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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.

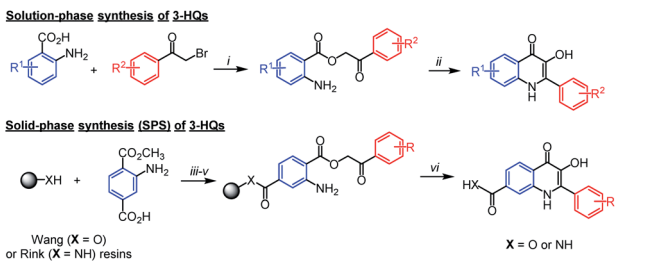
3-Hydroxyquinolin-4(1*H*)-ones (3-HQs), flavones aza-analogues, represent an interesting family of biologically active compounds.[1–3] The methodology for 3-HQ's synthesis is well established, starting from anthranilic acid derivatives and bromoacetophenones.[4] The formed phenacylesters cyclize upon 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 polymerization[1] 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 physicochemical 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 trimethylsilanolate (TMSOK), DMF; (v) 2-bromoacetophenone, triethylamine, DMF; (vi) CH_2Cl_2/TFA 1 : 1, then reflux in acid.

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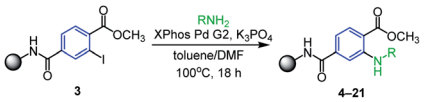
3HQs[5] towards their *N*-alkylated analogues. Rink AM resin **1** was acylated with 1-methyl-2-aminoterephthalate and subjected to *N*-alkylation (Scheme 2). Although *N*-substituted anthranilic acids belong to pharmaceutically relevant intermediates,[13–15] their preparation on solid support has not 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).

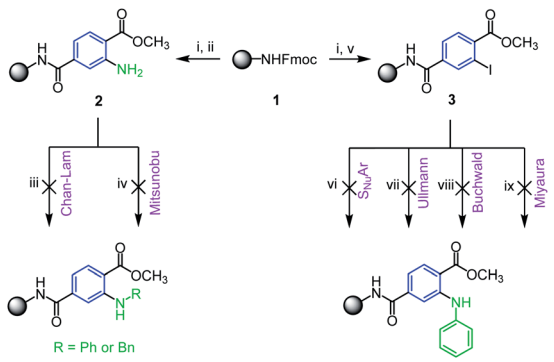
Luckily, we finally succeeded in optimizing the Buchwald–Hartwig amination[20–22] (Table 1) with aniline using the second generation of XPhos palladium as the pre-catalyst and K_3PO_4 as a base in the mixture of toluene/DMF at 100 °C. Under these conditions the desired intermediate **4** was received 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 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.

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-Fluorphenyl	**8**	95
6	2-Trifluormethylaniline	**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.

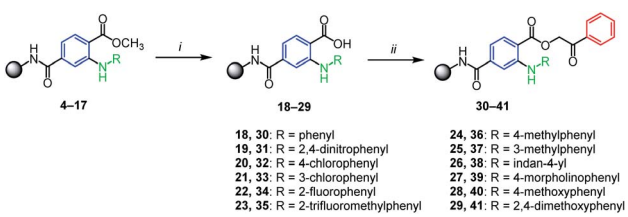
[a] Calculated from UHPLC-UV traces, n.d. = not detectable.



Scheme 2 Attempted preparation of *N*-substituted aminoterephthalates on solid support. Reagents and conditions (per 100 mg of **1**): (i) DBU/CH_2Cl_2 1 : 1, r.t., 10 min (ii) 1-methyl-2-aminoterephthalate (0.3 M), HOBt (0.3 M), DIC (0.3 M), CH_2Cl_2/DMF 1 : 1, r.t., 16 h; (iii) phenylboronic acid (0.2 M), $Cu(OAc)_2$ (0.2 M), triethylamine (0.4 M), CH_3CN, 80 °C, 16 h; (iv) benzyl alcohol (0.3 M), PPh_3 (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; (vii) aniline (0.3 M), K_3PO_4 (0.3 M), CuI (0.03 M), ethylene glycol (0.3 M), DMSO, 100 °C, 16 h; (viii) aniline (0.4 M), LiHMDS (1 M in THF, 0.4 M) Pd_2dba_3 (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), $Pd(PPh_3)Cl_2$ (0.03 M), PPh_3 (0.06 M), toluene, reflux, 16 h, then (viii).

The successfully prepared *N*-arylated methyl esters **4–17** were then hydrolyzed by typical procedure for SPS chemistry[23] employing potassium trimethylsilanolate (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

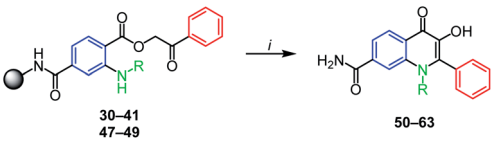


Scheme 3 Hydrolysis of methyl esters and alkylation to phenacyl esters. Reagents and conditions: (i) TMSOK, THF, r.t., 16 h; (ii) 2-bromoacetophenone, triethylamine, DMF, r.t., 16 h.

conditions typical for solid support, *i.e.* sodium triacetoxyborohydride or sodium cyanoborohydride as the reductive agents.[6,24] Thus we adopted the solution-phase protocol for catalytic silane-based direct reductive amination in refluxing THF reported by Apodaca *et al.*[25] (Scheme 4). Using this procedure, benzyl moiety was successfully introduced and derivative **42** was obtained in 90% crude purity (according to UHPLC-UV traces). Intermediate **42** was hydrolyzed to carboxylic acid **43** and alkylated with 2-bromoacetophenone but an equimolar mixture of compounds **44** and **45** was formed (Scheme 4). Formation of **45** was caused by an excess of solution-phase reagents which is a typical feature of solid-phase synthesis. Therefore, we changed the reaction sequence and performed the reductive amination in the stage of phenacyl ester **46**. The reaction proceeded well with benzaldehyde, cyclohexanecarboxaldehyde and pentanal (Scheme 4, compounds **47–49**).

The final step leading to targeted *N*-substituted 3-HQs **50–63** was performed by traditional acid-catalyzed cyclization. Several acids (PPA, AcOH, H_2SO_4) were employed, however the successful cyclization occurred only when neat refluxing trifluoracetic acid (TFA) was used. Due to acid-lability of the Rink amide linker these conditions led to cleavage of phenacyl esters from the resin and their subsequent cyclization. The cyclization was feasible for phenacyl esters **36–38** and **40–41** prepared from electron-rich anilines (products **56–58**, **60–61**, Table 2). Interestingly, although sterically demanding, *N*-indanyl 3-HQ **58** was obtained smoothly and with excellent purity. Similarly, phenacyl esters with halogen atoms on *N*-phenyl ring **32–34** can be cyclized as well (products **52–54**, Table 2). In this case the mesomeric effect of halogens probably prevails the inductive effect. Going down with nitrogen nucleophilicity the reaction gets problematic. Derivatization of *N*-phenyl ring by nitro groups or trifluormethyl group (compounds **51** and **55** respectively, Table 2) led to low reactivity of phenacyl esters towards cyclization. 4-Morpholinophenyl derivative **39** did not react to expected product **59**, probably due to the protonation of morpholine nitrogen under acidic conditions causing electron-withdrawal from the aniline NH. The cyclization to 3-HQs did not work with *N*-aliphatic substitution (benzyl derivatives as well as aliphatic ones), no matter if cyclized or acyclic (compounds **62–63**, Table 2). When compared to *N*-arylated esters, this result can be explained by the protonation of more basic *N*-alkylated intermediates by TFA which breaks down the cyclization. It is worth mentioning that in contrast to high crude purities (Table 2) the limited yields of final compounds were caused by problematic purification and not by the cyclization itself. Significant peak broadening and tailing were observed using reverse phase sorbents and for some derivatives, the RP HPLC, were not applicable.[26] Interestingly, in our case, the purification method strongly depended on *N*-phenyl substitution, where alkyl groups such as methyl or indanyl were feasible to purify by reversed-phase semipreparative HPLC, opposite to chloro- and methoxy moieties that required column chromatography using silica gel.

Table 2 Cleavage from solid support and cyclization of *N*-substituted phenacyl esters. Reagents and conditions: (i) CH_2Cl_2/TFA 1 : 1, r.t., 30 min to 2 h, then neat TFA, reflux, 24 h to 5 days



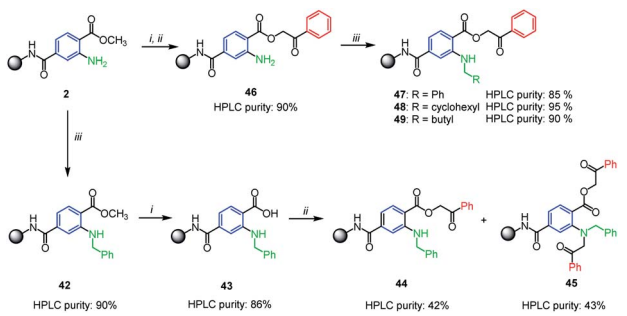
Cmp. no.	R–	Crude purity of products (%)	Overall yield[b] (%)
50	Phenyl-	78	80[c]
51	2,4-Dinitrophenyl	n.d[a]	—
52	4-Chlorphenyl	85	14[d]
53	3-Chlorphenyl	70	24[d]
54	2-Fluorphenyl	50	—
55	2-Trifluormehtylphenyl	n.d[a]	—
56	4-Methylphenyl	90	8[d]
57	3-Methylphenyl	90	14[d]
58	Indan-4-yl	85	8[d]
59	4-Morpholinophenyl	n.d[a]	—
60	4-Methoxyphenyl	85	42[c]
61	2,4-Dimethoxyphenyl	70	88[c]
62	Benzyl	n.d[a]	—
63	Cyclopentanemethyl	n.d[a]	—

[a] No conversion to product. [b] Yield is calculated after purification from the starting loading of the resin. [c] Purified *via* column chromatography on silica gel. [d] Reversed-phase semipreparative HPLC purification.

Due to unreactivity of some phenacyl esters towards TFA-mediated cyclization, other conditions[27] were screened on the representative examples: *N*-benzyl-phenacyl ester **47**, *N*-cyclopentanemethyl phenacyl ester **48** and *N*-2,4-dinitrophenyl-phenacyl ester **31** were heated in sulphuric acid, acetic acid, polyphosphoric acid, NMP or simply melted. Unfortunately, no conversion to desired products was observed.

Finally, as mentioned earlier, Wang *et al.*[10] managed to convert *N*-methyl phenacyl ester to corresponding 3-HQ by sodium hydride in THF. Thus, we tested this procedure, however, we only observed very rapid hydrolysis of ester to the carboxylic acid, without traces of desired product.

We successfully developed the solid-phase synthetic approach applicable for the preparation of collection of *N*-substituted anthranilic acid derivatives. The methodology covers wide range of substrate scope; aromatic substitution can



Scheme 4 Silane-based reductive amination on solid phase. Reagents and conditions: (i) TMSOK, THF, r.t., 16 h; (ii) 2-bromoacetophenone, triethylamine, DMF, r.t., 16 h; (iii) benzaldehyde, Bu_2SnCl_2, phenylsilane, THF, reflux, 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,[6,7] 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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