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Solid Phase Synthesis of chiral 3-substituted Quinazoline-2,4-diones

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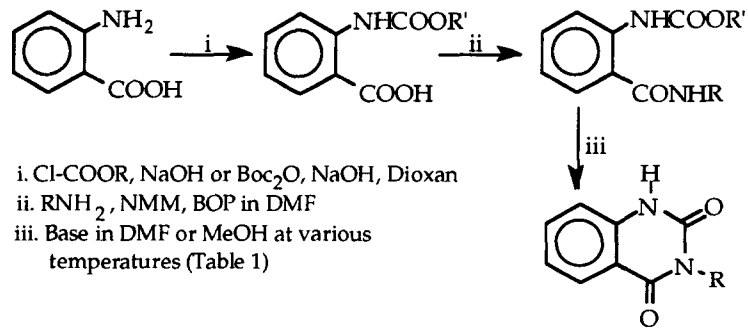
Abstract: The synthesis of chiral 3-substituted quinazoline-2,4-diones was performed starting from N-urethane anthranilamides. This synthetic pathway was applied in solid phase, from commercially available anthranilic acid that was bound to hydroxymethyl polystyrene resin via a carbamate linker. In both cases, cyclisation occurred under basic conditions to afford non-racemized quinazolinediones in high purity.

Quinazoline-2,4-diones are attractive pharmacophores. They present a wide range of pharmacological activities. They have been shown to possess anticonvulsant activity against electroshock[1a], they exhibit sedative and hypotensive activities[1b], they cause vasodilation[1c] in animals. They are also useful antiinflammatory agents.[1d] In recent years, quinazoline derivatives have attracted attention as potential inhibitors of protein tyrosine kinase.[1e] Hence, there are several synthetic pathways for their preparation[2], most of them starting from anthranilic acid derivatives. One of the first method of synthesis was described by Canonne and al.[2e], from 2-carbomethoxyphenyl isocyanate obtained from phtalic half-esters. We decided to use a more practical approach to synthesize our chiral quinazoline-2,4-diones, performing the synthesis from urethane protected anthranilamide, adapting the method described by Gadekar and al.[2b] We were particularly interested in the synthesis of chiral 3-substituted quinazoline-2,4-diones, in order to insert these structures in peptide chains to use them as constrained structures.



i. Cl-COOR, NaOH or Boc_2O, NaOH, Dioxan
ii. RNH_2, NMM, BOP in DMF
iii. Base in DMF or MeOH at various temperatures (Table 1)

Scheme 1. Synthesis of quinazoline-2-4-diones

[&]This paper is dedicated to the memory of Doctor François Winternitz.

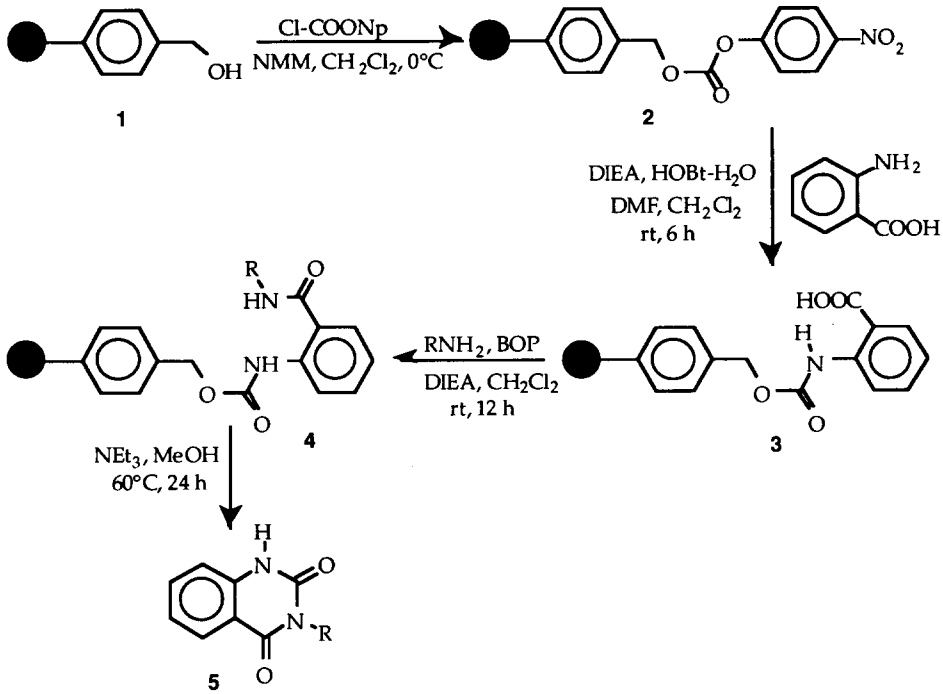
Anthranilic acid was converted into its N-urethane derivative using alkylchloroformate (Boc_2O, when R'= tBu) in 1M NaOH. Coupling of the C-terminal protected aminoacid (or amine) was achieved with BOP[3] in the presence of N-methylmorpholine (NMM), in DMF. Cyclisation was accomplished in DMF or MeOH, using NaOH, diazabicyclo[5,4,0]undec-7-ene (DBU) or NEt_3 as base, at various temperatures (Scheme 2 and Table 1). In order to optimize the cyclisation conditions, we have used different bases, along with several N-urethane protecting group. Results are reported in Table 1.

$R\text{-}NH_2$	R'	Base	t_R (hours)	t°C	mp°C	yield %
H-Gly-OMe	tBu	NaOH 2M (3 eq)	18	20	299-301[c]	81[c]
H-Ala-OMe	Bzl	NaOH 1M (3 eq)	12	''	268-270[c]	92[c]
''	''	DBU (5 eq)	6	60	134-136	93
H-βAla-OMe	Et	NaOH 1M (3 eq)	12	''	211-213	80[c]
H-Leu-OMe	Bzl	NaOH 2M (3 eq)	18	''	160-162[c]	88[c]
Z-Lys-OMe	Bzl	DBU (10 eq)	18	20	131-133	82
''	''	NaOH 1M (3 eq)	12	20	189-191[c]	80[c]
H-Phe-OEt	Et	NaOH 1M (3 eq)	12	20	265-267[c]	85[c]
H-Phe-NH_2	Et	DBU (5 eq)	4.5	60	228-230	80
''	tBu	''	7 days	''	''	78
''	iBu	''	4	''	''	83
''	Bzl	''	2.5	''	''	85
''	''	NaOH (5 eq)	0.1	''	''	82
''	''	NEt_3 (5 eq)	48	''	''	78
$H_2N\text{-}(CH_2)_2\text{-}NHBoc$	Et	DBU (10 eq)	1	80	228-230	75

Table 1. Synthesis of quinazoline-2,4-diones in different cyclisation conditions.[a]Melting point and yield of the corresponding acid are indicated (these products were first saponified, then cyclisation occurred).

3-substituted quinazoline-2,4-diones were obtained in high yield and characterized by ^1H NMR spectroscopy and mass spectrosmetry. After the cyclization step, no racemization could be detected by ^1H

NMR spectroscopy or HPLC[4]. In order to obtain a wide diversity of quinazoline-2,4-diones and to apply this strategy to combinatorial chemistry, we decided to transfer this methodology to solid phase synthesis. Recently, several solid phase synthesis of heterocycles were published[5], including a solid phase synthesis of 1,3-dialkyl quinazoline-2,4-diones.[6] We would like to report here a novel method for the solid phase synthesis of quinazoline-2,4-diones via N-terminal amino group linkage to the solid support and a base-catalyzed cyclisation/cleavage strategy already used for the synthesis of dipeptides[7] and hydantoins.[8] The general method for the synthesis of 3-substituted quinazoline-2,4-diones is shown in scheme 2.



Scheme 2. Solid phase synthesis of quinazoline-2,4-diones

Hydroxymethyl polystyrene resin **1** (0,96 mmol/g) was easily converted into its N-urethane derivative **2** (a robust polymer-bound reagent that can be produced on large scale and stable for long periods[8]) using NMM and paranitrophenyl chloroformate in nearly quantitative yield.[9] Anthranilic acid (5 eq) was then dissolved in a mixture of DMF/CH_2Cl_2 (1 : 2) along with HOBt (3 eq) and N,N-diisopropylethylamine (DIEA) (6 eq), and added to the activated resin to yield **3**. The amino compound (or C-terminal protected aminoacid derivative) was then coupled using BOP and DIEA to yield **4**. Treatment of the resin intermediate with excess NEt_3 (10 eq) in methanol at 60°C for 24 h afforded 3-substituted quinazoline-2,4-diones **5** in high purity (table 2). They were analyzed for purity by HPLC and characterized by mass spectrometry and ^{1}H-NMR spectroscopy. By choice of appropriate commercially available anthranilic acid derivatives, 3-substituted quinazoline-2,4-diones **5** with varied R substituents can be easily synthesized.

RNH_2	[M+H]$^+$	Retention time (min)[a]	purity %	yield %[b]
H-Ala-OMe	249	22.2	96	45
H-Phe-NH_2	310	23	98.3	52
H-Trp-NH_2	349	21.7	98.5	72
H-Phe-OtBu	367	33.3	90	30
H-Leu-OBzl	367	28.7	97.3	22
H-Lys(Z)-OtBu	482	34.2	80	25
Ph-CH_2-NH_2	253	25.2	99.2	25
HO-$(CH_2)_3$-NH_2	221	17.6	99	68

Table 2. Physical characteristics of quinazoline-2,4-diones synthesized by solid phase. [a]Lichrosorb 250 x 4.6 RP-18 column, 5µM, Flow rate 1 ml/min, Solvent water/acetonitrile/0.1% TFA, gradient 0 to 100% acetonitrile in 50 min, detection 220 nM ; [b]Yield of quinazoline-2,4-diones **5** based on the theoretical recovery starting from 0,96 mmol/g hydroxymethyl polystyrene resin.

In conclusion, an efficient process for the solid phase synthesis of 3-substituted quinazoline-2,4-diones from both commercially available anthranilic acid and amino compounds, including aminoacids, has been developed by using a novel cyclisation/cleavage strategy. The synthesis yields 3-substituted quinazoline-2,4-diones of high purity and can be amenable to automation. Therefore, this strategy could be useful for the synthesis of diverse libraries of quinazoline-2,4-diones derivatives. Syntheses of other heterocycles using a similar approach is currently under investigation in our laboratory.

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4. Coupling with H-Leu-OBzl of quinazoline-2,4-dione (acid derivative) obtained from H-Phe-OEt, using BOP, afforded a compound as a single diastereomer as shown by ^{1}H NMR spectroscopy and HPLC).
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9. Hydroxymethyl polystyrene resin (0,96 mmol/g) was purchased from Bachem Biochimie. An aliquot of the activated resin was washed three times with a solution of aqueous ammonia in DMF. UV titration of paranitrophenol in the filtrate afforded the approximate loading of the activated resin.

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