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Ugi–Smiles Couplings of 4-Substituted Pyridine Derivatives: A Fast Access to Chloroquine Analogues

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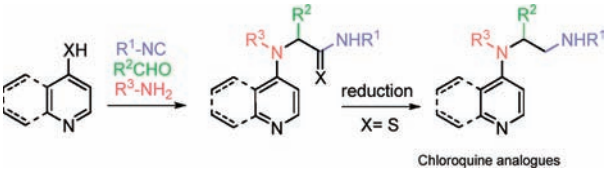
ABSTRACT

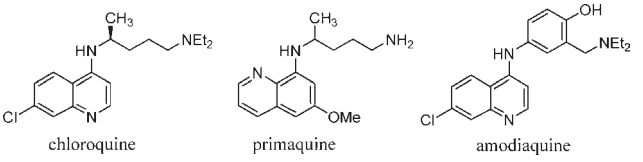


4-Hydroxy and mercapto pyridines were successfully tested in Ugi–Smiles couplings. Such multicomponent reactions applied to quinoline derivatives afford a very convenient and short synthesis of antimalarial analogues.

The aminoquinoline motif is a prominent feature of antimalarial pharmacophores, as for instance in chloroquine, primaquine, or amodiaquine (Scheme 1). Malaria is the fifth leading cause of death from infectious diseases worldwide and the second in Africa.[1] The emergence of multidrug-resistant falciparum malaria creates continuing demand for new biologically active compounds. Multicomponent reactions (MCRs) constitute very efficient synthetic tools to generate diversity.[2] Chibale and co-workers have recently employed a Ugi coupling of 4-aminoquinolines to synthesize new potential antimalarial compounds.[3]

A few years agon we reported a new Ugi-type coupling for rapid access to aminoaryl and heteroaryl carboxamides.

Scheme 1. 4-Hydroxy Pyridines in Ugi–Smiles Coupling



This Ugi–Smiles (US) reaction, initially developed using electron-deficient phenols as acidic partner,[4] was soon after extended to hydroxy heterocyclic compounds, such as 2-hydroxy pyridines, pyrimidines,[5] and pyrazines[6] (Scheme 2). In connection with our ongoing projects on extending the scope of this new isocyanide-based MCR, we envisaged a high modular synthesis of aminoquinolines by assembling the quinoline moiety and the amine in the key step.

The formation of antimalarial quinolines using Ugi–Smiles couplings requires the use of 4-hydroxy- or 4-mercapto-substituted quinoline as starting material. However, following our computational study of the Ugi–Smiles reaction with

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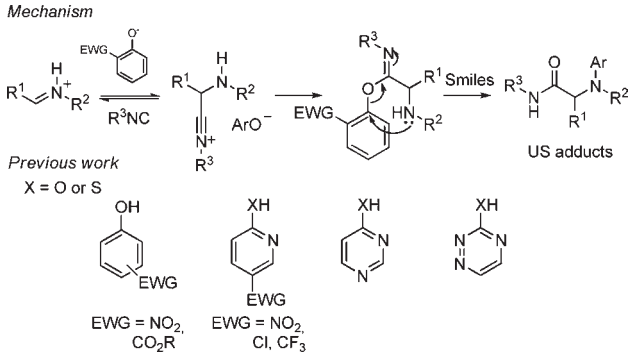
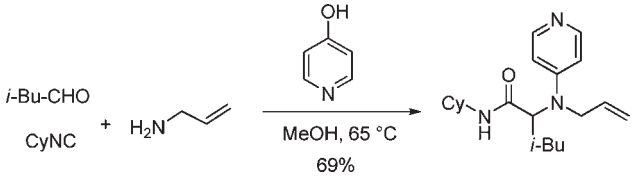
Scheme 2. Ugi–Smiles Coupling Mechanism and Previous Work



nitrophenol, 4-substituted pyridines are expected to be less reactive than their 2-analogues because of the existence of potential hydrogen bonds in the reactive intermediates of the latter.[4b,7] As all reported Ugi–Smiles of pyridines and quinolines were perfomed on their 2-substituted derivatives, we initiated this study by testing 4-hydroxy pyridine. For this purpose, classical conditions were tested, and methanol was selected as a solvent of choice to solubilize all the partners. A stoichiometric amount of 4-hydroxy pyridine, cyclohexyl isocyanide, allyl amine, and isovaleraldehyde heated for two days at 65 °C affords the corresponding 4-amino pyridine in 69% isolated yield (Scheme 3).

Scheme 3. 4-Hydroxy Pyridines in Ugi–Smiles Coupling



Surprisingly, 4-hydroxy pyridine undergoes smooth couplings under these conditions, whereas 2-hydroxy pyridine requires the presence of an electron-withdrawing group to react.[4a] The difference of reactivity between both regiomers is not easy to rationalize. It is worth noting that 4-hydroxy pyridine derivatives such as mesylates, tosylates, or 4-halogeno pyridines generally require harsher conditions for SNAr: high temperature and pressure[8] or catalyzed processes.[9] In our case, an activation due to the acidity of the hydroxy heterocycle or to the proticity of the solvent cannot be excluded.

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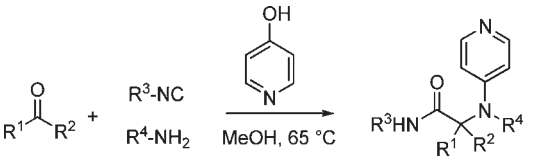
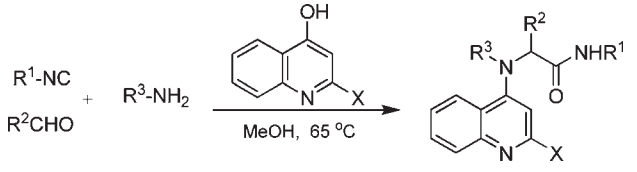
Table 1. 4-Hydroxy Pyridine in Ugi–Smiles Coupling



entry	R^1	R^2	R^3	R^4	yield (%)
1	*i*-Bu	H	Cy	All	69
2	*i*-Bu	H	Cy	$MeO(CH_2)_2$	65
3	*i*-Bu	H	Cy	$3,4\text{-}(MeO)_2Ar(CH_2)_2$	72
4	*i*-Bu	H	*t*-Bu	All	43
5	Et	H	4-ClBn	$HCCCH_2$	50
6	$(CH_2)_4$		4-ClBn	$MeO(CH_2)_2$	26
7	*i*-Bu	H	4-ClBn	H	40

The scope of the reaction was next examined varying the other partners. As usually observed, ketones are less reactive than aldehydes, and the yields do not exceed 30% (Table 1, entry 6). Various amines could be used. Albeit less efficient, ammonia undergoes smooth coupling under microwave irradiation.[10]

Table 2. 4-Hydroxyquinolines in Ugi–Smiles Coupling



entry	X	R^1	R^2	R^3	yield (%)
1	CF_3	Cy	*i*-Bu	All	71
2	CF_3	Cy	4-ClPh	All	36
3	CF_3	4-MeOBn	*i*-Bu	All	69
4	CF_3	Cy	4-ClPh	$MeO(CH_2)_2$	36
5	H	Cy	*i*-Bu	All	46
6	H	4-MeOBn	*i*-Bu	$MeO(CH_2)_2$	60
7	H	4-MeOBn	*i*-Bu	All	47
8	H	Cy	*i*-Bu	4-ClBn	49
9	H	*t*-Bu	*i*-Bu	$MeO(CH_2)_2$	7

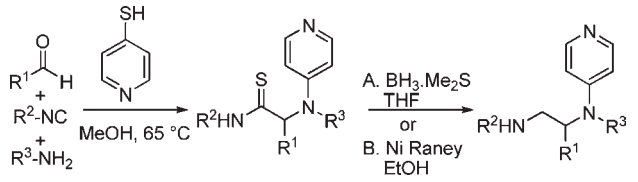
After these preliminary results with pyridines, we next examined the behavior of quinolines to obtain new muticomponent access to antimalarial drugs. The reaction performed in the same conditions affords the desired adducts in satisfying yields with both 4-hydroxy quinoline and the 2-trifluoromethyl-substituted one. Various aldehydes, amines, and isocyanides have been coupled successfully as listed in Table 2, except for *tert*-butylisocyanide.

(10) Barthelon, A.; El Kaim, L.; Gizzi, M.; Grimaud, L. *Synlett* **2010**, 2784–2788.

This method seems to be quite appealing to obtain chloroquine analogues, as the amine and the quinoline could be linked via a four-component coupling. In order to approach even closer to the structure of active drugs, the amide moiety should be reduced. Borane-induced reduction of Ugi adducts was reported by Tron and Giovenzana.[11] Unfortunately, the reduction of these adducts under their reported conditions failed to give any diamine.

Facing problems in the reduction step, we decide to examine the behavior of the mercapto heterocycle analogues. Their Ugi–Smiles couplings could form thioamides, privileged functional groups for further synthetic transformations. 4-Mercapto pyridine was first evaluated in Ugi–Smiles couplings. The corresponding *N*-pyridino thiocarboxamides were obtained in moderate to good yields as displayed in Table 3. The resulting thiocarboxamides could be further transformed into diamines under reductive conditions. In our case, the reduction could be performed either using $BH_3 \cdot Me_2S$ in THF or with Raney Nickel in ethanol. The corresponding diamines, which constitute *N*,*N*-dimethylaminopyridine analogues, were isolated in good yields (Table 3).

Table 3. 4-Mercaptopyridine in Ugi–Smiles Coupling

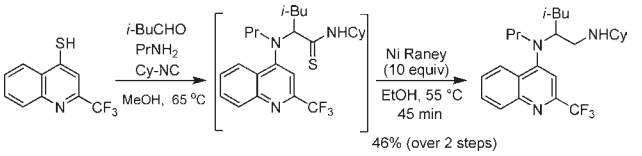


entry	R^1	R^3	R^4	US (%)	reduction (%)
1	*i*-Bu	Cy	All	80	
2	*i*-Bu	4-ClBn	All	57	
3	*i*-Bu	Cy	$MeO(CH_2)_2$	55	60[a]
4	*i*-Bu	Cy	$Ph(CH_2)_2$	60	73[a]
5	*i*-Bu	Cy	Pr	55	76[a]
6	$4\text{-}ClC_6H_4$	Cy	$MeO(CH_2)_2$	34	

[a] The yields are given for condition A, except for entry 3 tested under the two reductive conditions: A 60% and B 59%.

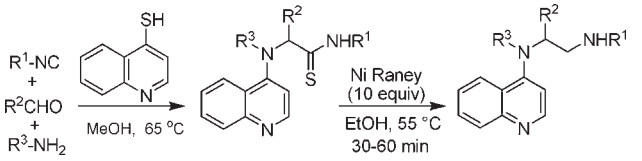
The whole sequence was then tested using the 4-mercapto-2-trifluoromethylquinoline. The reduction of the crude US adduct with borane gave a complex mixture, but the attempted aminoquinoline was isolated in 46% over two steps by treatment with Raney Nickel in ethanol at 55 °C for 30 min to 1 h (Scheme 4). The scope of this sequence was next examined. In all cases, the US products were isolated in excellent to good yields (Table 4), and the desulfurization of thioamides afforded the corresponding diamines with satisfying yields (Table 4).

Scheme 4. Two-Step Access to Aminoquinolines



To conclude, 4-hydroxy and 4-mercapto pyridine derivatives are efficient partners in Ugi–Smiles couplings, being even more reactive than their 2-substituted analogues, which require further activating groups. We developed an efficient and straightforward acess to 4-aminoquinolines, which makes the method potentially attractive for the synthesis of new antimalarial pharmacophores.

Table 4. 4-Mercaptoquinoline in Ugi–Smiles Coupling



entry	R^1	R^2	R^3	US (%)	desulfurization (%)
1	Cy	*i*-Bu	Pr	87	55
2	Cy	*i*-Pr	Pr	81	42
3	Cy	H	Pr	56	67
4	*t*-Bu	*i*-Bu	Pr	81	39
5	*t*-Bu	*i*-Pr	Pr	78	41
6	*t*-Bu	H	Pr	51	67
7	Cy	*i*-Bu	Bu	99	75
8	Cy	*i*-Bu	$Ph(CH_2)_2$	98	
9	Cy	*i*-Bu	$MeO(CH_2)_2$	82	
10	Cy	4-ClPh	Pr	89	37
11	Cy	3,4,5-$(MeO)_3$Ph	$Ph(CH_2)_2$	64	

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Supporting Information Available. Experimental procedures and spectral data for new compounds are detailed. This material is available free of charge via the Internet at http://pubs.acs.org.

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