ChemPubSoc Europe

DOI: 10.1002/ejoc.201600377

EurJOC European Journal of Organic Chemistry

Communication

Heterocycles

Synthesis of 6-Arylpyridin-3-ols by Oxidative Rearrangement of (5-Arylfurfuryl)amines

Michael C. D. Fürst,[a] Caroline S. Sauer,[a] Takaaki Moriyama,[a,b] Akio Kamimura,[b] and Markus R. Heinrich*[a]

Abstract: The synthesis of 6-arylpyridin-3-ols and their 2,4-dibrominated analogues has been achieved by the oxidative rearrangement of (5-arylfurfuryl)amines. The desired arylpyridols were obtained in good to high yields, and the reactions were shown to be suitable for preparation on a gram scale.

Introduction

Arylpyridines are a common structural motif in medicinal chemistry research.[1] A particularly interesting subgroup of such compounds are 6-arylpyridin-3-ol derivatives (Figure 1). Phenylpyridyl ether **1** has recently been found to be an Hsp90 C-terminal inhibitor. The inhibition of Hsp90 represents a promising strategy for the treatment of breast cancer and neurodegenerative diseases.[2] Pyridol **2** has been described as a niacin receptor agonist for the treatment of lipometabolic disorders.[3] Furthermore, 6-arylpyridin-3-ol derivatives have been discovered as remedies for diseases attributable to abnormal plasma uric acid levels,[4] and, as exemplified by the comparably simple heterobiaryl **3**, also as antiinflammatory agents.[5] Arylpyridyl ether **4** shows antiinfective properties and was investigated as an antitubercolosis agent.[6]

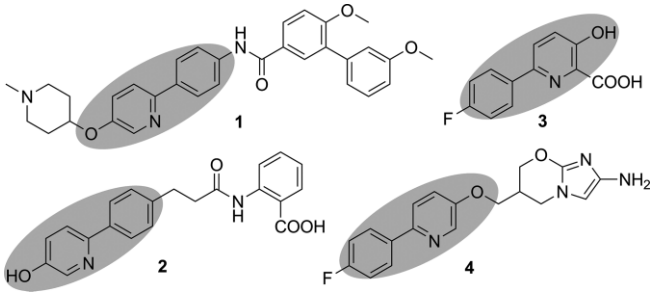


Figure 1. 6-Arylpyridin-3-ol derivatives as anticancer, antineurodegenerative, lipometabolic, antiinflammatory and antituberculosis agents.

[a] *Department of Chemistry and Pharmacy, Pharmaceutical Chemistry, Friedrich-Alexander-Universität Erlangen-Nürnberg Schuhstraße 19, 91052 Erlangen, Germany E-mail: markus.heinrich@fau.de http://www.medchem.uni-erlangen.de/heinrichlab/*

[b] *Department of Applied Molecular Bioscience, Graduate School of Medicine, Yamaguchi University Ube 755-8611, Japan*

Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under http://dx.doi.org/10.1002/ejoc.201600377.

As for a wide range of other biaryls, the synthesis of phenylpyridol building blocks today mainly relies on Suzuki aryl–aryl coupling reactions, which, however, require comparably demanding starting materials as well as an expensive catalyst.[7,8] Regarding palladium-free routes to the target compounds, the preparation of phenylpyridol **3** from 4-fluorobenzaldehyde even required eight steps, of which the final one was a Kolbe–Schmitt reaction to introduce the carboxylic acid.[5] Against this background, it was a challenging question whether the preparation of 6-arylpyridin-3-ol derivatives could also be achieved by a short sequence involving a radical arylation step. Radical arylations for the synthesis of biaryls have recently gained much interest,[9] but reactions of substituted benzenes are often not easy to conduct due to low rate constants in the addition step[10] and insufficient regioselectivity.[11] Similarly difficult are direct arylations of pyridine, which commonly give moderate yields and insufficient regioselectivities in the case of the free base.[11a] Arylations of pyridinium salts usually require a blocking substituent in 4-position to selectively give 2-arylpyridines.[12] Comparably good results in terms of yield and selectivity can be obtained with anilines,[13] phenols,[14] and especially electron-rich heterocycles such as furans[14b,15] and pyrroles.[16] Starting from aryldiazonium salts,[12,13a,14,15] aryl halides[17] or aryl hydrazines[13b–13e,18] as aryl radical sources, typical reaction conditions include stoichiometric oxidants, reductants or bases, and alternatively photo- or base catalysis.

In the overall context it was interesting to notice that the oxidative rearrangement of furfurylamine to 3-pyridol is known,[19,20] with a number of applications in total synthesis,[21] medicinal chemistry[22] and food chemistry.[23] However, no examples have yet been reported for the oxidative ring-opening of 5-arylated furfurylamines to give 6-arylpyridin-3-ol derivatives after cyclization involving the originally exocyclic amino group. Such a reaction could – in combination with previous radical arylation of furfurylamine – allow an expedient access to the desired target molecules. Moreover, the advantageous tolerance of radical arylations towards halogens such as chlorine and bromine would provide substituted arylpyridols,

which are not easy to prepare by transition-metal-catalyzed reactions.

Results and Discussion

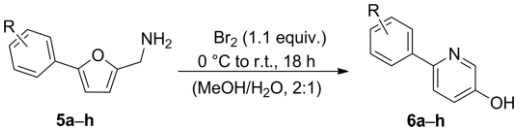
Radical arylation of furfurylamine occurs with high regioselectivity for the 5-position, and yields in the range of 70–80 % can be obtained with typical aryldiazonium salts by using titanium(III) chloride as a reductant.[14b] Based on this straightforward access to the required starting materials, a series of optimization experiments with [5-(4-chlorophenyl)furfuryl]amine (**5a**) was carried out (Table 1). A control reaction to probe the direct arylation of 3-hydroxypyridine with 4-chlorophenyldiazonium chloride and titanium(III) chloride had provided only trace amounts of arylpyridol **6a**.

An initial attempt with *N*-bromosuccinimide under typical Achmatowicz[24,25] conditions failed completely and did not even give traces of the desired product **6a** (Entry 1).[26] Based on a moderately successful experiment with bromine as an alternative oxidant (Entry 2),[20d] it was possible to improve the yield of **6a** to 69 % by variation of reaction time and solvent mixture (Entries 3 and 4). A further prolongation of the reaction time combined with a large excess of bromine led to a mixture of **6a** (21 %) and its mono- and dibrominated analogues **7a** and **8a**. With suitable conditions available, we turned to investigate the reaction scope with different substituents on the benzene core. The results of this study are summarized in Table 2.

All desired 6-arylpyridin-3-ols **6a**–**h** were obtained in good yields with a maximum yield of 86 % (Entry 3) for the 4-bromophenyl derivative **6c**; *ortho* substitution, which could complicate the rearrangement, did only have a marginal effect on the outcome (Entries 7 and 8). From a synthetic point of view, the brominated compounds **6c**,**f**,**h** are of particular value, since they cannot be easily prepared by Pd-catalyzed coupling reactions.[27]

The formation of the mono- and dibrominated pyridols **7a** and **8a** within the original optimization (Table 1, Entry 5) prompted us to investigate whether the oxidative rearrangement could be combined with selective bromination of the pyridol core. Polybrominated pyridines are versatile synthetic building blocks, since substitution of the bromine atoms can often be achieved with high regioselectivity.[28] Results from the related optimization experiments are summarized in Table 3.

Table 2. Variation of substituents of the benzene core.



5a–h **6a–h**

Entry	Furfurylamine **5**: R =	Pyridol **6**: [%][a]	Entry	Furfurylamine **5**: R =	Pyridol **6**: [%][a]
1	**5a**: 4-Cl	**6a**: 69	5	**5e**: 3-Cl	**6e**: 68
2	**5b**: 4-F	**6b**: 62	6	**5f**: 3-Br	**6f**: 66
3	**5c**: 4-Br	**6c**: 86	7	**5g**: 2-Cl	**6g**: 58
4	**5d**: 3-F	**6d**: 70	8	**5h**: 2-Br	**6h**: 60

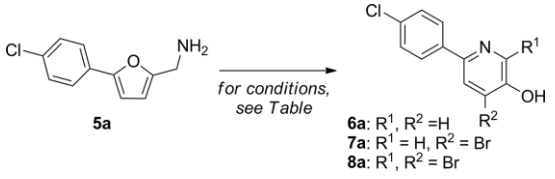
[a] For reaction conditions, see Exp. Sect. Yields determined after purification by column chromatography.

Analysis of the reaction time dependent product distribution revealed that the monobrominated arylpyridol **7a** cannot be obtained in a sufficiently high yield (Entries 1–6). The maximum yield of the dibrominated product **8a** of 48 % (Entry 5) could not be further increased by reaction under argon (Entry 7), but by the addition of hydrobromic acid (Entries 8 and 9). Hydrobromic acid thereby appears to slow down the third bromation step converting **8a** into **9a** (Entries 6, 8 and 9), which enables yields for **8a** of up to 60 %.

The results obtained with various (5-arylfurfuryl)amines under the optimized conditions (Table 3, Entry 8) are summarized in Table 4. In this study, all halogenated (5-arylfurfuryl)amines **5a**–**5i** (Entries 1–9) were tolerated with no remarkable negative effect of *ortho* substitution (Entries 7–9). Electon-withdrawing groups on the phenyl ring led to a slightly increased average yield among the products **8j**–**8m** (Entries 10–13), which can be explained by smaller amounts or the absence of the tribrominated analogues **9**. By conjugation, electron acceptors thereby appear to retard the third bromination step.

Finally, two representative reactions were carried out on a larger scale (Scheme 1) under conditions identical to those used for the syntheses summarized in Tables 2 and 4. The desired

Table 1. Optimization experiments: Oxidative rearrangement of (5-arylfurfuryl)amine **1a** to 6-arylpyridin-3-ol derivatives **6a**–**8a**.



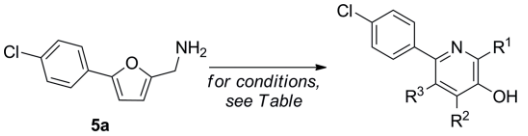
5a

6a: R^1, R^2 =H
7a: R^1 = H, R^2 = Br
8a: R^1, R^2 = Br

Entry	Reagent[a] (equiv.)	Solvent system (ratio, reaction time)	**6a**/**7a**/**8a**[b] [%/%/%]
1	NBS (1.1)	THF/H_2O (1:1, 24 h)	–/–/–
2	Br_2 (1.1)	MeOH (1.5 h), MeOH/H_2O (1:1, 1.5 h)	34/–/–
3	Br_2 (1.1)	MeOH (15 h), MeOH/H_2O (1:1, 2 h)	41/–/–
4	Br_2 (1.2)	MeOH/H_2O (2:1, 18 h)	69/–/–
5	Br_2 (4.0)	MeOH/H_2O (4:1, 24 h)	21/32/37

[a] Reagent added at 0 °C, mixture then left to warm to room temperature. Reactions conducted under air. NBS: *N*-bromosuccinimide. [b] Yields determined by ^{1}H NMR spectroscopy using dimethyl terephthalate as internal standard.

Table 3. Optimization experiments: Oxidative rearrangement of **5a** combined with bromination of the pyridol core.



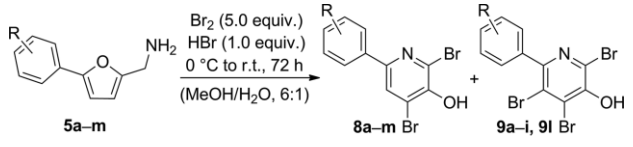
5a

6a: R^1, R^2, R^3 = H
7a: R^1, R^3 = H, R^2 = Br
8a: R^1, R^2 = Br, R^3 = H
9a: R^1, R^2, R^3 = Br

Entry	Conditions[a]	**6a**/**7a**/**8a**/**9a**[b] [%/%/%/%]
1	Br_2 (4.0 equiv.), MeOH/H_2O (4:1), 3 h	32/10/9/7
2	Br_2 (4.0 equiv.), MeOH/H_2O (4:1), 6 h	24/14/27/9
3	Br_2 (4.0 equiv.), MeOH/H_2O (4:1), 12 h	22/19/30/10
4	Br_2 (4.0 equiv.), MeOH/H_2O (4:1), 24 h	21/32/37/12
5	Br_2 (4.0 equiv.), MeOH/H_2O (4:1), 36 h	15/20/48/14
6	Br_2 (4.0 equiv.), MeOH/H_2O (4:1), 48 h	1/2/41/38
7	Br_2 (4.0 equiv.), MeOH/H_2O (4:1), argon, 48 h	–/–/35/30
8	Br_2 (5.0 equiv.), HBr (1 equiv.), MeOH/H_2O (6:1), 72 h	–/–/***60***/28
9	Br_2 (5.0 equiv.), HBr (2 equiv.), MeOH/H_2O (6:1), 72 h	–/–/59/32

[a] Reagent added at 0 °C, mixture then left to warm to room temperature. Reactions conducted under air except for Entry 7. [b] Yields determined by ^1H NMR spectroscopy using dimethyl terephthalate as internal standard.

Table 4. Oxidative rearrangement combined with bromination of the pyridol core: variation of substituents.

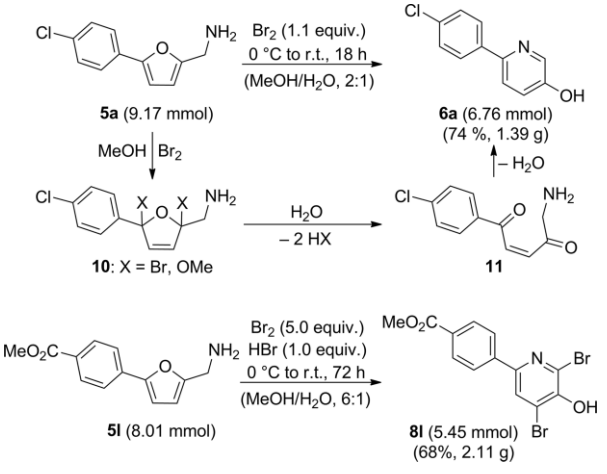


5a–m **8a–m** Br **9a–i, 9l** Br

Entry	Furfurylamine **5**: R =	Dibromopyridol **8**: [%][a]	Tribromopyridol **9**: [%][a]
1	**5a**: 4-Cl	**8a**: 60	**9a**: 28
2	**5b**: 4-F	**8b**: 50	**9b**: 23
3	**5c**: 4-Br	**8c**: 63	**9c**: 33
4	**5d**: 3-F	**8d**: 44	**9d**: 21
5	**5e**: 3-Cl	**8e**: 52	**9e**: 35
6	**5f**: 3-Br	**8f**: 55	**9f**: 31
7	**5g**: 2-F	**8g**: 54	**9g**: 33
8	**5h**: 2-Cl	**8h**: 56	**9h**: 35
9	**5i**: 2-Br	**8i**: 70	**9i**: 23
10	**5j**: 4-CN	**8j**: 54	**9j**: –
11	**5k**: 4-NO_2	**8k**: 67	**9k**: –
12	**5l**: 4-CO_2Me	**8l**: 68	**9l**: 18
13	**5m**: 3-CN	**8m**: 71	**9m**: –

[a] For reaction conditions, see Exp. Sect. Yields determined after purification by column chromatography.

pyridols **6a** and **8l** were obtained in yields of 74 % and 68 %, which demonstrates the synthetic applicability. Scheme 1 further shows plausible intermediates occurring in the reaction course to **6a**.[20d,25] Oxidation of (5-arylfurfuryl)amine **5a** leads to dihydrofurans **10**, which can undergo ring-opening to diketone **11** by hydrolysis. Pyridol **6a** is obtained in a final condensation step.



Scheme 1. Reactions on larger scales and intermediates.

Conclusions

We have shown that the oxidative rearrangement of furfurylamines to pyridols allows a straightforward access to 6-arylpyridin-3-ols. The reaction could be extended to dibrominated analogues, and both transformations were conducted on a larger scale.

Experimental Section

General Procedure for the Synthesis of 6-Arylpyridin-3-ol Derivatives: Table 2. (5-Arylfurfuryl)amine **5** (1.0 mmol, 1 equiv.) was dissolved in MeOH (6 mL) and H_2O (3 mL), and the mixture was cooled to 0 °C. Then Br_2 (1.2 mmol, 61 µL, 1.2 equiv.) was added. The mixture was warmed to room temperature and stirred for 18 h.

After the reaction had been quenched with saturated aqueous sodium bisulfite (3 mL), saturated aqueous Na_2CO_3 was added to the mixture until pH 7, and the aqueous phase was extracted with ethyl acetate (3 × 50 mL). The combined organic phases were dried with Na_2SO_4, filtered, and the solvent was removed under reduced pressure. Purification by column chromatography (Hex/EtOAc, 8:1 → 2:1 → 0:1) provided the arylpyridoles **6a**–**h**.

General Procedure for the Synthesis of 6-Aryl-2,4-dibromopyridin-3-ol Derivatives: Table 4: (5-Arylfurfuryl)amine **5** (1.0 mmol, 1 equiv.) was dissolved in MeOH (6 mL) and H_2O (1 mL), and the mixture was cooled to 0 °C. Then HBr (48 %, 1.0 mmol, 112 µL, 1 equiv.) and Br_2 (5.0 mmol, 256 µL, 5 equiv.) were added. The mixture was warmed to room temperature and stirred for 72 h. After the reaction had been quenched with saturated aqueous $NaHSO_3$ (3 mL), saturated aqueous Na_2CO_3 was added until pH 7, and the aqueous phase was extracted with ethyl acetate (3 × 50 mL). The combined organic phases were dried with Na_2SO_4, filtered, and the solvent was removed under reduced pressure. Purification by column chromatography (Hex/EtOAc, 8:1 → 2:1 → 0:1) provided the dibrominated arylpyridoles **8a**–**m** along with tribrominated analogues **9a**–**i** and **9l**.

Acknowledgments

The authors would like to thank the Studienstiftung des deutschen Volkes (M. C. D. F.) as well as the Deutsche Forschungsgemeinschaft (DFG) (HE5413/2-2) for financial support. We are further grateful for a travel grant (New Choshu-five scholarship) by Yamaguchi University (T. M.) and for the experimental assistance by Laura Hofmann (FAU Erlangen-Nürnberg).

Keywords: Rearrangement · Furan · Pyridine · Bromine · Oxidation

[1] a) For Lumacaftor (Orkambi®), see: C. E. Wainwright, J. S. Elborn, B. W. Ramsey, G. Marigowda, X. Huang, M. Cipolli, C. Colombo, J. C. Davies, K. De Boeck, P. A. Flume, M. W. Konstan, S. A. McColley, K. McCoy, E. F. McKone, A. Munck, F. Ratjen, S. M. Rowe, D. Waltz, M. P. Boyle, *N. Engl. J. Med.* **2015**, *373*, 220–231; b) for Netupitant (Akynzeo®), see: L. A. Raedler, *Am. Health Drug Benefits* **2015**, *8*, 44–48.

[2] H. Zhao, G. Garg, J. Zhao, E. Moroni, A. Girgis, L. S. Franco, S. Singh, G. Colombo, B. Blagg, *Eur. J. Med. Chem.* **2015**, *89*, 442–*466*.

[3] H. C. Shen, F. Ding, S. Leull, M. J. Forrest, E. Carballo-Jane, K. K. Wu, T. Wu, K. Cheng, L. C. Wilsie, M. L. Krsmanovic, A. K. Taggart, N. Ren, T. Cai, Q. Deng, Q. Chen, J. Wang, M. S. Wolff, X. Tong, T. G. Holt, M. G. Waters, M. L. Hammond, J. R. Tata, S. L. Coletti, *J. Med. Chem.* **2007**, *50*, 6303–6306.

[4] Kissei Pharmaceutical Co. Ltd., WO2010044410, **2010**; *Chem. Abstr.* **2010**, 152, 476973.

[5] G. L. Walford, H. Jones, T. Y. Shen, *J. Med. Chem.* **1971**, *14*, 339–344.

[6] A. M. Thompson, A. Blaser, B. D. Palmer, S. G. Franzblau, B. Wan, Y. Wang, Z. Ma, W. A. Denny, *Bioorg. Med. Chem. Lett.* **2015**, *25*, 3804–3809.

[7] For reviews on Suzuki cross-coupling reactions, see: a) M. Beller, C. Bolm, *Transition Metals for Organic Synthesis*, 2nd ed., Wiley-VCH, Weinheim, **2004**; b) A. de Meijere, F. Diederich, *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed., Wiley-VCH, Weinheim, **2004**; c) H. Bonin, E. Fouquet, F.-X. Felpin, *Adv. Synth. Catal.* **2011**, *353*, 3063–3084; d) I. Maluenda, O. Navarro, *Molecules* **2015**, *20*, 7528–7557; e) L. Xu, S. Zhang, P. Li, *Chem. Soc. Rev.* **2015**, *44*, 8765–8942.

[8] a) P. S. Yang, M. T. Tsai, M. H. Tsai, C. W. Ong, *Chem. Asian J.* **2015**, *10*, 849–852; b) see also ref.[2]

[9] For reviews on radical arylation, see: a) A. Studer in *Radicals in Organic Synthesis*, vol. 2, 1st ed. (Eds.: P. Renaud, M. P. Sibi), Wiley-VCH, Weinheim, **2001**, pp. 44–60; b) W. R. Bowman, J. M. D. Storey, *Chem. Soc. Rev.* **2007**, *36*, 1803–1822; c) S. E. Vaillard, B. Schulte, A. Studer in *Modern Arylation Methods* (Ed.: L. Ackermann), Wiley-VCH, Weiheim, **2009**, pp. 475–511; d) S. E. Vaillard, A. Studer, *Radical Arylations in Encyclopedia of Radicals in Chemistry, Biology, and Materials*, vol. 2 (Eds.: C. Chatgilialoglu, A. Studer), Wiley-VCH, Weinheim, **2012**; e) G. Pratsch, M. R. Heinrich in *Topics in Current Chemistry*, vol. 320 (Eds.: M. R. Heinrich, A. Gansäuer), Springer, Berlin, **2012**.

[10] J. C. Scaiano, L. C. Stewart, *J. Am. Chem. Soc.* **1983**, *105*, 3609–3614.

[11] a) J. R. Baedle, S. H. Korzeniowski, D. E. Rosenberg, B. J. Garcia-Slanga, G. W. Gokel, *J. Org. Chem.* **1984**, *49*, 1594–1603; b) M. J. Perkins in *Free Radicals*, vol. 2 (Ed.: J. K. Kochi), Wiley, New York, **1973**, p. 231.

[12] D. Xue, Z.-H. Jia, C.-J. Zhao, Y.-Y. Zhang, C. Wang, J. Xiao, *Chem. Eur. J.* **2014**, *20*, 2960–2965.

[13] a) G. Pratsch, T. Wallaschkowski, M. R. Heinrich, *Chem. Eur. J.* **2012**, *18*, 11555–11559; b) H. Jasch, J. Scheumann, M. R. Heinrich, *J. Org. Chem.* **2012**, *77*, 10699–10706; c) J. Hofmann, H. Jasch, M. R. Heinrich, *J. Org. Chem.* **2014**, *79*, 2314–2320; d) T. Jiang, S.-Y. Chen, G.-Y. Zhang, R.-S. Zeng, J.-P. Zou, *Org. Biomol. Chem.* **2014**, *12*, 6922–6926; e) T. Jiang, S.-Y. Chen, H. Zhuang, R.-S. Zeng, J.-P. Zou, *Tetrahedron Lett.* **2014**, *55*, 4549–4552.

[14] a) A. Wetzel, V. Ehrhardt, M. R. Heinrich, *Angew. Chem. Int. Ed.* **2008**, *47*, 9130–9133; *Angew. Chem.* **2008**, *120*, 9270–9273; b) A. Wetzel, G. Pratsch, R. Kolb, M. R. Heinrich, *Chem. Eur. J.* **2010**, *16*, 2547–2556.

[15] a) D. P. Hari, P. Schroll, B. König, *J. Am. Chem. Soc.* **2012**, *134*, 2958–2961; b) J. Zoller, D. C. Fabry, M. Rueping, *ACS Catal.* **2015**, *5*, 3900–3904.

[16] A. Honraedt, M.-A. Raux, E. Le Grognec, D. Jacquemin, F.-X. Felpin, *Chem. Commun.* **2014**, *50*, 5236–5238.

[17] a) Y. Wu, S. M. Wong, F. Mao, T. L. Chan, F. Y. Kwong, *Org. Lett.* **2012**, *14*, 5306–5309; b) S. De, S. Ghosh, S. Bhunia, J. A. Sheikh, A. Bisai, *Org. Lett.* **2012**, *14*, 4466–4469; c) W. C. Chen, Y. C. Hsu, W. C. Shih, C. Y. Lee, W. H. Chuang, Y. F. Tsai, P. P. Chen, T. G. Ong, *Chem. Commun.* **2012**, *48*, 6702–6704; d) Y. Cheng, X. Gu, P. Li, *Org. Lett.* **2013**, *15*, 2664–2667; e) A. Dewanji, S. Murarka, D. Curran, A. Studer, *Org. Lett.* **2013**, *15*, 6102–6105; f) H. Zhao, J. Shen, J. Guo, R. Ye, H. Zeng, *Chem. Commun.* **2013**, *49*, 2323–2325; g) M. E. Budén, J. F. Guastavino, R. A. Rossi, *Org. Lett.* **2013**, *15*, 1174–1177; h) D. Ghosh, J.-Y. Lee, C. Y. Liu, Y.-H. Chiang, H. M. Lee, *Adv. Synth. Catal.* **2014**, *356*, 406–410.

[18] a) A. S. Demir, Ö. Reis, E. J. Özgül-Karaaslan, *J. Chem. Soc. Perkin Trans. 1* **2001**, 3042–3045; b) A. S. Demir, H. Findik, *Tetrahedron* **2008**, *64*, 6196–6201; c) A. S. Demir, Ö. Reis, M. Emrullahoğlu, *Tetrahedron* **2002**, *58*, 8055–8058.

[19] For pioneering work, see: a) N. Clauson-Kaas, N. Elming, US2806852, **1957**; *Chem. Abstr.* **1958**, 56322; b) N. Clauson-Kaas, N. Elming, Z. Tyle, *Acta Chem. Scand.* **1955**, *9*, 1–*8*.

[20] a) H. Ren, C. Wu, X. Ding, X. Chen, F. Shi, *Org. Biomol. Chem.* **2012**, *10*, 8975–8984; b) W. Hass, W. A. König, *Liebigs Ann. Chem.* **1982**, *9*, 1615–1622; c) A. G. M. Barrett, S. A. Lebold, *Tetrahedron Lett.* **1987**, *28*, 5791–5792; d) C. Müller, V. Diehl, F. W. Lichtenthaler, *Tetrahedron* **1998**, *54*, 10703–10712; e) Y. Kuo, K. Shih, *Chem. Pharm. Bull.* **1991**, *39*, 181–*183*.

[21] a) K. M. Peese, D. Y. Gin, *Org. Lett.* **2005**, *7*, 3323–3325; b) K. M. Peese, D. Y. Gin, *Chem. Eur. J.* **2008**, *14*, 1654–1665.

[22] a) Merck and Co., WO2007/120574, **2007**; *Chem. Abstr.* **2007**, 1204653; b) Merck and Co., WO2008/30369, **2008**; *Chem. Abstr.* **2008**, 319715; c) T. D. Penning, N. S. Chandrakumar, B. B. Chen, H. Y. Chen, B. N. Desai, S. W. Djuric, S. H. Docter, A. F. Gasiecki, R. A. Haack, J. M. Miyashiro, M. A. Russell, S. S. Yu, D. G. Corley, R. C. Durley, B. F. Kilpatrick, B. L. Parnas, L. J. Askonas, J. K. Gierse, E. I. Harding, M. K. Highkin, J. F. Kachur, S. H. Kim, G. G. Krivi, D. Villani-Price, E. Yvonne, P. Walter, G. Smith, N. S. Ghoreishi-Haack, *J. Med. Chem.* **2000**, *43*, 721–735; d) C. Laurence, M. Rivard, I. Lachaise, J. Bensemhoun, T. Martens, *Tetrahedron* **2011**, *67*, 9518–9521.

[23] R. Villard, F. Robert, I. Blank, G. Bernardinelli, T. Soldo, T. Hofmann, *J. Agric. Food Chem.* **2003**, *51*, 4040–4045.

[24] O. Achmatowicz Jr., P. Bokowski, B. Szechner, Z. Zwierzchowska, A. Zamojski, *Tetrahedron* **1971**, *27*, 1973–1996.

[25] For a review article on the aza-Achmatowicz reaction, see: F. van der Pijl, F. L. van Delft, F. P. J. T. Rutjes, *Eur. J. Org. Chem.* **2015**, 4811–4829.

[26] For recent applications, see: a) C. A. Leverett, M. P. Cassidy, A. Padwa, *J. Org. Chem.* **2006**, *71*, 8591–8601; b) H. Guo, G. A. O'Doherty, *Org. Lett.* **2006**, *8*, 1609–1612.

[27] a) L. Niu, H. Yang, D. Yang, H. Fu, *Adv. Synth. Catal.* **2012**, *354*, 2211–2217; b) Y.-L. Rao, H. Amarne, S.-B. Zhao, T. M. McCormick, S. Martic, Y. Sun, R.-Y. Wang, S. Wang, *J. Am. Chem. Soc.* **2008**, *130*, 12898–12900.

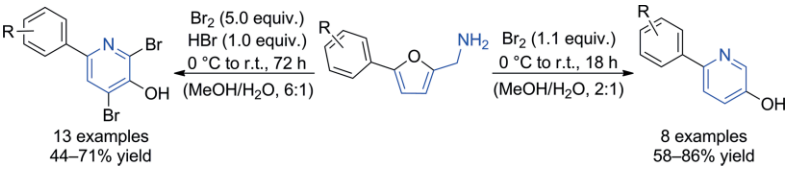
[28] a) H. M. Müller, O. Delgado, T. Bach, *Angew. Chem. Int. Ed.* **2007**, *46*, 4771–4774; *Angew. Chem.* **2007**, *119*, 4855–4858; b) O. Delgado, H. M. Müller, T. Bach, *Chem. Eur. J.* **2008**, *14*, 2322–2339; c) Q. Zhou, B. Zhang, T. Du, H. Gu, Y. Ye, H. Jiang, R. Chen, *Tetrahedron* **2013**, *69*, 327–333; d) Q. Zhou, B. Zhang, L. Su, T. Jiang, R. Chen, T. Du, Y. Ye, J. Shen, G. Dai, D. Han, H. Jiang, *Tetrahedron* **2013**, *69*, 10996–11003.

Received: March 26, 2016
Published Online: ■

Heterocycles

*M. C. D. Fürst, C. S. Sauer, T. Moriyama, A. Kamimura, M. R. Heinrich** 1–6

Synthesis of 6-Arylpyridin-3-ols by Oxidative Rearrangement of (5-Arylfurfuryl)amines



A new straightforward access to 6-arylpyridin-3-ols and their 2,4-dibrominated analogues has been developed. Key to the successful oxidative rearrangement of readily available (5-arylfurfuryl)amines are accurately defined reaction conditions, which include bromine as oxidant.

DOI: 10.1002/ejoc.201600377