Molecules **2002**, *7*, 507-510

molecules

ISSN 1420-3049
http://www.mdpi.org

Synthesis of Novel Quinazoline Derivatives via Pyrimidine *ortho*-Quinodimethane

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Received: 24 September 2001; in revised form: 3 July 2002 / Accepted: 8 July 2002 / Published: 31 July 2002

Abstract: The [4+2] cycloaddition between 2,4-diphenylpyrimidine *ortho*-quinodimethane and dimethyl acetylenedicarboxylate leads to 2,4-diphenylquinazoline-6,7-dicarboxylate (**6**). 2,4-Diphenylfuro[3,4-g]quinazoline-6,8-dione (**7**) is also obtained by basic hydrolysis of compound **6**, followed by the closure of the resulting diacid in acetic anhydride.

Keywords: [4+2] Cycloaddition, Diels-Alder adduct, dimethyl 2,4-diphenylquinazoline dicarboxylate.

Introduction

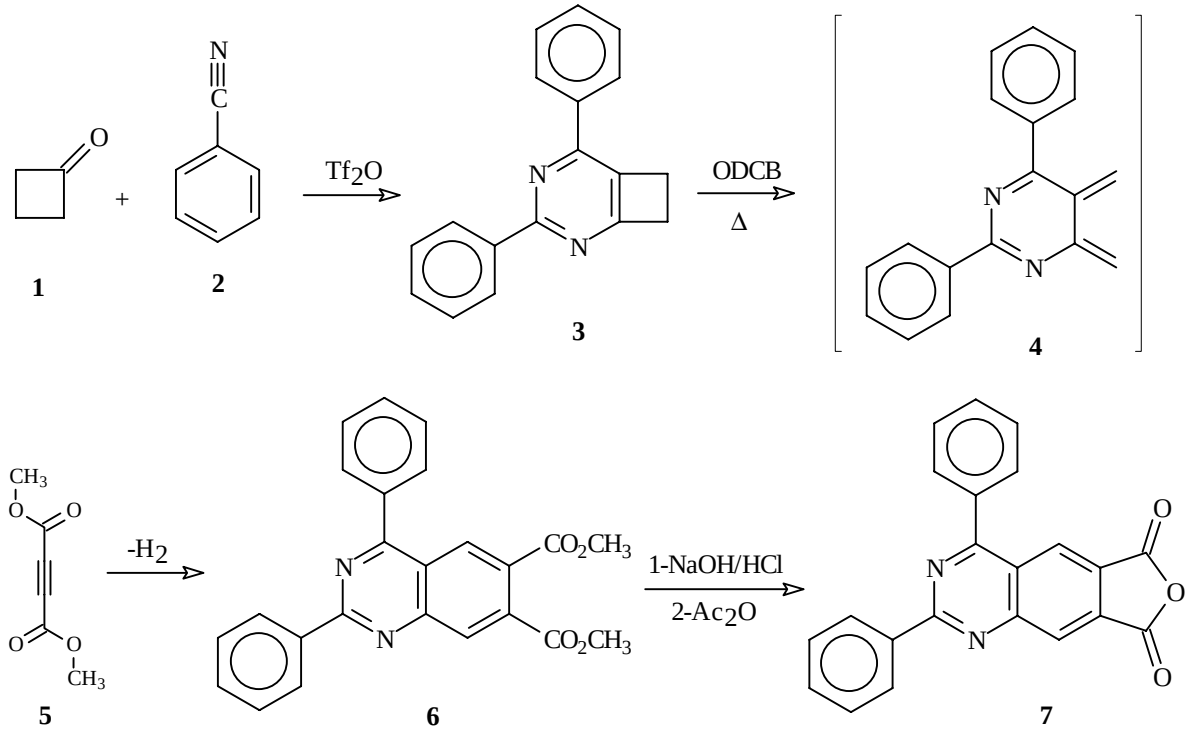
The presence of a pyrimidine nucleus in many heterocyclic compounds, for example, the quinazolines, often leads to very interesting biological and pharmaceutical activities [1,2] so many methods for preparing quinazolines are reported in the literature [3,4]. In this work, we have developed an original method to prepare novel quinazoline derivatives based on cycloaddition between 2,4-disubstituted pyrimidine *ortho*-quinodimethanes and suitable dienophiles [5].

Results and Discussion

The 2,4-diphenylpyrimidine *ortho*-quinodimethanes **4** were obtained according to a reported method [5]. The reaction of cyclobutanone (**1**) with benzonitrile (**2**) and triflic anhydride (Tf_2O) leads to the formation in one step of 3,5-diphenyl-2,4-diaza-bicyclo[4.2.0]octa-1(6),2,4-triene (**3**) in moderate yield.

Heating compound **3** in *o*-dichlorobenzene (ODCB) at 180°C leads to the *in situ* generation of the extremely reactive pyrimidine diene **4**, which was further reacted with dimethyl acetylenedicarboxylate (**5**), via a [4+2]cycloaddition, to give the Diels-Alder adduct dimethyl 2,4-diphenylquinazoline-6,7-dicarboxylate (**6**) in 50 % yield in which loss of H_2 has occured.

Scheme 1



The diester **6** when treated with a 1N solution of NaOH, afforded the expected 2,4-diphenylquinazoline-6,7-dicarboxylic acid in quantitative yield after two hours of stirring at 80°C. Subsequent heating of the diacid in acetic anhydride leads to 2,4-diphenylfuro[3,4-g]quinazoline-6,8-dione (**7**) (Scheme 1).

Conclusions

We have presented an easy method for the formation of dimethyl 2,4-diphenylquinazoline-6,7-dicarboxylate. Basic hydrolysis of this diester followed by the closure of the resulting diacid in acetic anhydride gives 2,4-diphenylfuro[3,4-g]quinazoline-6,8-dione. This result opens an access for the

synthesis of other interesting derivatives such as the β-amino acid derivatives of quinazoline which could exhibit interesting biological activity. The synthesis of these compounds is underway in our laboratory.

Acknowledgements

We are grateful to the Agencia Española de Cooperación Internacional (AECI) for financial support. We thank the Centro de Espectroscopía de la UCM for determining NMR and mass spectra.

Experimental

General

^{1}H- and ^{13}C-NMR spectra were obtained using *Varian VXR* 300S, *Bruker AC-200* and *Bruker AM-300* instruments. Melting points were determined on a *Gallenkamp* apparatus and are uncorrected. I.R spectra were recorded on a *Shimadzu FTIR* 8300. The 70 eV mass spectra were recorded using a HP5989A quadrupole instrument (Hewlett Packard, Palo Alto, CA, USA) with a source temperature of 250°C.

Synthesis of dimethyl 2,4-diphenylquinazoline-6,7- dicarboxylate (**6**).

2,4-Diphenylcyclobutapyrimidine (**3**, 200 mg, 0.77 mmol) was refluxed with dimethyl acetylenedicarboxylate (**5**, 0.2 mL) in *o*-dichlorobenzene (5 mL) at 180°C for 48 h. The solvent was removed under vacuum and the residue was subjected to silica gel chromatography with hexane/ethyl acetate (8:2) as the eluent. Compound (**6**) was thus obtained as a white solid (150 mg, 50 %), mp (from hexane): 156-158 °C; ^{1}H-NMR ($CDCl_3$) δ: 3.86 (s, 3H, CO_2CH_3), 3.94 (s, 3H, CO_2CH_3), 7.48 (m, 3H, C_6H_5), 7.58 (m, 3H, C_6H_5), 7.83 (m, 2H, C_6H_5), 8.36 (s, 1H, H-5), 8.52 (s, 1H, H-8), 8.64 (m, 2H, C_6H_5); ^{13}C-NMR ($CDCl_3$) δ: 53.05, 53.18, 128.78, 129, 129.13, 129.82, 130.37, 130.51, 130.72, 131.47, 137.79, 138.13, 155, 167.03, 167.16; IR (KBr) cm^{-1}: 1728, 1560, 1294, 1261, 1157; MS (*m/z*): 398 ($M^{+\bullet}$, $C_{24}H_{18}N_2O_4$, 78 %), 339 (100 %), 367 (31 %), 351 (42 %), 280 (64 %).

Synthesis of 2,4-diphenylfuro[3,4-g]quinazoline-6,8-dione (**7**).

Dimethyl 2,4-diphenylquinazoline dicarboxylate (**6**) (150 mg, 0.37 mmol) and 1 N NaOH solution (2 mL) in methanol (5 mL) were heated for 2 h; after cooling the solution was concentrated under vacuum and the residue was dissolved in water (5 mL) and acidified with 2 N HCl solution. The resulting suspension was filtered to give 2,4-diphenylquinazoline-6,7-dicarboxylic acid (130 mg, 96 %), which was dissolved in acetic anhydride (5 mL) and heated under reflux for 2 h. After cooling, the product precipitated and was isolated by filtration (115 mg, 93 %), mp (from acetic anhydride): 280-282 °C; ^{1}H-NMR (DMSO-d_6) δ: 7.6 (m, 3H, C_6H_5), 7.77 (m, 3H, C_6H_5), 8 (m, 2H, C_6H_5), 8.35 (s, 1H,

H-5), 8.53 (s, 1H, H-8), 8.69 (m, 2H, C_6H_5); IR (KBr) cm^{-1}: 1716, 1687, 1616, 1600, 1388, 1244, 1215, 1170; MS (m/z): 352 ($M^{+\bullet}$, $C_{22}H_{12}N_2O_3$, 43 %), 351 (18 %), 283 (21 %) 280 (74 %), 280 (74 %), 149 (11 %), 105 (14 %).

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Sample Availability: Available from the authors.

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