Short communication

Synthesis of 7-cycloalkylimino substituted 3-amino-6-fluoro-2-methyl-3H-quinazolin-4-ones

Emiliya V. Nosova a,*, Galina N. Lipunova b, Pavel A. Slepukhin b, Valery N. Charushin a,b

a Department of Organic Chemistry, Chemical Technology Institute, Ural Federal University, 19 Mira Str., 620002 Ekaterinburg, Russia
b Postovsky Institute of Organic Synthesis, Ural Division of the Russian Academy of Sciences, 22 S. Kovalevskoy Str., 620219 Ekaterinburg, Russia

A R T I C L E   I N F O
Article history:
Received 11 August 2012
Received in revised form 3 October 2012
Accepted 4 October 2012
Available online 17 October 2012

Keywords:
Fluorine-containing quinazolines
3-Aminoquinazolin-4-ones
Nucleophilic displacement reactions
X-ray crystallography

A B S T R A C T
A versatile pathway for the synthesis of 7-cycloalkylimino substituted 3-amino-6-fluoro-2-methyl-3H-quinazolin-4-ones from 4,5-difluoroanthranlyic acid has been advanced. Nucleophilic amination–defluorination reaction of the 6,7-difluoro derivative of 3-amino-2-methyl-3H-quinazolin–4-one has been established to occur at position 7, as shown by X-ray crystallographic analysis.
© 2012 Elsevier B.V. All rights reserved.

1. Introduction

3-Amino-7-cycloalkylimino substituted 6-fluoroquinazolin-2,4-diones have recently been identified as high effective inhibitors of the bacterial type-2 topoisomerase [1]. Nucleophilic displacement of fluorine atoms proved to be a versatile synthetic tool for structural modifications of fluorinated quinazolin-4-ones [2], however the available data on the synthesis of biologically active compounds through amination–defluorination of fluorquinazolines are limited with a few publications [3], dealing mainly with substitution of a fluorine atom in the benzene ring [4]. Meanwhile, quinazolines, bearing a fluorine atom and a cycloalkylimino moiety in the benzene ring, are of interest due to a profound antitumor activity exhibited by 2-aryl-7-fluoro-6-(4-methylpyperazin-1-yl)-4(3H)-quinazolin-4-one, obtained in 5 steps from 4-fluoro-2-nitro-5-(4-methylpyperazin-1-yl)aniline [5]. It should be noted that hydrazination-defluorination at C(7)-F in 3-amino-6,7,8-trifluoro-2-methylquinazolin-4-one was described earlier [6], although no data on substitution of F(7) in 6,7-difluoro-2-methylquinazolin-4-one are available in the literature. Here we report a simple synthetic approach toward new fluorinated quinazolines.

2. Results and discussion

Heating of difluorobenzoxazine 1 with hydrazine hydrate for a short time did not result in displacement of fluorine atom at 7-position with the hydrazino moiety, as shown earlier [6]. The optimal conditions for preparation of difluoroquinazolone 2 proved to be reflux of 1 with 1.5 equiv. of hydrazine hydrate in ethanol for 1 h. Also the compound 3 was obtained in a high yield when benzoxazine 1 was allowed to be kept on reflux in ethanol with 4 equiv. of hydrazine hydrate for 10 h in order to transform the oxazine ring into the pyrimidine one, as well as to cause substitution of fluorine atom at 7-position with hydrazine. The structure of hydrazine compound 3 is evidenced by 1H NMR spectra, showing the presence of NHNH2 group signals in addition to doublets of H(5) and H(8) protons (scheme).

The fluorine atom at position 7 of 3-amino-6,7-difluoro-2-methyl-3H-quinazolin-4-one (2) was shown to be displaced smoothly by action cycloalkylimines to give compounds 4 in high yields on heating under reflux with 1-methylpyperazine, 3-methylpyperidine, morpholine or 1-ethoxycarbonylpyperazin in DMSO for 9 h (Scheme 1).

The structure of fluoroquinazolines 4a–d was substantiated with 1H NMR, 19F NMR and mass spectrometry data. The 1H NMR spectra of 4a–d reveal two doublets of H(5) and H(8) protons with the characteristic values of coupling constants J[H(5), F(6)] and J[H(8), F(6)] in the ranges of 12.8–13.1 and 7.9–8.1 Hz correspondingly.

Since displacement of F(6) atom would also give a rise to two doublets in 1H NMR with close values of J[H(8), F(7)] and
3. Conclusion

A versatile synthetic route to the family of 7-substituted 6-fluoroquinazolines 4 has been developed. Presently, the antibacterial and antifungal properties of these compounds are under investigation. The corresponding results will be reported elsewhere in due course.

4. Experimental

4.1. General

X-ray structural analyses of compound 4b was accomplished with using “Xcalibur S” diffractometer with CCD (λ(Mo Kα) = 0.71073 Å, T = 295(2) K, ω-scans with 1.0° steps in ω and 20 s per frame exposure) for prismatic light brown crystal 0.25 mm × 0.20 mm × 0.15 mm. Absorption correction not performed (μ = 0.092 mm−1). Crystal is monoclinic, a = 11.1363(16) Å, b = 12.3042(10) Å, c = 11.7801(17) Å, β = 111.457(13), space group P2₁/n. In limits 3.16 < θ < 28.29, 7879 reflections were collected, 3478 independent reflections (Rint = 0.0409), 1042 reflections with I > 2σ(I). Completeness for θ = 26.00° 95.7%. The structure was solved by direct method and refined by full-matrix least-squares technique against F² in anisotropic (isotropic for H-atoms) approximation. Hydrogen atoms were located from Fourier synthesis and refined in riding model. All calculations were performed using SHELXTL [8]. Results of refinement: R₁ = 0.0630, wR₂ = 0.1585 (for I > 2σ(I)), R₁ = 0.1720, wR₂ = 0.1714 (for all data), S = 1.005. Δρmax = 0.552/−0.200 eÅ⁻³.

The X-ray diffraction data for structure 4b have been deposited with the Cambridge Crystallographic Data Center (CCDC No. 885182). These data are free and can be made available upon request at www.ccdc.cam.ac.uk/data_request/cif.

Synthesis of compound 2 from 4,5-difluoroanthranylic acid was reported in [6], the reaction time for transformation 1 → 2 was diminished to 1 h.

NMR, MS and analytical data for compound obtained are presented in Supporting Information.

4.2. Synthesis of 3-amino-6-fluoro-7-hydrazino-2-methyl-3H-quinazolin-4-one (3)

Hydrazine hydrate (98%) (0.4 mL, 8 mmol) was added to a solution of benzoxazine 1 (0.4 g, 2 mmol) in 10 mL of ethanol. The reaction mixture was kept at 80 °C reflux for 10 h. After the mixture was cooled, the precipitate formed was collected by filtration and washed with water (15 mL) to give 0.45 g (92%) of 3, mp 238–240 °C.

4.3. Typical procedure for the synthesis of 3-amino-7-cycloalkylimino-6-fluoro-2-methyl-3H-quinazolin-4-ones 4a-d

The 1-alkylpiperazine 1a (0.4 g, 4 mmol) was added to a solution of difluoroquinazoline (2) (0.3 g, 1.5 mmol) in 2 mL of DMSO. The reaction mixture was heated at 120 °C for 9 h. After the mixture was cooled the precipitate formed was collected by filtration, washed with hot ethanol (5 mL) and recrystallized from DMSO to give 0.36 g (82%) of 4a.

Acknowledgments

This work was supported by the Ministry of Education and Science (grant 3.1941.2011) and by the Russian Foundation for Basic Research (grant 11-03-00718).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jfluchem.2012.10.003.

References


(c) R.J. Sciotti, J.T. Starr, WO 26153 (2005);


