Pergamon

Tetrahedron Letters 42 (2001) 1851–1854

TETRAHEDRON LETTERS

One-step synthesis of 4(3*H*)-quinazolinones

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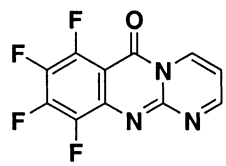
Received 15 December 2000; revised 12 January 2001; accepted 15 January 2001

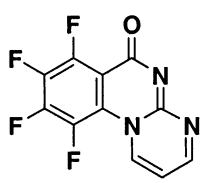
Abstract—2-Fluoro substituted benzoyl chlorides undergo cyclocondensation with 2-amino-*N*-heterocycles to form 4(3*H*)-quinazolinones. The reaction proceeds in moderate yields with different combinations of benzoyl chlorides and 2-amino-*N*-heterocycles. The products generally precipitate from the reaction mixture and require no further purification. Two tetrafluoro quinazolinones were found to be moderately active against a number of tumor cell lines. © 2001 Elsevier Science Ltd. All rights reserved.

It has been more than a century since the initial studies on 4(3*H*)-quinazolinones,[1] and they are well known as biologically active compounds.[2] It has also been long recognized that incorporation of fluorine atoms into a molecular skeleton can significantly alter a compound's biological activity.[3] While there exist numerous methods for the synthesis of 4(3*H*)-quinazolinones and their derivatives,[4] there are few general methods that easily produce fluorinated analogs.[5] Herein, we report the synthesis of 4(3*H*)-quinazolinone derivatives, **1**, using a simple, one-step reaction that generally requires no purification. The structural scope of the reaction is broad and allows quick access to quinazolinones bearing a range of peripheral functionality.

The structure of the products, **1**, were elucidated using multinuclear NMR spectroscopy, mass spectrometry, and X-ray crystallography. Evidence that quinazolinone **1a** was its *linear* 4(3*H*)-isomer was gained from a fluorine decoupled ^{13}C NMR spectrum. The ^{13}C signal corresponding to the carbonyl carbon, C4, exists as a doublet with $J_{CH} = 3.0$ Hz. This is indicative of coupling through three bonds,[6] a condition that is met by the *linear* 4(3*H*)-quinazolinone, **1a**, but not with an alternative *angular* 4(1*H*)-quinazolinone, **3a**, which would have resulted if the amine nitrogen reacted first with the acid chloride. Definitive evidence for the 4(3*H*)-isomer was gained by an X-ray crystal structure of the benzothiazole derivative, **1k** (Fig. 1).[7] The generality of the reaction was probed by reacting various 2-amino-*N*-heterocycles with 2-fluorobenzoyl chlorides. The general procedure involves treatment of a dichloromethane solution of 2-amino-*N*-heterocycle and *i*-Pr_2EtN with acyl chloride at room temperature.[8] The quinazolinone precipitates immediately, is collected by filtration and normally requires no further purification. The results are shown in Table 1.



1a



3a

Examination of Table 1 shows that as the number of fluorines on the benzoyl chloride decreases, the isolated yields of cyclized product also decreases. Introduction of a nitro group at the 5-position leads to more efficient ring closure (compare entries 4 and 5), which is consistent with the ability of a *para*-nitro group to promote nucleophilic aromatic substitution.[9] In most cases the major by-product is the corresponding amide **2** (Scheme 1). In the case of pentafluorobenzenesulfonyl chloride (entry 6), reaction with 2-aminopyrimidine yielded solely the corresponding sulfonamide with no evidence of cyclized product. Entries 7–11 in Table 1 show that

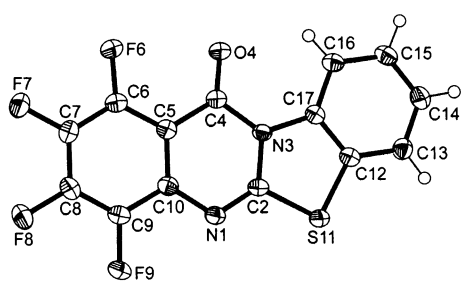


Figure 1. X-Ray crystal structure of **1k**.[7]

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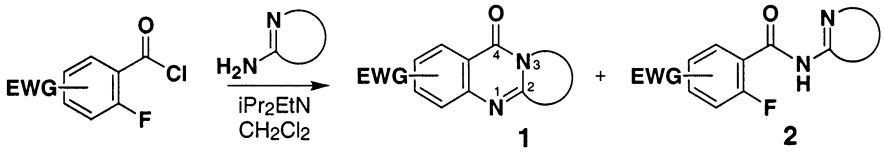
PII: S0040-4039(01)00096-X

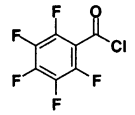
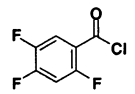
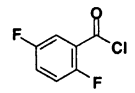
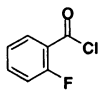
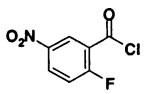
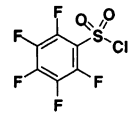
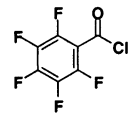
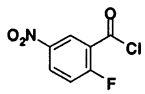
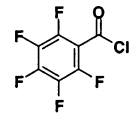
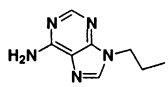
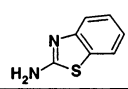
the cyclocondensation reaction can tolerate a number of other 2-amino-*N*-heterocycles. To confirm that 2,3 fusion takes place with all of these systems, the ^{19}F NMR chemical shifts of the cyclized products were compared with those of the known *linear* 4(3*H*)-quinazolinone, **1k** (Table 2). The close correlation is consistent with the *linear* product in all cases.[10] The probable reaction mechanism is initial nucleophilic attack of the ring nitrogen on the benzoyl chloride followed by intramolecular nucleophilic aromatic substitution of the 2-fluoro substituent. It is known that in 2-aminopyrimidine, the ring nitrogen is the most nucleophilic atom.[11]

Treatment of **1a** with methanol and butylamine, as model nucleophiles, results in ring-opened products, **4** (Table 3).[12] This formal amide bond scission occurs



Scheme 1.

Table 1. Reactions of 2-fluorobenzoyl chlorides with 2-amino-*N*-heterocycles

Entry	Acyl chloride	2-Amino-*N*-heterocycle	Product	Yield (%)[a]
1			**1a**	40
2		"	**1b**	12
3		"	**1c**	9
4		"	**1d**	3
5		"	**1e**	36
6		"	**1f**	-[b]
7			**1g**	39
8		"	**1h**	40
9			**1i**	10
10	"		**1j**	20
11	"		**1k**	30

[a] Isolated yields. [b] No evidence of cyclocondensation product was observed.

under relatively mild conditions. The identity of ring-opened product, **4a**, was elucidated using long range ^{1}H–^{13}C COSY (HMBC), with observation of a cross peak between the carbonyl carbon signal (163.5 ppm) and the methyl ester protons (3.90 ppm). The hydrolytic stability of **1a** was evaluated quantitatively by monitoring the disappearance of the UV absorption at $\lambda = 355$ nm. In 1:1 THF/H_2O at 25°C, hydrolysis is very slow at pH 7 ($k = 1.8\times10^{-6}$ L/mol·s), but is about 50 times faster at pH 4 ($k = 8.6\times10^{-5}$ L/mol·s) and 35 times faster at pH 10 ($k = 6.1\times10^{-5}$ L/mol·s).

Compounds **1a** and **1i** were subjected to the National Cancer Institute in vitro anticancer screen.[13] The screen revealed that **1a** and **1i** have good broad-spectrum activity against the 60 tumor cell lines. The average median growth inhibition (GI_{50}) for quinazolinone **1a** was 5.1 μM which was slightly more potent than the 17 μM for **1i**. Thus, these compounds are potential antitumor agents.[14]

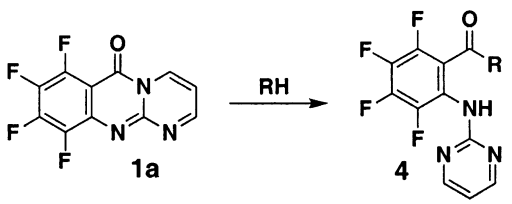
In conclusion, we have presented a one-step method for the preparation of highly functionalized 4(3*H*)-quinazolinone derivatives. In most cases the products precipitate from the reaction mixture and require no further purification. The cyclocondensation requires 2-fluoro benzoyl chlorides bearing electron withdrawing substituents and can tolerate a number of 2-amino-*N*-heterocycles. The products are susceptible to ring-opening attack by alcohols and amines. Efforts are currently underway to improve the yields, elucidate the reaction mechanism, and to determine the mode of biological action.

Table 2.

Compound	^{19}F chemical shift (ppm)[a]			
	F_6	F_7	F_8	F_9
1a	−61.1	−65.9	−70.8	−80.3
1g	−61.6	−68.0	−74.0	−82.3
1i	−60.1	−65.9	−70.8	−81.9
1j	−61.4	−67.8	−73.5	−81.9
1k	−61.4	−67.8	−73.5	−81.1

[a] In $CDCl_3$ with external reference CF_3CO_2H (0 ppm).

Table 3. Nucleophilic ring-opening of **1a**



Compound	RH	% Yield **4**[a]
4a	MeOH[b]	30
4b	n-BuNH_2[c]	60

[a] Isolated yields.

[b] Reaction conditions: 5 molar equivalents of MeOH in CH_2Cl_2, reflux 24 h.

[c] Reaction conditions: 5 molar equivalents of n-BuNH_2 in CH_2Cl_2, room temperature 30 min.

Acknowledgements

We would like to thank Dr. Jaroslav Zajicek and Mr. Don Schifferl for assistance with the NMR experiments. Financial support was provided by the National Science Foundation (USA) and the University of Notre Dame (J. Peter Grace Prize fellowship for M.J.D.).

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7. Single crystals were obtained by slow diffusion of hexane into a dichloromethane solution of **1k**. Crystallographic summary: $C_{14}H_4F_4N_2OS$, monoclinic, space group $P2_1/n$,

$a=9.7115(6)$ Å, $b=5.4565(3)$, $c=22.3937(13)$, $\beta=96.7600(10)°$, $V=1178.41(12)$ Å^3, $Z=4$, $D_{calcd}=1.828$ g cm^{-1}, $F(000)=648$. The structure was refined on F^2 to $R_w=0.1007$, with a conventional $R=0.0362$ (2445 reflections with $I>2\sigma(I)$), and a goodness of fit = 1.117 for 199 refined parameters. The X-ray data can be retrieved from the Cambridge Crystallographic Data Center using deposition number CCDC 154332.

8. Selected spectroscopic data: **1a** mp = dec. 220°C. ^{1}H NMR ($CDCl_3$) δ 9.13 (dd, 1H, $J=7.3$, 2.3 Hz), 9.01 (dd, 1H, $J=3.6$, 2.4 Hz), 7.04 (dd, 1H, $J=7.3$, 3.7 Hz). ^{19}F NMR ($CDCl_3$, external reference CF_3CO_2H at 0 ppm) δ −63.4 (ddd, 1F, $J=21.0$, 14.6, 6.4 Hz), −69.2 (ptd, 1F, $J=21.4$, 6.4 Hz), −74.2 (dd, 1F, $J=20.1$, 14.6 Hz), −83.7 (t, 1F, $J=21.4$ Hz). ^{13}C NMR (^{19}F dec.) (DMSO-d_6) δ 164.6 (ddd, $J=186$, 6, 3 Hz), 155.1 (d, $J=3$ Hz), 148.8 (dd, $J=20$, 4 Hz), 144.9, 144.0, 140.7, 136.3, 136.1, 136.1 (dt, $J=193$, 5 Hz), 111.1 (ddd, $J=179$, 8, 4 Hz), 103.4. MS (FAB$^+$) exact mass calcd for $C_{11}H_4F_4N_3O$ [M+H]$^+$ 270.0290, found 270.0298. **1k** mp = 223–225°C. ^{1}H NMR (DMSO-d_6) δ 8.82–8.79 (m, 1H), 8.07–8.04 (m, 1H), 7.63–7.54 (m, 1H). ^{19}F NMR ($CDCl_3$, external reference CF_3CO_2H at 0 ppm) δ −61.4 (m, 1F), −67.8 (ptd, 1F, $J=20.6$, 7.6 Hz), −73.5 (dd, 1F, $J=19.7$, 13.8 Hz), −81.1 (t, 1F, $J=20.6$ Hz). MS (FAB$^+$) exact mass calcd for $C_{14}H_5F_4N_2OS$ [M+H]$^+$ 325.0059, found 325.0050. **4a** ^{1}H NMR ($CDCl_3$) δ 8.41 (d, 2H, $J=5.0$ Hz), 8.01 (bs, 1H), 6.82 (t, 1H, $J=4.8$ Hz), 3.89 (s, 3H). ^{13}C NMR (^{19}F dec.) ($CDCl_3$) δ 163.5, 159.6 (t, $J=11$ Hz), 158.3 (d, $J=182$ Hz), 146.5, 143.3, 142.8, 138.2, 124.6, 114.2 (d, $J=170$ Hz), 111.4, 53.3 (q, $J=149$ Hz).
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