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Polymer-supported synthesis of *N*-substituted anthranilates as the building blocks for preparation of *N*-arylated 3-hydroxyquinolin-4(1*H*)-ones†

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Fast and simple access to *N*-arylated 3-hydroxyquinolin-4(1*H*)-ones starting from easily available 1-methyl-2-iodoterephthalate and variously substituted anilines is presented. *N*-Alkylated anthranilic acid derivatives represent important intermediates. They can be advantageously prepared by solid-phase synthesis, by Buchwald–Hartwig amination or reductive amination with wide substrate scope and with excellent crude purities.

3-Hydroxyquinolin-4(1*H*)-ones (3-HQs), flavones aza-analogues, represent an interesting family of biologically active compounds.^{1–3} The methodology for 3-HQ's synthesis is well established, starting from anthranilic acid derivatives and bromoacetophenones.⁴ The formed phenacylestere cyclize upon heating in various acids or *N*-methyl-2-pyrrolidone (NMP) (Scheme 1). The synthetic pathway was later successfully adapted to using a solid support which enabled simple, fast and high-throughput organic synthesis of larger collections of 3-HQs for biological screening (Scheme 1).⁵

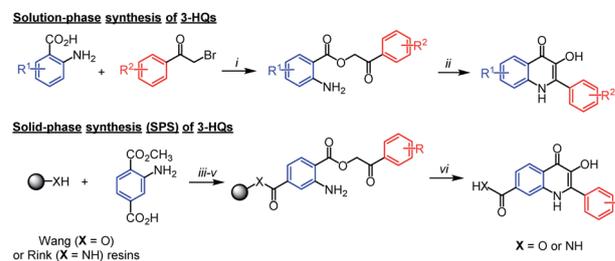
Although the synthesis of 3-HQs substituted on 2-phenyl as well as the quinoline benzene ring is relatively widely explored,^{6,7} preparation of *N*-substituted 3-HQs was yet barely described. Hradil *et al.*⁸ studied the effect of substituents at the nitrogen atom in the course of cyclization of phenacyl anthranilates. *N*-methyl and *N*-phenyl derivatives were studied; however, the desired *N*-methyl-3-HQ was obtained in very low yield and *N*-phenyl-3-HQ was even not isolated. Spacilova *et al.*⁹ managed to prepare *N*-amino-3-HQ by the cyclization of 2-hydrazinobenzoic acid phenacyl ester, however, the procedure lacks general application. Recently Wang *et al.*¹⁰ reported synthesis of aza-rocaglates involving *N*-methyl-3-HQ as one of the intermediates. Interestingly, they used basic conditions for the cyclization of *N*-methylphenacyl ester and obtained the product in 85% yield. Nevertheless, a wider application of the method was not studied. It is worth mentioning that direct *N*-alkylation of the 3-HQ scaffold is not feasible as it leads to

a mixture of mono- and dialkylated products due to the presence of reactive hydroxy group.⁴

3-HQs have been reported as strong cytotoxic agents, they act as inhibitors of microtubule formation in tubulin polymerization¹ or the species able to target translation elongation factor.² Furthermore, 3-HQs were recognized to exhibit antiprotozoal and immunosuppressive effects.³ In the field of physico-chemical properties, compounds bearing 3-HQ scaffold have been identified as promising fluorescent agents.^{11,12} In this regard they exhibit dual fluorescence spectra with sufficiently separated emission bands, with the intensities' ratio independent on the molecule concentration, thus enable the 3-HQs to be *e.g.* fluorescent probes in the biological system.

However, due to unavailability of the general method applicable for the preparation of *N*-substituted-3-HQs, the properties of such compounds are unknown.

With respect to well-known advantages of solid-phase synthesis (SPS) in the preparation of drug-like molecules we decided to modify the previously reported SPS synthesis of



Scheme 1 Routinely used synthesis of 3-HQs in solution and on a solid support. Reagents and conditions: (i) K_2CO_3 , DMF; (ii) refluxing acid or NMP; (iii) 1-hydroxybenzotriazole (HOBT), *N,N'*-diisopropylcarbodiimide (DIC), CH_2Cl_2 /DMF; (iv) potassium trimethylsilylanolate (TMSOK), DMF; (v) 2-bromoacetophenone, triethylamine, DMF; (vi) CH_2Cl_2 /TFA 1 : 1, then reflux in acid.

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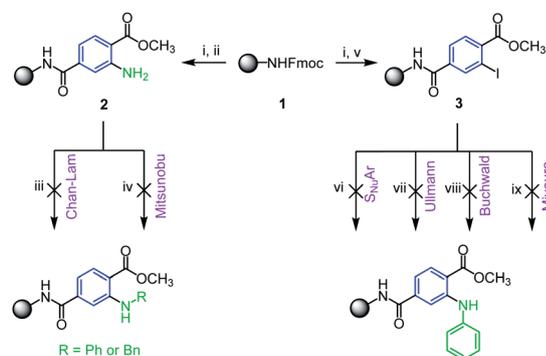
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3HQs⁵ towards their *N*-alkylated analogues. Rink AM resin **1** was acylated with 1-methyl-2-aminoterephthalate and subjected to *N*-alkylation (Scheme 2). Although *N*-substituted anthranilic acids belong to pharmaceutically relevant intermediates,^{13–15} their preparation on solid support has not been reported yet. Consequently we adopted conditions from traditional solution-phase chemistry describing *N*-arylation by Ullmann type reactions^{16,17} and copper or nickel catalyzed Chan–Evans–Lam cross-coupling.^{18,19} However, we were not able to convert **2** to corresponding *N*-substituted derivatives (Scheme 2, reaction conditions iii–iv) and the starting material only was isolated. For this reason, we prepared immobilized 1-methyl-2-iodoterephthalate **3** and subjected this intermediate to amination by aromatic nucleophilic substitution, Buchwald reaction, Ullmann reaction and Miyaura coupling. Either no conversion of the starting material to the product was observed (Scheme 2, reaction conditions vi–vii) or we detected only dehalogenation of the starting iodo-derivative (Scheme 2, reaction conditions viii–ix).

Luckily, we finally succeeded in optimizing the Buchwald–Hartwig amination^{20–22} (Table 1) with aniline using the second generation of XPhos palladium as the pre-catalyst and K₃PO₄ as a base in the mixture of toluene/DMF at 100 °C. Under these conditions the desired intermediate **4** was received in an excellent crude purity of 94% (calculated from UHPLC–UV traces). Motivated by this result we subsequently tested variously substituted anilines, benzylamines and other aliphatic amines. The reaction worked smoothly with all tested anilines, with both electron-withdrawing (entries 2–8, Table 1) and electron-donating (entries 9–14, Table 1) substituents as it afforded the products in high crude purities. It is worth mentioning that only use of SPS allows to isolate the corresponding products in such high crude purities because the residual catalyst and solution-phase reagents were simply



Scheme 2 Attempted preparation of *N*-substituted amino-terephthalates on solid support. Reagents and conditions (per 100 mg of **1**): (i) DBU/CH₂Cl₂ 1 : 1, r.t., 10 min (ii) 1-methyl-2-aminoterephthalate (0.3 M), HOBt (0.3 M), DIC (0.3 M), CH₂Cl₂/DMF 1 : 1, r.t., 16 h; (iii) phenylboronic acid (0.2 M), Cu(OAc)₂ (0.2 M), triethylamine (0.4 M), CH₃CN, 80 °C, 16 h; (iv) benzyl alcohol (0.3 M), PPh₃ (0.3 M), diisopropyl azodicarboxylate (DIAD) (0.3 M), THF, 0 °C to r.t., 16 h; (v) 1-methyl-2-iodoterephthalate (0.2 M), HOBt (0.2 M), DIC (0.2 M), DMF, r.t. 4 h; (vi) aniline (0.3 M), K₃PO₄ (0.3 M), CuI (0.03 M), ethylene glycol (0.3 M), DMSO, 100 °C, 16 h; (vii) aniline (0.4 M), LiHMDS (1 M in THF, 0.4 M) Pd₂dba₃ (0.02 M), XPhos (0.04 M), THF, 60 °C, 16 h; (ix) bis(pinacolato)diboron (0.3 M), KBr (0.3 M), PhOK (0.3 M), Pd(PPh₃)Cl₂ (0.03 M), PPh₃ (0.06 M), toluene, reflux, 16 h, then (viii).

Table 1 Buchwald–Hartwig amination on solid support^a

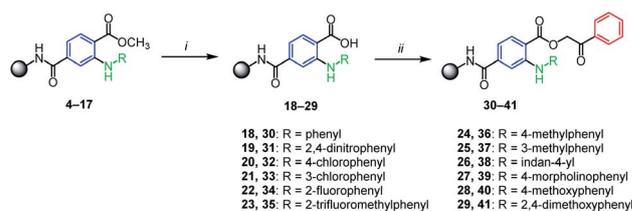
Entry	RNH ₂	Cmp. no.	Crude purity (%)
1	Aniline	4	94
2	2,4-Dinitroaniline	5	99
3	4-Chloraniline	6	90
4	3-Chloraniline	7	95
5	2-Fluorophenyl	8	95
6	2-Trifluoromethylaniline	9	70
7	4-Aminobenzoic acid	10	70
8	3-Aminobenzoic acid	11	60
9	4-Methylaniline	12	90
10	3-Methylaniline	13	81
11	4-Aminoindan	14	95
12	4-Morpholinoaniline	15	95
13	4-Methoxyaniline	16	85
14	2,4-Dimethoxyaniline	17	95
15	Benzylamine	18	n.d.
16	4-Methoxybenzylamine	19	n.d.
17	Cyclohexylamine	20	<10
18	Octylamine	21	n.d.

^a Calculated from UHPLC–UV traces, n.d. = not detectable.

removed by common washing procedure. In contrast, Buchwald–Hartwig amination in solution phase requires removal of the catalyst by tedious column chromatography. Compared to anilines no reaction was observed for aliphatic amines including benzylic, cyclic or acyclic ones (entries 15–18, Table 1), which was caused presumably due to the inefficient formation of active complex with palladium catalyst.

The successfully prepared *N*-arylated methyl esters **4–17** were then hydrolyzed by typical procedure for SPS chemistry²³ employing potassium trimethylsilylanolate (TMSOK) in THF (Scheme 3). All intermediates **18–29** were obtained in high crude purities (up to 90%) and were further reacting with 2-bromoacetophenone which yielded phenacyl esters **30–41** again with high crude purities (Scheme 3).

As the Buchwald–Hartwig coupling with aliphatic amines failed, we considered the possible alkylation using the reductive amination of immobilized aminoterephthalate **2**. Interestingly, we observed no conversion to desired products when using



Scheme 3 Hydrolysis of methyl esters and alkylation to phenacyl esters. Reagents and conditions: (i) TMSOK, THF, r.t., 16 h; (ii) 2-bromoacetophenone, triethylamine, DMF, r.t., 16 h.



be introduced by Buchwald–Hartwig amination, while aliphatic and benzylic moieties can be incorporated by reductive amination. With respect to use of immobilized starting materials the protocol enables to easily remove the catalysts by simple filtration which provides the intermediates in high crude purities. The resulting immobilized *N*-substituted anthranilic acid derivatives represent compounds of biological interest^{28,29} or can be theoretically used as precursors for the preparation of e.g. acridine/acridones derivatives with antimalarial,³⁰ antiviral,^{31,32} antibacterial,³³ and other^{34–36} activities. In our case we applied them for the preparation of *N*-substituted 3-HQs. The synthetic route is feasible for compounds bearing *N*-aryl moiety with electron donating substituents. Due to number of readily available electron rich anilines the developed strategy can be used, in combination with previously developed procedures,⁶⁷ to easily and rapidly prepare collections of novel 3-HQ's for determination of their biological and physicochemical properties.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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References

- J. Rehulka, K. Vychodilová, P. Krejci, S. Gurska, P. Hradil, M. Hajduch, P. Dzubak and J. Hlavac, *Eur. J. Med. Chem.*, 2020, **192**, 112176.
- K. Burglova, G. Rylova, A. Markos, H. Prichystalova, M. Sural, M. Petracek, M. Medvedikova, G. Tejral, B. Sopko, P. Hradil, P. Dzubak, M. Hajduch and J. Hlavac, *J. Med. Chem.*, 2018, **61**, 3027–3036.
- P. Hradil, J. Hlavac, M. Sural, M. Hajduch, M. Kolar and R. Vecerova, *Mini-Rev. Med. Chem.*, 2009, **9**, 696–702.
- P. Hradil and J. Jirman, *Collect. Czech. Chem. Commun.*, 1995, **60**, 1357–1366.
- M. Sural and V. Krchnak, *J. Comb. Chem.*, 2007, **9**, 793–796.
- M. Sural, J. Hlavac, P. Funk, P. Dzubak and M. Hajduch, *ACS Comb. Sci.*, 2011, **13**, 39–44.
- M. Sural, J. Hlavac, P. Hradil, I. Frysova, M. Hajduch, V. Bertolasi and M. Malon, *Eur. J. Med. Chem.*, 2006, **41**, 467–474.
- P. Hradil, J. Hlavac and K. Lemr, *J. Heterocycl. Chem.*, 1999, **36**, 141–144.
- L. Spacilova, J. Hlavac, P. Hradil, I. Frysova, M. Sural, P. Krejci and M. Malon, *J. Heterocycl. Chem.*, 2006, **43**, 1065–1070.
- W. Wang, R. Cencic, L. Whitesell, J. Pelletier and J. Porco, *Chem.–Eur. J.*, 2016, **22**, 12006–12010.
- P. Funk, K. Motyka, P. Dzubak, P. Znojek, S. Gurska, J. Kusz, C. McMaster, M. Hajduch and M. Sural, *RSC Adv.*, 2015, **5**, 48861–48867.
- K. Motyka, J. Hlavac, M. Sural, P. Hradil, P. Krejci, L. Kvapil and M. Weiss, *Tetrahedron Lett.*, 2011, **52**, 715–717.
- S. Sharma, V. K. Srivastava and A. Kumar, *Eur. J. Med. Chem.*, 2002, **37**, 689–697.
- A. Varnavas, L. Lassiani, V. Valenta, F. Berti, L. Mennuni and F. Makovec, *Bioorg. Med. Chem.*, 2003, **11**, 741–751.
- J. F. Sun, Y. J. Xu, X. H. Kong, Y. Su and Z. Y. Wang, *Neurosci. Lett.*, 2019, **696**, 67–73.
- H. Rao, H. Fu, Y. Jiang and Y. Zhao, *J. Org. Chem.*, 2005, **70**, 8107–8109.
- H. Rao, Y. Jin, H. Fu, Y. Jiang and Y. Zhao, *Chem.–Eur. J.*, 2006, **12**, 3636–3646.
- S. Liu and L. Xu, *Asian J. Org. Chem.*, 2018, **7**, 1856–1863.
- S. Ando, Y. Hirota, H. Matsunaga and T. Ishizuka, *Tetrahedron Lett.*, 2019, **60**, 1277–1280.
- A. S. Guram, R. A. Rennels and S. L. Buchwald, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 1348–1350.
- J. Louie and J. F. Hartwig, *Tetrahedron Lett.*, 1995, **36**, 3609–3612.
- V. Zimmermann and S. Brase, *J. Comb. Chem.*, 2007, **9**, 1114–1137.
- R. C. D. Brown, J. Keily and R. Karim, *Tetrahedron Lett.*, 2000, **41**, 3247–3251.
- S. Krajcovicova, J. Stankova, P. Dzubak, M. Hajduch, M. Sural and M. Urban, *Chem.–Eur. J.*, 2018, **24**, 4957–4966.
- R. Apodaca and W. Xiao, *Org. Lett.*, 2001, **3**, 1745–1748.
- T. Volná, K. Motyka and J. Hlaváč, *Chromatographia*, 2016, **79**, 1153–1163.
- M. Sural, P. Hradil, S. Krupkova and J. Hlavac, *Mini-Rev. Org. Chem.*, 2012, **9**, 426–432.
- V. B. Oza, H. M. Petrassi, H. E. Purkey and J. W. Kelly, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 1–6.
- D. Tiwari, S. Haque, S. Misra and R. Chandra, *Int. J. Drug Dev. Res.*, 2011, **3**, 265–271.
- J. X. Kelly, M. J. Smilkstein, R. Brun, S. Wittlin, R. A. Cooper, K. D. Lane, A. Janowsky, R. A. Johnson, R. A. Dodean, R. Winter, D. J. Hinrichs and M. K. Riscoe, *Nature*, 2009, **459**, 270–273.
- J. R. Goodell, A. A. Madhok, H. Hiasa and D. M. Ferguson, *Bioorg. Med. Chem.*, 2006, **14**, 5467–5480.
- J. R. Goodell, F. Puig-Basagoiti, B. M. Forshey, P. Y. Shi and D. M. Ferguson, *J. Med. Chem.*, 2006, **49**, 2127–2137.
- A. R. Benoit, C. Schiaffo, C. E. Salomon, J. R. Goodell, H. Hiasa and D. M. Ferguson, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 3014–3017.
- S. H. Watterson, P. Chen, Y. Zhao, H. H. Gu, T. G. M. Dhar, Z. Xiao, S. K. Ballentine, Z. Shen, C. A. Fleener, K. A. Rouleau, M. Obermeier, Z. Yang, K. W. McIntyre, D. J. Shuster, M. Witmer, D. Dambach, S. Chao, A. Mathur, B. C. Chen, J. C. Barrish, J. A. Robl, R. Townsend and E. J. Iwanowicz, *J. Med. Chem.*, 2007, **50**, 3730–3742.
- L. A. Howell, A. Howman, M. A. O'Connell, A. Mueller and M. Searcey, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 5880–5883.
- L. I. James, V. K. Korboukh, L. Krichevsky, B. M. Baughman, J. M. Herold, J. L. Norris, J. Jin, D. B. Kireev, W. P. Janzen, C. H. Arrowsmith and S. V. Frye, *J. Med. Chem.*, 2013, **56**, 7358–7371.

