j** remained in the reaction mixture. This can be explained by the fact that the halide anion addition and the formation of the dihydropyridine are likely to be reversible, and their direction is strongly shifted toward the formation of the parent compounds. The introduction of the oxidant leads to irreversible aromatization and releases the final pyridines **2a–j**. As oxidants we used tetracyanoethylene, potassium permanganate, aerial oxygen, bromine, and selenium dioxide. The best results were obtained with selenium dioxide for compounds **2a–j** and bromine for compounds **2a–j**.

In conclusion, functionally substituted 4-amino-2-halopyridines are known to be precursors of pharmacologically active compounds,[7] and therefore our goal is further modification of the substituents on the pyridine ring and the study of the biological activity of these products.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.10.015. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

1. (a) Palmer, A. M.; Münch, G.; Brehm, C.; Zimmermann, P. J.; Buhr, W.; Feth, M. P.; Simon, W. A. *Bioorg. Med. Chem.* **2008**, *16*, 1511–1530; (b) Searls, T.; McLaughlin, L. W. *Tetrahedron* **1999**, *55*, 11985–11996; (c) Wozniak, M.; Baranski, A.; Szpakiewicz, B. *Liebigs Ann. Chem.* **1991**, 875–878.
2. (a) Mittelbach, M.; Junek, H. *Liebigs Ann. Chem.* **1986**, 533–544; (b) Little, E. L., Jr.; Middleton, W. J.; Coffman, D. D.; Engelhardt, V. A.; Sausen, G. N. *J. Am. Chem. Soc.* **1958**, *80*, 2832–2838; (c) Mascal, M.; Hext, N. M.; Warmuth, R.; Arnall-Culliford, J. R.; Moore, M. H.; Turkenburg, J. P. *J. Org. Chem.* **1999**, *64*, 8479–8484; (d) Mittelbach, M. *Monatsh. Chem.* **1987**, *118*, 617–626; (e) Carboni, R. A.; Coffman, D. D.; Howard, E. G. *J. Am. Chem. Soc.* **1958**, *80*, 2838–2840.
3. (a) Bardasov, I. N.; Golubev, R. V.; Ershov, O. V.; Kayukov, Ya. S.; Nasakin, O. E. *Tetrahedron Lett.* **2011**, *52*, 4724–4725; (b) Belikov, M. Yu.; Ershov, O. V.; Eremkin, A. V.; Nasakin, O. E.; Tafeenko, V. A.; Nurieva, E. V. *Tetrahedron Lett.* **2011**, *52*, 6407–6410; (c) Eremkin, A. V.; Molkov, S. N.; Ershov, O. V.; Kayukov, Ya. S.; Nasakin, O. E.; Tafeenko, V. A.; Nurieva, E. V. *Mendeleev Commun.* **2006**, *16*, 115–116; (d) Eremkin, A. V.; Ershov, O. V.; Kayukov, Ya. S.; Sheverdov, V. P.; Nasakin, O. E.; Tafeenko, V. A.; Nurieva, E. V. *Tetrahedron Lett.* **2006**, *47*, 1445–1447.
4. (a) Gazit, A.; Yaish, P.; Gilon, C.; Levitzki, A. *J. Med. Chem.* **1989**, *32*, 2344–2352; (b) Boila-Goeckel, A.; Junek, H. *J. Prakt. Chem.* **1999**, *341*, 20–28; (c) Fahmy, S. M.; Abd Allah, S. O.; Mohareb, R. M. *Synthesis* **1984**, 976–978; (d) Junek, H.; Thierrichter, B.; Wibmer, P. *Monatsh. Chem.* **1979**, *110*, 483–492; (e) Junek, H.; Wolny, B. *Monatsh. Chem.* **1976**, *107*, 999–1006.
5. *Typical procedure for the preparation of 4-amino-6-aryl-2-chloropyridine-3,5-dicarbonitriles* ***2a–e***: A solution of 2-amino-4-arylbuta-1,3-diene-1,1,3-tricarbonitrile (**1**) (2.20 g, 10 mmol), SeO_2 (1.2 g, 11 mmol) and concentrated HCl (2 mL) in 1,4-dioxane (70 mL) was stirred at 70 °C for 6–8 h (TLC). After neutralization with sat $NaHCO_3$ solution, the resulting precipitate was filtered and washed with 1,4-dioxane and H_2O (40 mL) and, then recrystallized from 1,4-dioxane. Compound **2a**: mp 247–249 °C; ^1H NMR (500.13 MHz, DMSO-d_6): δ 7.54–7.61 (3H, m, C_6H_5), 7.79 (2H, d, J = 7.4 Hz, C_6H_5), 8.20 (2H, s, NH_2). IR 3373, 3360, 3242 (NH_2), 2234 (C≡N). MS (EI, 70 eV): m/z (%) 256 [M^+ (^{37}Cl), 16], 254 [M^+ (^{35}Cl), 100), 219 ($[C_{13}H_7N_4]^+$, 38). Anal. Calcd for $C_{13}H_7ClN_4$: C, 61.31; H, 2.77; N, 22.00. Found C, 61.42; H, 2.72; N, 21.94. Compound **2b:** mp 237–239 °C; ^1H NMR (500.13 MHz, DMSO-d_6): δ 7.59 (1H, t, J = 7.9 Hz, C_6H_4), 7.67 (1H, ddd, ^3J = 8.0 Hz, ^4J = 2.1 Hz, ^4J = 1.0 Hz, C_6H_4), 7.76 (1H, dt, ^3J = 7.8 Hz, ^4J = 1.3 Hz, C_6H_4), 7.81 (1H, t, J = 1.9 Hz, C_6H_4), 8.28 (2H, s, NH_2). ^{13}C NMR (125.76 MHz, DMSO-d_6): δ 91.87, 92.02 (C-3, C-5), 113.19, 114.52 (CN), 127.61, 128.57, 130.53, 130.88, 133.21, 137.90 (C_6H_4), 155.35, 158.72, 162.22 (C-2, C-4, C-6). IR 3368, 3346, 3244 (NH_2), 2233 (C≡N). MS (EI, 70 eV): m/z (%) 290 [M^+ (^{37}Cl), 70], 288 [M^+ (^{35}Cl), 100]. Anal. Calcd for $C_{13}H_6Cl_2N_4$: C, 54.01; H, 2.09; N, 19.38. Found C, 54.07; H, 2.02; N, 19.39. Compound **2c**: mp 264–266 °C; ^1H NMR (500.13 MHz, DMSO-d_6): δ 2.40 (3H, s, CH_3), 7.36 (2H, d, J = 8.1 Hz, C_6H_4), 7.71 (2H, d, J = 8.2 Hz, C_6H_4), 8.16 (2H, s, NH_2). IR 3387, 3338, 3237 (NH_2), 2227 (C≡N). MS (EI, 70 eV): m/z (%) 270 [M^+ (^{37}Cl), 34], 268 [M^+ (^{35}Cl), 100]. Anal. Calcd for $C_{14}H_9ClN_4$: C, 62.58; H, 3.38; N, 20.85. Found C, 62.68; H, 3.36; N, 20.89. Compound **2d**: mp 285–287 °C; ^1H NMR (500.13 MHz, DMSO-d_6): δ 7.38–7.42 (2H, m, C_6H_4), 7.85–7.90 (2H, m, C_6H_4), 8.23 (2H, s, NH_2). IR 3375, 3244 (NH_2), 2232 (C≡N). MS (EI, 70 eV): m/z (%) 274 [M^+ (^{37}Cl), 31], 272 [M^+ (^{35}Cl), 100], 237 ($[C_{13}H_6FN_4]^+$, 29). Anal. Calcd for $C_{13}H_6ClFN_4$: C, 57.26; H, 2.22; N, 20.55. Found 57.36; H, 2.23; N, 20.44. Compound **2e**: mp 206–208 °C; ^1H NMR (500.13 MHz, DMSO-d_6): δ 7.50–7.59 (3H, m, C_6H_4), 7.64 (1H, dd, ^3J = 8.0 Hz, ^4J = 0.9 Hz, C_6H_4), 8.37 (2H, s, NH_2). IR 3369, 3233 (NH_2), 2225 (C≡N). MS (EI, 70 eV): m/z (%) 290 [M^+ (^{37}Cl), 66], 288 [M^+ (^{35}Cl), 100], 253 ($[C_{13}H_6ClN_4]^+$, 87). Anal. Calcd for $C_{13}H_6Cl_2N_4$: C, 54.01; H, 2.09; N, 19.38. Found C, 54.13; H, 2.07; N, 19.28.
6. *Typical procedure for the preparation of 4-amino-6-aryl-2-bromopyridine-3,5-dicarbonitriles* ***2f–j***: A solution of 2-amino-4-arylbuta-1,3-diene-1,1,3-tricarbonitrile (**1**) (2.20 g, 10 mmol), Br_2 (0.88 g, 11 mmol) and concentrated HBr (2 mL) in 1,4-dioxane (70 mL) was stirred at 70 °C for 6–8 h (TLC). After neutralization with sat $NaHCO_3$ solution, the resulting precipitate was filtered and washed with 1,4-dioxane and H_2O (40 mL) and, then recrystallized from 1,4-dioxane. Compound **2f**: mp 285–286 °C; ^1H NMR (500.13 MHz, DMSO-d_6): δ 7.54–7.61 (3H, m, C_6H_5), 7.79 (2H, d, J = 7.0 Hz, C_6H_5), 8.14 (2H, s, NH_2). ^{13}C NMR (125.76 MHz, DMSO-d_6): δ 91.74, 94.72 (C-3, C-5), 114.57, 114.89 (CN), 128.54, 128.92, 131.12, 135.92 (C_6H_4), 147.65, 158.40, 163.69 (C-2, C-4, C-6). IR 3375, 3344, 3245 (NH_2), 2230 (C≡N). MS (EI, 70 eV): m/z (%) 300 [M^+ (^{81}Br), 12], 298 [M^+ (^{79}Br), 11], 219 ($[C_{13}H_7N_4]^+$, 100). Anal. Calcd for $C_{13}H_7BrN_4$: C, 52.20; H, 2.36; N, 18.73. Found C, 52.30; H, 2.23; N, 18.76. Compound **2g**: mp 252–253 °C; ^1H NMR (500.13 MHz, DMSO-d_6): δ 7.59 (1H, t, J = 7.9 Hz, C_6H_4,), 7.67 (1H, ddd, C_6H_4, ^3J = 8.1 Hz, ^4J = 2.1 Hz, ^4J = 1.0 Hz), 7.75 (1H, dt, ^3J = 7.7 Hz, ^4J = 1.4 Hz, C_6H_4), 7.80 (1H, t, J = 1.9 Hz, C_6H_4), 8.22 (2H, s, NH_2). IR 3367, 3319, 3231 (NH_2), 2215, 2237 (C≡N). MS (EI, 70 eV): m/z (%) 334 [M^+ (^{81}Br), 2], 332 [M^+ (^{79}Br), 6], 253 ($[C_{13}H_6ClN_4]^+$, 56). Anal. Calcd for $C_{13}H_6BrClN_4$: C, 46.81; H, 1.81; N, 16.80. Found C, 46.71; H, 1.90; N, 16.81. Compound **2h**: mp 289–291 °C; ^1H NMR (500.13 MHz, DMSO-d_6): δ 2.40 (3H, s, CH_3), 7.36 (2H, d, J = 8.1 Hz, C_6H_4), 7.70 (2H, d, J = 8.1 Hz, C_6H_4), 8.10 (2H, s, NH_2). IR 3388, 3341, 3238 (NH_2), 2228 (C≡N). MS (EI, 70 eV): m/z (%) 314 [M^+ (^{81}Br), 13], 312 [M^+ (^{79}Br), 19], 233 ($[C_{14}H_9N_4]^+$, 100). Anal. Calcd for $C_{14}H_9BrN_4$: C, 53.70; H, 2.90; N, 17.89. Found C, 53.63; H, 2.90; N, 17.93. Compound **2i**: mp 281–281 °C; ^1H NMR (500.13 MHz, DMSO-d_6): δ 7.38–7.42 (2H, m, C_6H_4), 7.86–7.89 (2H, m, C_6H_4), 8.18 (2H, s, NH_2). IR 3371, 3349, 3240 (NH_2), 2230 (C≡N). MS (EI, 70 eV): m/z (%) 318 [M^+ (^{81}Br), 95], 316 [M^+ (^{79}Br), 100], 237 ($[C_{13}H_6FN_4]^+$, 95). Anal. Calcd for $C_{13}H_6BrFN_4$: C, 49.24; H, 1.91; N, 17.67. Found C, 49.34; H, 1.92; N, 17.56. Compound **2j**: mp 208–210 °C; ^1H NMR (500.13 MHz, DMSO-d_6): δ 7.49–7.59 (2H, m, C_6H_4), 7.64 (2H, dd, ^3J = 8.0,^4J = 0.8, C_6H_4), 8.31 (2H, s, NH_2). IR 3378, 3216 (NH_2), 2222 (C≡N). MS (EI, 70 eV): m/z (%) 334 [M^+ (^{81}Br), 6), 332 [M^+ (^{79}Br), 1), 253 ($[C_{13}H_6ClN_4]^+$, 24). Anal. Calcd for $C_{13}H_6BrClN_4$: C, 46.81; H, 1.8; N, 16.80. Found: C, 46.71; H, 1.92; N, 16.78.
7. (a) Zhao, H.; Serby, M. D.; Xin, Z.; Szczepankiewicz, B. G.; Liu, M.; Kosogof, Ch.; Liu, B.; Nelson, L. T. J.; Johnson, E. F.; Wang, S.; Pederson, T.; Gum, R. J.; Clampit, J. E.; Haasch, D. L.; Abad-Zapatero, C.; Fry, E. H.; Rondinone, C.; Trevillyan, J. M.; Sham, H. L.; Liu, G. *J. Med. Chem.* **2006**, *49*, 4455–4458; (b) Liu, G.; Zhao, H.; Liu, B.; Xin, Zh.; Liu, M.; Kosogof, Ch.; Szczepankiewicz, B. G.; Wang, S.; Clampit, J. E.; Gum, R. J.; Haasch, D. L.; Trevillyan, J. M.; Sham, H. L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5723–5730.