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# Synthesis of Highly Functionalized 4-Aminoquinolines

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*Dedicated to Professor Dieter Enders on the occasion of his 70th birthday*

***Abstract:*** *A diverse set of highly substituted 4-aminoquinolines was synthesized from ynamides, triflic anhydride, 2-chloropyridine, and readily accessible amides in a mild one-step procedure.*

Quinolines are well known for their antimalarial properties,[1] with prominent examples including chloroquine, amodiaquine, and mefloquine (Figure 1). However, owing to the increasing resistance towards these and other antimalarial drugs[1a,2] and the spreading of resistant *Plasmodium falciparum* species,[3] the synthesis of new antimalarial agents is of great importance.[2a,4]

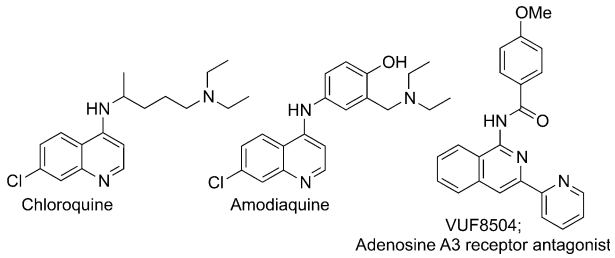
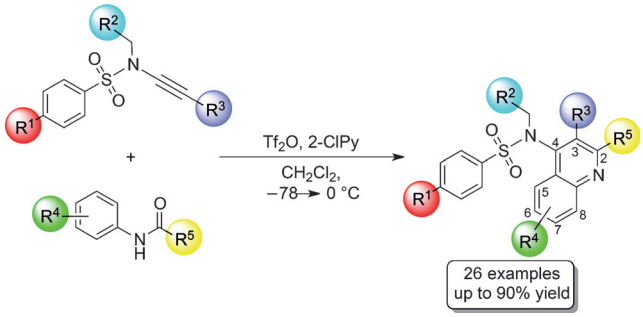



***Figure 1.*** Pharmaceutically relevant isoquinoline and 4-aminoquinoline derivatives.[4a,5]

4-Amino-substituted quinolines are of particular pharmaceutical interest,[4a,6] and over the years, several synthetic routes to these compounds have been explored.[7] The main drawback of a lot of the existing quinoline syntheses is the difficulty of functionalization at the C2 and C3 positions.

Herein, we present the synthesis of a diverse array of new, highly substituted 4-aminoquinolines from sulfonyl ynamides and electrophilically activated amides. In contrast to other methods, this approach allows for substitution at the C2 and C3 as well as at the C5 to C8 positions. Furthermore, the installed 4-amino group is accessible after deprotection, thus providing further points of diversity (Scheme 1).




***Scheme 1.*** Synthetic diversity of the developed approach towards 4-aminoquinolines.

Quinolines can be made in several different ways. More recently developed approaches for the formation of quinolines are based on the conversion of 2-alkynyl arylazides into substituted 4-acetoxyquinolines under gold catalysis,[8] one-pot $InCl_3/SiO_2$ catalyzed reactions towards 4-methylquinolines,[9] and the use of ring-closing metathesis to access 4-hydroxy- or 4-methylquinolines.[10] 4-Phenylquinolines are accessible by a $Yb(OTf)_3$ catalyzed multicomponent reaction[11] or by a "green" solvent-free one-pot process between 2-aminoaryl ketones and aryl acetylenes.[12] 4-Aminoquinolines can be prepared by the reduction of quinoline-4-phenylhydrazine,[13] by hypobromite oxidation of 2,3-dimethylquinoline-4-carboxyamides,[14] via a 4-chloroquinoline precursor,[6a] by rearrangements of pyrazolium-3-carboxylates via pyrazol-3-ylidene intermediates,[15] by reacting 2-(trifluoromethyl)-4*H*-3,1-benzoxazinones with ynamines,[16] or by an aerobic oxidative Pd-catalyzed imidoylative coupling with double C–H activation.[17] These approaches usually allow for some degree of functionalization on the quinoline core, and with the 4-chloro precursor strategy, 4-aminoquinolines with a wide range of functional groups at the C5 to C8 positions have been synthesized and found to be promising in antimalarial assays.[18] However, accessing both the C2, C3 and the C5 to C8 positions has remained a challenge thus far.

The key to our synthesis of 4-aminoquinolines is the activation of the amides with a combination of triflic anhydride[19] ($Tf_2O$) and 2-chloropyridine (2-ClPy), a procedure used by Movassaghi and co-workers to prepare a wide

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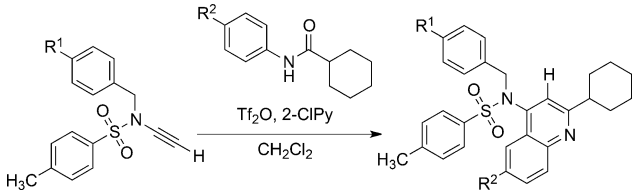
range of pyridine, pyrimidine, and β-carboline derivatives.[20] While exploring the scope of this transformation, they were also able to prepare a few 3-phenyl-4-oxazolidinone-based 4-aminoquinolines. Our approach, however, encompasses a modular ynamide approach, providing full flexibility with regard to substitution at the C2 and C3 positions as well as indirect access to the 4-amino position. Structurally related 1-aminoisoquinolines have recently been synthesized by employing a similar approach; silver triflate was employed to cyclize 2-alkynylbenzaldoximes, which were then transformed into 1-aminoisoquinolines in the presence of $Tf_2O$ and 2-fluoropyridine-activated amides in a domino fashion.[21]

To investigate the synthesis of 4-aminoquinolines, first, several sulfonyl ynamides were prepared.[22] These can generally be accessed by attaching acetylene derivatives onto sulfonamides by copper[23] or iron[24] catalysis, by copper-catalyzed alkynylative cross-couplings of 1,1-dibromoalkenes with sulfonamides,[25] or by the formylation of sulfonamides followed by dibromomethylenation and subsequent elimination to the ynamide.[26] We proceeded by protecting tosylamines by a reductive amination with a benzaldehyde derivative or furfural[27] or by reacting benzylamine with tosyl chloride; one of the prepared amides was analyzed by X-ray crystallography (**61**; for details see the Supporting Information). An acetylene bromide was then coupled with the desired sulfonamide in the presence of copper sulfate (0.1 equiv), 1,10-phenanthroline (0.2 equiv), and potassium carbonate as the base. We thus prepared 14 different ynamides in good to reasonable yields (see Figure 2, route A). One of the prepared ynamides was analyzed by X-ray crystallography (**7**; for details see the Supporting Information). Similar ynamide systems were recently also employed in gold-catalyzed [2+2+2] cycloadditions for the formation of 4-aminopyrimidines.[28]

The acetylene bromides can easily be made on larger scale (5 g) by bromination of the alkyne precursor with *N*-bromosuccinimide with catalytic silver nitrate in acetone, but care should be taken as some of the products were found to be volatile.[23f] In order for the coupling to work as desired, it was helpful to thoroughly grind the copper sulfate and 1,10-phenanthroline before use. To synthesize an even greater diversity of ynamides (and thus differently C3-substituted quinolines), the corresponding terminal ynamide can first be prepared by deprotecting the triisopropylsilyl-protected ynamide (to obtain **5**–**9**, **16**) and subsequently be converted in a Sonogashira process (route B),[29] as shown for compounds **24**–**26**. Alternatively, a procedure recently published by Anderson et al.,[30] which involves the synthesis of a dichloroenamide precursor and subsequent elimination and halogen exchange, followed by quenching with a suitable electrophile (route C) provides very convenient access to a wide range of ynamides. Using this method, we were able to prepare larger quantities of our ynamides with ease, but it must be stressed that it is crucial to work under fully water-free conditions to prevent the formation of a mixture of products (e.g., of the desired ynamide and the terminal ynamide resulting from hydrolysis).

To explore the scope of the quinoline-forming reaction, several different amides were synthesized by acetylating anilines or using conventional peptide chemistry. The amides were activated with $Tf_2O$ and 2-chloropyridine at −78 °C, before they were reacted with ynamides at 0 °C to form quinolines. The optimized conditions for this transformation were identified by performing a series of experiments (Table 1). It was found that increasing the activated amide/ynamide ratio yielded larger amounts of side products, resulting in very complicated isolation.

***Table 1:*** Selected examples for the optimization of the reaction conditions for the generation of 4-aminoquinolines by amide activation.




| $R^1$ | $R^2$ | Amide [equiv] | 2-ClPy [equiv] | $Tf_2O$ [equiv] | Ynamide [equiv] | $T$[a] [°C] | Yield[b] [%] |
|---|---|---|---|---|---|---|---|
| OMe | H | 1.0 | 1.2 | 1.2 | 1.2 | 0 | 55 |
| OMe | H | 1.3 | 1.3 | 1.3 | 1.0 | 0 | 30 |
| OMe | H | 1.3 | 1.3 | 1.3 | 1.0 | 50 | 26 |
| OMe | H | 1.3 | 2.6 | 1.5 | 1.0 | 0 | 32 |
| H | H | 1.0 | 1.2 | 1.2 | 1.2 | 0 | 25 |
| H | H | 1.3 | 1.3 | 1.3 | 1.0 | 0 | 41 |
| H | H | 1.3 | 1.3 | 1.3 | 1.0 | 50 | 18 |
| H | H | 1.0; 4Å M.S. | 1.2 | 1.2 | 1.2 | 0 | 51 |
| H | Cl | 1.0 | 1.2 | 1.1 | 1.2 | 0 | 43 |
| H | Cl | 1.3 | 1.3 | 1.2 | 1.0 | 0 | 23 |
| H | Cl | 1.0; 4Å M.S. | 1.2 | 1.1 | 1.2 | 0 | 53 |

[a] The reaction mixtures were prepared at −78 °C and stirred at this temperature for 5 min before they were stirred at the indicate temperature; heating was facilitated by microwave irradiation. [b] Yields of isolated products.

Additionally, it was found that using the ynamide as the limiting reagent did not always improve the conversion and that an increased amount of 2-chloropyridine did not have a clear beneficial effect. Heating the reaction was not advantageous, but in some cases, the quinolines (e.g., **36** and **38**) were still formed in reasonable yields (at 120 °C under microwave irradiation for 20 min). The best results were obtained with the conditions originally proposed by Movassaghi and co-workers, with the additional use of activated 4 Å molecular sieves to remove any traces of water (which is detrimental to the reaction) and for consistent yields.

For the prepared 4-aminoquinolines to be useful from a pharmaceutical point of view, it is highly desirable to be able to deprotect the tosylated and benzylated amines with ease. The free amines can then be used to prepare libraries for screening purposes. However, conventional detosylation reactions usually employ inelegant and harsh conditions, such as lithium metal with catalytic amounts of naphthalene at low temperatures,[31] that are unsuitable for more delicate compounds. Fortunately, the tosyl group can be easily removed according to the procedure recently reported by Tomooka et al. and the use of potassium diphenylphosphide;[32] quinoline **62** was thus isolated in 79% yield

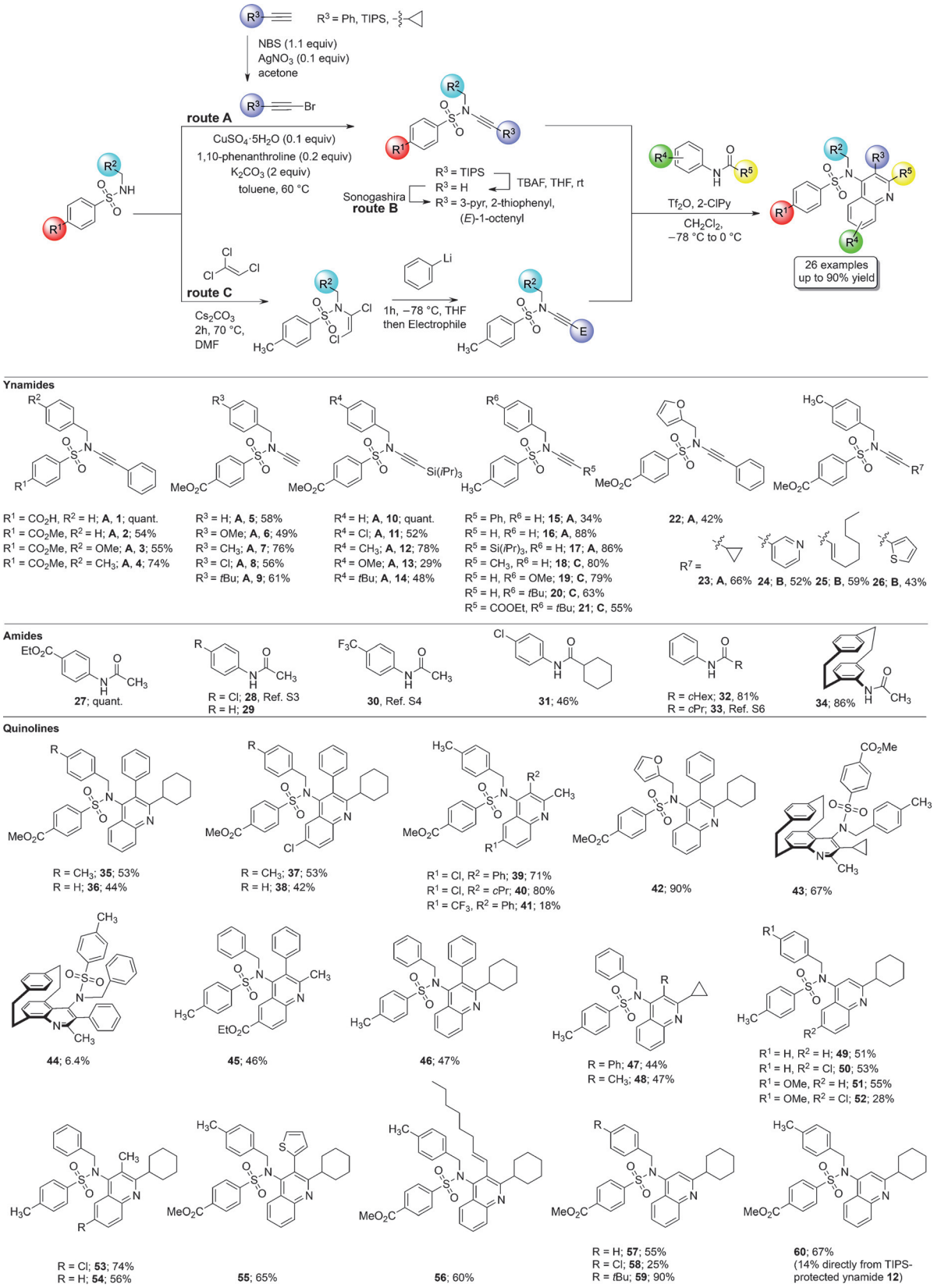
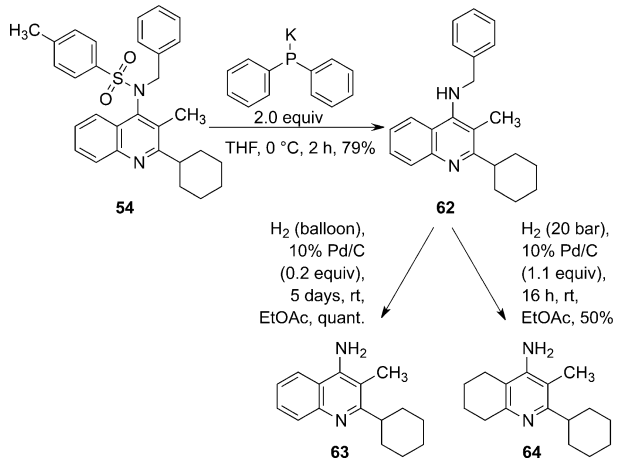



***Figure 2.*** Modular synthesis of functionalized 4-aminoquinolines via ynamides prepared by A) copper catalysis, B) Sonogashira chemistry, or C) elimination, lithium–halogen exchange, and quenching of the dichloroenamide intermediate with a suitable electrophile. E = electrophile, NBS = *N*-bromosuccinimide, TBAF = tetrabutylammonium fluoride, TIPS = triisopropylsilyl.




***Scheme 2.*** Stepwise detosylation and debenzylation of the prepared 4-aminoquinolines.

(Scheme 2). Subsequently, the benzyl protecting group at the 4-amino position can be easily removed by hydrogenation with wetted Pd/C (0.2 equiv) and a balloon of hydrogen gas at room temperature for several days or by several iterations using the H-Cube flow system with a Pd/C cartridge at 60 °C. A quick solvent screen revealed that the reaction did not proceed notably faster in ethanol or acetic acid. In an attempt to find reaction conditions for faster deprotection, we submitted *N*-benzyl-4-aminoquinoline to 20 bar of $H_2$ with 0.2 equiv of dry Pd/C. As after three hours no promising conversion was observed, we increased the catalyst loading to 1.1 equiv, and the reaction mixture was stirred overnight in the pressure reactor. To our surprise, not only the *N*-benzyl group was removed, but also the benzene ring of the quinoline was reduced, and product **64** was thus obtained. The benzyl group could also be removed first under identical conditions with similar yields (91 %), at which point the tosyl group can be removed with $SmI_2$.[33] Even though the tosyl deprotection was observed to occur almost instantaneously (according to LCMS and TLC), the potassium diphenylphosphide approach was preferred because of reproducibility issues with the $SmI_2$ route.

X-ray crystal structures were obtained for two of the synthesized quinolines, unequivocally confirming the structure and regiochemistry of the proposed products (Figure 3). When quinoline syntheses with TIPS-protected ynamides were attempted, the TIPS group was removed during the reaction, and only quinolines with a proton at the C3 position were obtained. As compound **60** can be obtained either from the terminal ynamide in 67 % yield or from the TIPS ynamide in 14 % yield, all other TIPS ynamides were also deprotected before use. To show the broad applicability of this method, we showed that the ynamides also readily react with paracyclophane-based amides and thus yield compounds **43** and **44** creating very interesting planar chiral compounds, albeit in a racemic manner. However, owing to issues with purification, product **43** was obtained as a mixture with an inseparable side product and **44** in rather low yield.

In conclusion, we have shown that electrophilically activated amides react readily with sulfonyl amides to form

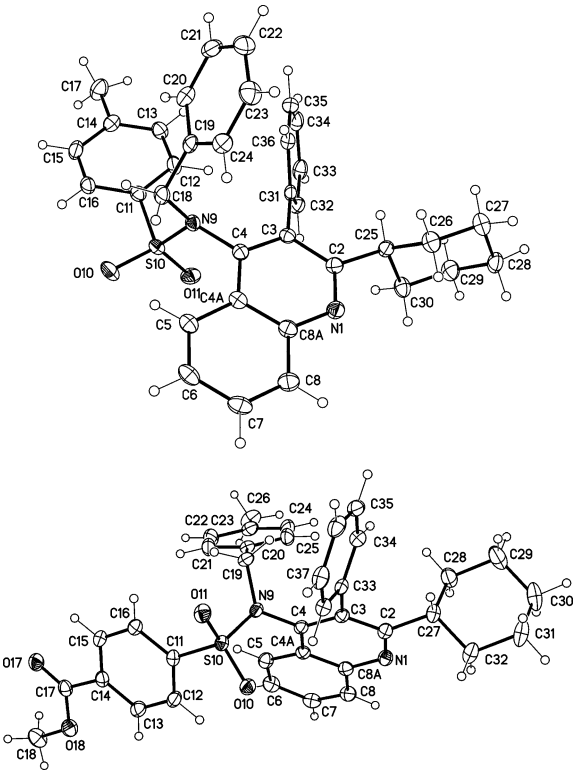



***Figure 3.*** Molecular structures of the 4-aminoquinolines **46** (top) and **35** (bottom); ellipsoids set at 50 % probability.

a diverse set of 4-aminoquinolines. The ynamides can be easily modified by Sonogashira couplings or prepared via a dichloroenamide precursor, which results in various substituents at the quinoline C3 position, and the choice of amide allows for great diversity at the C2 and C5 to C8 positions. Complex amides, for example, those derived from paracyclophanes, are also tolerated. Furthermore, the prepared 4-aminoquinolines can be deprotected in excellent yields.[34]

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[34] CCDC 1402829 (**7**), 1402826 (**35**), 1402827 (**46**), and 1402828 (**61**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre. For details see the Supporting Information.

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