Available online at www.sciencedirect.com

ScienceDirect

Mendeleev Commun., 2021, **31**, 265–267

Mendeleev Communications

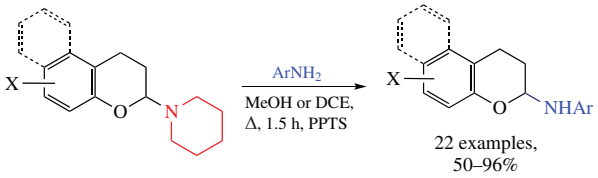
Transamination of 2-piperidinochromanes with (het)arylamines as a convenient route to 2-(het)arylaminochromanes

Kirill S. Korzhenko, Vitaly A. Osyanin,* Dmitry V. Osipov and Yuri N. Klimochkin

Samara State Technical University, 443100 Samara, Russian Federation. E-mail: vosyanin@mail.ru

DOI: 10.1016/j.mencom.2021.03.041

Reaction between 2-piperidinochromane and (hetero)-aromatic amines in the presence of pyridinium tosylate affords the products of replacement of the piperidine fragment by the (hetero)arylamino moiety in good yields. This single-stage process opens facile and efficient way to the functionalized *N*-arylchroman-2-amines.



Keywords: chroman-2-amines, *N*,*O*-acetals, aminals, arylamines, nucleophilic substitution, transamination, transacetalization.

Chromanes and their areno- and hetareno-fused analogues are attractive due to their high biological activity as well as interesting chemical reactivity.[1–4] Among them, compounds with antithrombotic[5,6] and anticancer[7] activity, antidepressant[8] and nonsteroidal antagonist of glucocorticoid receptors[9] were found. 2-Aminochromanes can be considered as semicyclic *N*,*O*-acetals with exocyclic nitrogen atom and they can be used as key intermediates for the formation of C–C bonds under acid catalysis. For example, functionalized α,ω-amino alcohols were obtained by Ni-catalysed homoallylation of semicyclic *N*,*O*-acetals with conjugated dienes[10] or through the nucleophilic addition of organozinc reagents.[11] Reactions of *trans*-2-hydroxycinnamaldehydes with various C-nucleophiles *via in situ* generation of *N*,*O*-acetals were used for the C–C bond formation and preparation of 2-substituted 2*H*-chromenes.[12] Among the main methods for the synthesis of 2-aminochromanes, reactions of *o*-quinone methides with *N*-vinylpyrrolidone or enamines,[13–15] transformations of salicylic aldehydes or their imino derivatives and enamides,[16–18] reactions of 2-chromanols with amines[19,20] are documented.

Previously, we have shown that the reaction of 3-trifluoroacetyl-4*H*-chromenes and 2-trifluoroacetyl-1*H*-benzo[*f*]chromenes with cyclic secondary amines (morpholine, pyrrolidine, piperidines and piperazines) led to amino-chromanes,[21] while the reaction with primary aromatic amines gave β-aminovinyl trifluoromethyl ketones as the products of pyran ring opening.[22]

Here, we report a new synthesis of *N*-arylaminochromanes through the acid-catalyzed reaction of 2-piperidinochromane **1** with arylamines (Scheme 1, Table 1). For the model reactants, we chose 3-piperidino-2,3-dihydro-1*H*-benzo[*f*]chromene **1a** and *p*-nitroaniline. At first, the transamination was attempted without any catalyst (see Table 1, entry 1), when product **2a** was not formed and the starting compounds were recovered after refluxing for 1 h. When *p*-nitroaniline hydrochloride was applied, product **2a** was obtained in 63% yield in 30 min (entry 2). Apparently, bound hydrogen chloride was acting as the catalyst. Further prolongation of the reaction time to 1.5 h did not significantly affect the yield (entry 3). Several experimental conditions including different catalysts were evaluated to improve the reaction outcome. The best results were achieved with the use of 1 equiv. pyridinium tosylate (PPTS). Studying the solvent effect (entries 4, 6–8) showed that 1,2-dichloroethane (DCE) should be the choice. Attempted reduction of the catalyst amount (see entry 8, footnotes *c*, *d*) and the reaction time (entries 9, 10) caused some decrease in the yield.

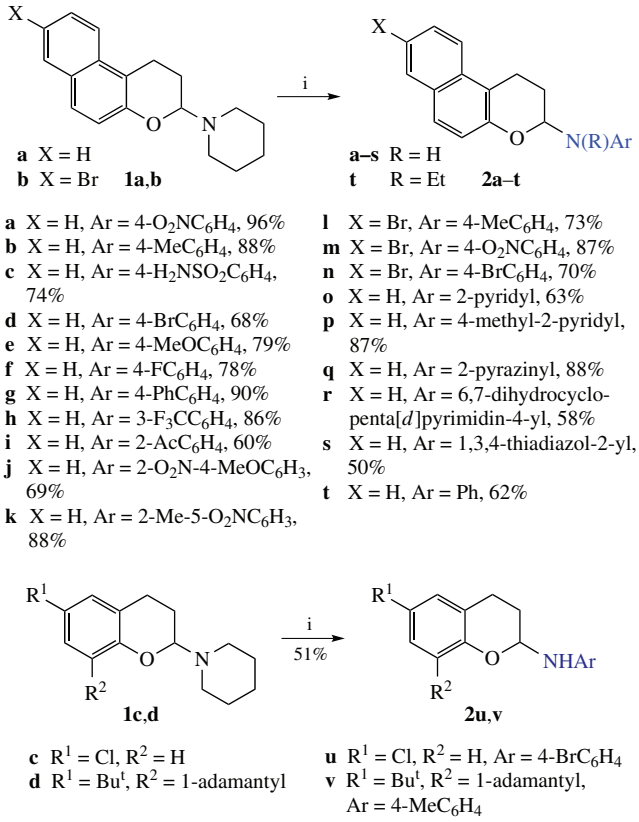
An important factor in the successful proceeding of the synthesis is low solubility of the final aminochromane **2** in the chosen solvent that leads to its crystallization from the reaction medium and shifts the equilibrium towards the final product. In the case of compounds **2a**,**j**,**l–n**, DCE was the optimal solvent, however in other cases methanol provided higher yields. Besides, the choice of a solvent depends on the solubility of the starting reactants, for example, for the preparation of compound **2v** we had to use a MeOH–DCE (2 : 1) mixture instead of pure MeOH. It should be noted that attempts to isolate aminochromanes **2** by column chromatography caused their decomposition on silica gel.

Using the optimized reaction conditions, we obtained a series of *N*-aryl substituted aminochromanes **2a–v** in 50–96% yields

Table 1 Optimization of the reaction conditions on model aminochromane **1a** and *p*-nitroaniline.[a]

Entry	Solvent	Catalyst	*t*/h	Yield of **5a** (%)
1	MeOH	none	1.0	–
2	MeOH	'HCl'[b]	0.5	63
3	MeOH	'HCl'[b]	1.5	67
4	MeOH	PPTS	1.5	79
5	MeOH	TsOH	1.5	63
6	MeCN	PPTS	1.5	92
7	1,4-dioxane	PPTS	1.5	84
8	DCE	PPTS	1.5	96 (88,[c] 67[d])
9	DCE	PPTS	0.5	84
10	DCE	PPTS	1.0	88

[a] A mixture of piperidinochromane **1a** (0.5 mmol) and *p*-nitroaniline (0.5 mmol) with catalyst (0.5 mmol, 1 equiv.) was stirred under reflux. [b] *p*-Nitroaniline hydrochloride was used. [c] With 0.5 equiv. PPTS. [d] With 0.2 equiv. PPTS.



Scheme 1 *Reagents and conditions*: i, ArNHR, PPTS (1 equiv.), MeOH or DCE, reflux, 1.5 h.

(see Scheme 1).† Note that both anilines containing electron-donating substituents (Me, MeO, Ph) and those with electron-withdrawing substituents (NO_2, CF_3, Br, F, Ac, SO_2NH_2) as well as primary heteroaromatic amines (pyridine, pyrazine, pyrimidine and 1,3,4-thiadiazole derivatives) can be introduced into this reaction. In the case of 4-aminobenzenesulfonamide, the the sulfonamide fragment remained intact. Using *N*-ethylaniline as an example, we showed that the reaction could also proceed with secondary aromatic amines (product **2t**). Finally, besides benzochromane derivatives **1a**,**b**, 2-piperidinochromanes **1c**,**d** can be used for the preparation of compounds **2u**,**v**.

We also found that the reaction between aminochromane **2a** and an excess of piperidine (5 equiv., MeOH, 30 min reflux) led to formation of the starting 2-piperidinochromane **1a**. This result confirms our suggestion that the transamination reaction is reversible. It should be noted that we were not able to introduce phloroglucinol, pyrimidine-2-thiol and 1-aminoadamantane into the reaction with 2-piperidinochromane **1a**. Also, the reaction did not proceed with benzimidazole, imidazole, diphenylamine and 2,4-dinitroaniline due to their insufficient nucleophilicity.

The obtained *N*,*O*-acetals **2** are storage stable. They possess cyclic structure both in the solid state and in DMSO or $CHCl_3$ solution. IR spectra of aminochromanes **2** contain, as a rule, narrow absorption bands for NH group in the range of 3410–3340 cm^{-1}. In the ^1H NMR spectra, acetal protons resonate at 5.39–6.34 ppm. The position of NH-proton varies greatly depending on the nature of the amine moiety. In the ^{13}C NMR spectra, the signals for the methylene groups in the α- and β-positions with respect to the aromatic fragment, as well as *N*,*O*-acetal carbon atoms, are found at 19.4–25.3, 26.3–28.0, and 77.3–81.8, or 85.1–87.2 ppm (compounds **2g**,**t**), respectively.

We assume that the formation of aminochromanes **2** proceeds according to the generally accepted mechanism of transamination *via* the iminium cation (see Online Supplementary Materials, Scheme S1).

In conclusion, we have accomplished an acid-catalyzed transamination that produces *N*-(het)aryl substituted α-aminochromanes. This reaction is reversible, however low solubility of the final products favours the shift of the equilibrium towards them. The advantages of the proposed procedure include the use of available and inexpensive reagents, simple reaction conditions, broad substrate scope, no metal catalysts, scalability, and easy isolation by a chromatography-free protocol.

This work was supported by the Russian Science Foundation (grant no. 19-13-00421).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2021.03.041.

References

1 M. Miao, M. Jin, H. Xu, P. Chen, S. Zhang and H. Ren, *Org. Lett.*, 2018, **20**, 5718.
2 K. S. Levchenko, K. A. Chudov, E. V. Zinoviev, K. A. Lyssenko, A. N. Fakhrutdinov, D. U. Demin, N. O. Poroshin, A. A. Zhukova, P. S. Shmelin and E. P. Grebennikov, *Mendeleev Commun.*, 2019, **29**, 301.
3 K. S. Levchenko, K. A. Chudov, D. Yu. Demin, G. E. Adamov, E. V. Zinoviev, K. A. Lyssenko, A. V. Shokurov, P. S. Shmelin and E. P. Grebennikov, *Russ. Chem. Bull., Int. Ed.*, 2019, **68**, 1883 (*Izv. Akad. Nauk, Ser. Khim.*, 2019, 1883).
4 V. Yu. Korotaev, I. B. Kutyashev, A. Yu. Barkov and V. Ya. Sosnovskikh, *Russ. Chem. Rev.*, 2019, **88**, 27.
5 O. Bruno, C. Brullo, A. Ranise, S. Schenone, F. Bondavalli, E. Barocelli, V. Ballabeni, M. Chiavarini, M. Tognolini and M. Impicciatore, *Bioorg. Med. Chem.*, 2001, **9**, 1397.
6 O. Bruno, S. Schenone, A. Ranise, F. Bondavalli, E. Barocelli, V. Ballabeni, M. Chiavarini, S. Bertoni, M. Tognolini and M. Impicciatore, *Bioorg. Med. Chem.*, 2001, **9**, 629.
7 N. Jiang, X. Wang, Y. Yang and W. Dai, *Mini-Rev. Med. Chem.*, 2006, **6**, 885.
8 C. E. Beyer, Q. Lin, B. Platt, J. Malberg, G. Hornby, K. M. Sullivan, D. L. Smith, T. Lock, P. J. Mitchell, N. T. Hatzenbuhler, D. A. Evrard, B. L. Harrison, R. Magolda, M. N. Pangalos, L. E. Schechter, S. Rosenzweig-Lipson and T. H. Andree, *Br. J. Pharmacol.*, 2009, **157**, 307.
9 Q.-Y. Li, M. Zhang, T. M. Hallis, T. A. DeRosier, J.-M. Yue, Y. Ye, D. E. Mais and M.-W. Wang, *Biochem. Biophys. Res. Commun.*, 2010, **391**, 1531.
10 T. Mori, Y. Akioka, G. Onodera and M. Kimura, *Molecules*, 2014, **19**, 9288.
11 X.-M. Wang, Y.-W. Liu, R.-J. Ma, C.-M. Si and B.-G. Wei, *J. Org. Chem.*, 2019, **84**, 11261.
12 C. Yu, H. Huang, X. Li, Y. Zhang, H. Li and W. Wang, *Chem. – Eur. J.*, 2016, **22**, 9240.
13 G.-Q. Xu, Z.-T. Feng, J.-T. Xu, Z.-Y. Wang, Y. Qin and P.-F. Xu, *Chem. – Eur. J.*, 2018, **24**, 13778.
14 A. V. Lukashenko, D. V. Osipov, V. A. Osyanin and Yu. N. Klimochkin, *Chem. Heterocycl. Compd.*, 2020, **56**, 529 (*Khim. Geterotsikl. Soedin.*, 2020, **56**, 529).
15 V. A. Osyanin, A. V. Lukashenko and D. V. Osipov, *Russ. Chem. Rev.*, 2021, **90**, 324.
16 L. He, L. Zhao, D.-X. Wang and M.-X. Wang, *Org. Lett.*, 2014, **16**, 5972.
17 L. He, H.-B. Liu, L. Zhao, D.-X. Wang and M.-X. Wang, *Tetrahedron*, 2015, **71**, 523.
18 J. Liu, J. Xu, Z. Li, Y. Huang, H. Wang, Y. Gao, T. Guo, P. Ouyang and K. Guo, *Eur. J. Org. Chem.*, 2017, 3996.

† *Synthesis of aminochromanes* **2** (*general procedure*). A mixture of 2-piperidinochromane **1a**–**d** (0.5 mmol), aromatic amine (0.5 mmol) and PPTS (125 mg, 0.5 mmol) in DCE (for products **2a**,**j**,**l**–**n**), MeOH–DCE (2 : 1) (for **2v**) or MeOH (4 ml) was stirred under reflux for 1.5 h. When the reaction was complete, the mixture was stored at −30 °C for 1 h, the solid was filtered off, washed with ice-cold MeOH (2×3 ml) and purified by recrystallization from a suitable solvent.

19 Y.-K. Liu, Z.-L. Li, J.-Y. Li, H.-X. Feng and Z.-P. Tong, *Org. Lett*., 2015, **17**, 2022.
20 I. A. Semenova, K. S. Korzhenko, D. V. Osipov, V. A. Osyanin and Yu. N. Klimochkin, *Chem. Heterocycl. Compd*., 2020, **56**, 311 (*Khim. Geterotsikl. Soedin*., 2020, **56**, 311).
21 V. A. Osyanin, D. V. Osipov, I. V. Melnikova, K. S. Korzhenko, I. A. Semenova and Yu. N. Klimochkin, *Synthesis*, 2020, **52**, 3604.
22 D. V. Osipov, I. V. Melnikova, K. S. Korzhenko, V. A. Osyanin and Yu. N. Klimochkin, *Chem. Heterocycl. Compd.*, 2020, **56**, 990 (*Khim. Geterotsikl. Soedin*., 2020, **56**, 990).

Received: 28th December 2020; Com. 20/6409