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Convenient Synthetic Approach to 2,4-Disubstituted Quinazolines

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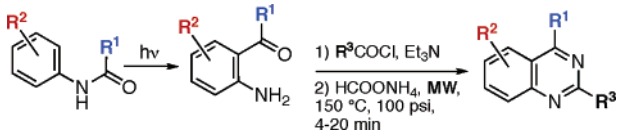
ABSTRACT



2,4-Dialkyl or aryl quinazolines have been prepared in three steps starting from easily available anilides. A photochemically induced Fries rearrangement of the anilides gave several *ortho*-aminoacylbenzene derivatives that were acylated at the NH_2. These acylamides underwent rapid cyclization to 2,4-disubstituted quinazolines (and benzoquinazolines) in the presence of ammonium formate under microwave activation. This procedure is compatible with different functional groups and allowed also the preparation of new quinazolines derived from naturally occurring amino acids.

Quinazolines have recently been the object of deep investigation due to their different biological properties. This heterocycle is present in powerful inhibitors of the epidermal growth factor (EGF) receptors of tyrosine kinase[1] and in molecules that show remarkable activity as anticancer,[2] antiviral,[3] and antitubercular agents.[4] Quinazolines have also been employed as ligands for benzodiazepine and GABA receptors in the CNS system[5] or as DNA binders.[6]

This large interest in medicinal chemistry stimulated the development of new and more efficient syntheses of this class of compounds.[7] The classical synthetic approach to quinazolines (the Niementowski quinazoline reaction)[8] involves the formation of the intermediate 3(*H*)-4-quinazolinone (derived from antranylic acid) followed by formation of 4-chloroquinazoline and subsequent nucleophilic aromatic substitution

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at the pyrimidine ring.[9] Although efficient, this method can be applied to the preparation of quinazolines substituted in position 4 with heteroatoms (N, O, S). The introduction of C substituents in position 4 has been limited to simple alkyl groups.[10] Other syntheses of 2,4-disubstituted quinazolines have been described starting from substituted anthranilic acids or *o*-fluorobenzoyl derivatives.[11] As relatively few examples of these kinds of compounds are available, there are still limits in preparing 2,4-disubstituted quinazolines with large molecular diversity.[12]

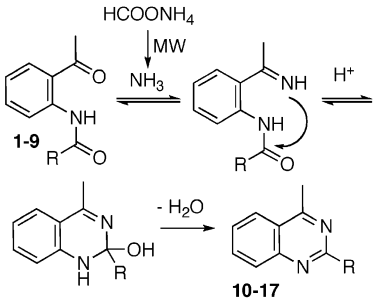
The cyclization of an amide derived from *ortho*-aminophenone in the presence of ammonia at high temperature (Bischler's synthesis) is a potential alternative.[13] However, this reaction has not found a practical application due to the harsh conditions employed, which are not compatible with many functional and protecting groups.

Nowadays, microwave (MW) irradiation provides a solution to reactions that require heating for long periods of time.[14] Following our interest in this field,[15] we decided to explore the possibility to accomplish Bischler's synthesis of quinazolines under MW irradiation in the presence of a source of NH_3. Compound **1** was chosen as the model to find the best reaction conditions. Reaction with aqueous or ethanolic ammonia did not give any results, whereas the use of neat $HCOONH_4$ allowed the formation of **10** in good yields. The reaction was carried out in a sealed vial by mixing $HCOONH_4$ and **1**, heating at 100 °C for 3−6 min, and maintaining the internal pressure at 150 psi.[16] To have good results, no solvent must be used in the reaction. When we tried to introduce DMF, H_2O, or MeOH to allow the reaction to be more homogeneous, no trace of **10** was observed even after prolonged heating. Probably $HCOONH_4$ is decomposed by the heating, and the NH_3 formed generates the imine that cyclizes in the acid environment due to the presence of excess ammonium formate (at least 20 equiv). Dehydration induced by the high temperature and the acid gives the required quinazoline (Scheme 1).

Different amides derived from *o*-amino acetophenone were prepared and cyclized, always giving good yields of the expected products (see Scheme 1). When amides, derived from *N*-Boc-protected α-amino acids, were cyclized, we observed the formation of the corresponding *N*-formyl derivative. This product was probably formed by thermic deprotection of the Boc and further reaction with the formate ion at high temperature. In the case of compounds **13** and **18** exclusively, the *N*-CHO derivative was isolated, whereas for compounds **14**, **15**, and **17**, the *N*-Boc derivative was the unique product observed. In the case of compound **16**, the *N*-Boc product was formed together with minor amounts (15%) of the *N*-CHO.[17] However, the *N*-Boc or the *N*-COH derivative can be easily deprotected to generate the corresponding amine suitable for further functionalization. To expand this process to a larger set of molecules, we required a general method to produce differently substituted *o*-aminophenones. Few of them are in fact commercially available, and their synthesis can be carried out via Friedel−Crafts acylation of anilines or through multistep procedures starting from *o*-nitro aromatics.[18]

The Fries rearrangement of esters is a useful method for the preparation of different *o*-hydroxy phenones with a high level of diversity at the alkyl substituent and around the aromatic ring.[19] Unfortunately this reaction has not been largely explored on amides as only few examples of rearrangements starting from simple acetanilides are de-

Scheme 1



R	product[a]		yield (%)[b]
$PhOCH_2$	**1**	**10**	65
$PhCH_2CH_2$-	**2**	**11**	55
EtOOCCO-	**3**	**12**	50
$BocNHCH_2$-	**4**	**13**	65[c]
(*S*)-MeCH(NHBoc)-	**5**	**14**	60[d]
(*S*)-Me_2CHCH(NHBoc)-	**6**	**15**	63[d]
(*S*)-$PhCH_2CH$(NHBoc)-	**7**	**16**	60[d]
(*S*)-$BnOOCCH_2CH_2CH$(NHBoc)-	**8**	**17**	60[d]
(*S*)-$CbzNH(CH_2)_4CH$(NHBoc)-	**9**	**18**	65[c]

[a] General reaction conditions: $HCOONH_4$ (20 equiv), 150 W, max internal temperature and pressure of 150 °C and 150 psi, 3−9 min. [b]Yields of isolated compounds. [c]Yields relative to the *N*-formyl derivative. [d]Yields relative to the NHBoc derivative.

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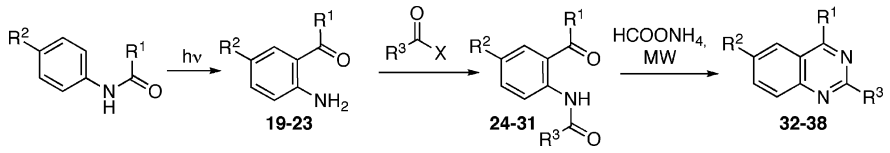
Table 1. Three-Step Sequence for the Transformation of Anilides into 2,4-Disubstituted Quinazolines

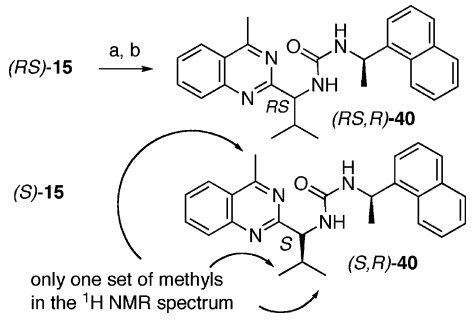


entry	R^1	R^2	aniline (yield %)	R^3	amide (yield %)	cyclization conditions	quinazoline (yield %)[a]
1	$PhCH_2-$	TBDMSO−	**19**	$PhCH_2CH_2-$	**24**	150 W, 150 °C,	R^2 = OH **32**
			66		81	100 psi, 4 min	78
2	$PhCH_2CH_2-$	TBDMSO−	**20**	*p*-CN-C_6H_4-	**25**	150 W, 150 °C,	R^2 = OH **33**
			56		73	100 psi, 16 min	76
3	$CH_3(CH_2)_{10}-$	TBDMSO−	**21**	$PhCH_2CH_2-$	**36**	50 W, 150 °C,	R^2 = OH **34**
			55		80	100 psi, 9 min	60[b]
5	$CH_3(CH_2)_{10}-$	TBDMSO−	**21**	$CH_3(CH_2)_{10}-$	**27**	50 W, 150 °C,	R^2 = OH **35**
					73	100 psi, 10 min	72
6	$CH_3(CH_2)_{10}-$	TBDMSO−	**21**		**28**	100 W, 150 °C,	R^2 = OH **36**
					80	100 psi, 16 min	73
7	$CH_3(CH_2)_{10}-$	TBDMSO−	**21**	*o*-Cl-C_6H_4-	**29**	100 W, 150 °C,	R^2 = OH **37**
					72	100 psi, 18 min	61[c]
8	$PhCH_2CH_2-$	Cl	**22**	Me_2CH-	**30**	150 W, 150 °C,	**38**
			56		68	100 psi, 16 min	51
9	MeCH(NHBoc)	H	**23**	$CbzNHCH_2-$	**31**	150 W, 150 °C,	**39**
			51		71	100 psi, 9 min	74[d]

[a] Yields of compounds isolated by column chromatography on silica gel. [b] The corresponding OTBDMS derivative was isolated in 15% yield. [c] The corresponding OTBDMS derivative was isolated in 18% yield. [d] When amide **31** was heated at 150 W, 150 °C, and 100 psi for 20 min, the quinazoline **39** with NHCO in the place of the NHBoc group was obtained.

scribed. The reaction takes place by heating in the presence of corrosive Lewis acids that are not compatible with several functional and protective groups such as Cbz and Boc.[20] Thus, we decided to explore the possibility of doing a photochemically induced Fries rearrangement on amide, finding that the reaction could be effectively carried out using a low-pressure Hg lamp at 254 nm in cyclohexane as the solvent. Better results were obtained with MeCN, although the reaction did not go to completion and some starting material was recovered. The best yields were obtained using deoxygenated MeCN and irradiating for 24 h at room temperature. Following this procedure, compounds **19**−**23** were obtained in acceptable yields (see Table 1).[21] Amides **24**−**30** were obtained by reaction with different acyl chlorides and Et_3N in CH_2Cl_2. Amide **31** was prepared by coupling **23** with *N*-Cbz-GlyOH in the presence of DCC, DMAP, and Et_3N in DMF. These products were submitted to microwave-assisted cyclization with $HCOONH_4$ that formed quinazolines **32**−**39** in acceptable to good yields (see Table 1).[22] During the reaction, the TBDMS protection was removed and quinazolines **32**−**37** were isolated with the free OH. The cyclization seemed to be influenced by the steric hindrance. When R^3 was an aromatic or a branched alkyl substituent (entries 2 and 6−8), heating for more than 10 min was necessary to obtain the product. The yields and the conditions reported in Scheme 1 and Table 1 are relative to reactions carried out on a 0.1 g scale of starting amides **1**−**9** and **24**−**31**. However, when cyclization of **24** was repeated on a 1.0 g scale, quinazoline **32** was isolated in 72% yield after 20 min of heating (150 W, 150 °C, 100 psi using an 80 mL vial).

Scheme 2



(a) TFA/Et_3SiH, CH_2Cl_2, room temperature, 12 h. (b) (*R*)-1-Naphthylethylisocyanate, Py, room temperature, 12 h, (86%).

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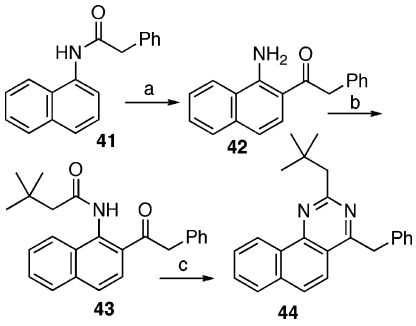
(21) Different amounts of the starting material were always observed at the end of the photo-Fries rearrangement. Increasing the reaction times gave degradation of the starting material without increasing the formation of the acetophenone. The yields reported (from 48 to 66%) are calculated without considering the recovery of the starting material that pushes yields to values of 65−80%.

Scheme 3



(a) Low-pressure Hg lamp, 254 nm, MeCN, 36 h, 65%. (b) Me_3CCH_2COCl, CH_2Cl_2, Et_3N, room temperature, 2 h (92%). (c) $HCOONH_4$, microwaves, 150 W, 150 °C, 100 psi, 14 min (86%).

To verify that racemization did not occur during the photo-Fries rearrangement and the microwave-assisted cyclization, the full synthetic procedure was repeated on the anilide derived from racemic Boc−Val−OH. The Boc was removed from the quinazoline. (*R*,*S*)-**15** was obtained, and free amine reacted with (*R*)-1-naphthylethylisocyanate to give diastereomeric (*RS*,*R*)-**40** (Scheme 2). The ^{1}H NMR 400 MHz spectrum of (*RS*,*R*)-**40** showed a marked difference in the resonances of the methyl groups due to the presence of two diastereoisomers.

When compound (*S*,*R*)-**40** was prepared using **15**, derived from L-Val, the NMR spectrum showed that racemization occurred in less than 10%.

This synthetic procedure can also be applied to the synthesis of benzoquinazolines,[23] starting from 1-naphthylamine. Amide **41** was prepared and submitted to photo-Fries rearrangement to give compound **42** that was coupled with 3,3-dimethylbutanoyl chloride and finally cyclized to **44** in 51% overall yield (Scheme 3).

In conclusion, we have developed a simple and rapid method for the synthesis of 2,4-disubstituted quinazolines and benzoquinazolines including enantiomerically pure quinazolines derived from naturally occurring amino acids. Moreover, compounds such as **39** can be considered as conformationally constrained scaffolds for the preparation of quinazoline arrays for hit discovery.

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Supporting Information Available: Experimental general procedure and characterization of compounds **10**−**23**, **32**−**39**, **40**, **42**, and **44**. This material is available free of charge via the Internet at http://pubs.acs.org.

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