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SHORT COMMUNICATIONS

Convenient Preparation Procedure for 3-Alkyl-4-imino-3,4-dihydro-1*H*-quinazolin-2-ones

M. B. Vovk

Institute of Organic Chemistry, National Academy of Sciences of the Ukraine, Kiev, 02094 Ukraine
e-mail: mvovk@i.com.ua

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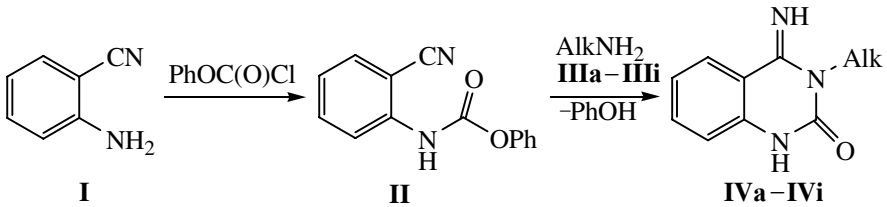
3-Substituted 4-iminoquinazolin-2-ones are valuable building blocks for preparation of important for pharmacology derivatives of 2,4-dioxoquinazoline [1–3] and imidazo[1,2-*c*]quinazoline [4–6]. Syntheses of 3-aryl and 3-allyl-4-iminoquinazolinones are performed commonly by the reaction between anthranylonitriles and isocyanates involving formation of the corresponding ureas which further undergo cyclization under conditions of alkaline [7, 8] or enzymatic [9, 10] catalysis. However due to the limited range of aliphatic isocyanates this method is not applied to preparation of 3-alkyl-4-iminoquinazolinones. Nomoto *et al.* [11] and Ohshima *et al.* [12] for the synthesis of some heteryl-substituted 3-methyl- and fused 3-benzyl-4-iminoquinazolinones tried to apply high-temperature (150° C) condensation of the corresponding *N*-ethoxycarbonylanthranylonitriles with methyl- or benzylamine.

We report here on a preparatively convenient procedure avoiding isocyanate application for the synthesis of 3-alkyl-substituted 4-iminoquinazolinones, in particular, those containing functional substituents in the aliphatic chain. The method is based on a preliminary modification of the amino group in anthranylonitrile (**I**) with phenyl chloroformate followed by treating the nearly quantitatively formed carbamate **II** with alkylamines **IIIa–IIIi**. We found that heating for two hours of reagents **II** and **III** in acetonitrile at reflux made it possible omitting the isolation of intermediate ureas to obtain analytically pure target compounds **IVa–IVi** in 76–85% yields (see scheme).

***N*-(2-Cyanophenyl)-O-phenylcarbamate (II)**. To a dispersion of 11.8 g (0.1 mol) of anthranylonitrile (**I**) in 60 ml of toluene was added while stirring and cooling with ice water a solution of 17.2 g (0.11 mol) of phenyl chloroformate in 20 ml of toluene, and the mixture was heated at reflux for 2 h. On cooling the separated precipitate was filtered off, washed with 40 ml of ethyl ether, and dried. Yield 96%, mp 141–142°C. IR spectrum, ν, cm^{-1}: 1720 (C=O), 2245 (C=N), 3330 (NH). ^1H NMR spectrum, δ, ppm: 7.19–7.42 m ($6H_{arom}$), 7.64 d.d ($2H_{arom}$), 7.76 s ($1H_{arom}$), 10.28 s (1H, NH). Found, %: C 70.78; H 4.05; N 11.59. $C_{14}H_{10}N_2O_2$. Calculated, %: C 70.58; H 4.23; N 11.76.

3-Alkyl-4-imino-3,4-dihydro-1*H*-quinazolin-2-ones IVa–IVi. A mixture of 0.6 g (2.5 mmol) of

Scheme.



I **II** **IVa–IVi**

Alk=$HOCH_2CH_2$ (**a**), $Me_2NCH_2CH_2$ (**b**), 2-morpholinoethyl (**c**), $HOCH_2CH_2CH_2$ (**d**), $Me_2NCH_2CH_2CH_2$ (**e**), C_4H_9 (**f**), $(CH_3)_2CHCH_2CH_2$ (**g**), C_6H_{13} (**h**), (1-ethylpyrrolidin-2-yl)methyl (**i**).

carbamate **II** and 2.5 mmol of amine **IIIa–IIIi** in 10 ml of acetonitrile was heated at reflux for 3 h. On cooling the separated precipitate was filtered off, washed with 10 ml of ethyl ether, and dried.

3-(2-Hydroxyethyl)-4-imino-3,4-dihydro-1*H*-quinazolin-2-one (IVa). Yield 82%, mp 195–196°C. IR spectrum, ν, cm^{-1}: 1700 (C=O), 3320 (NH), 3490 (OH). ^1H NMR spectrum, δ, ppm: 3.58 t (2H, CH_2), 4.11 t (2H, CH_2), 4.87 br.s (1H, OH), 7.03–7.08 m ($2H_{arom}$), 7.44 t ($1H_{arom}$), 8.02 d ($1H_{arom}$), 8.89 s (1H, NH), 10.70 br.s (1H, NH). Found, %: C 58.31; H 5.59; N 20.65. $C_{10}H_{11}N_3O_2$. Calculated, %: C 58.53; H 5.40; N 20.48.

3-(2-Dimethylaminoethyl)-4-imino-3,4-dihydro-1*H*-quinazolin-2-one (IVb). Yield 80%, mp 206–207°C. IR spectrum, ν, cm^{-1}: 1700 (C=O), 3340 (NH). ^1H NMR spectrum, δ, ppm: 2.58 t (2H, CH_2), 4.13 t (2H, CH_2), 7.01–7.12 m ($2H_{arom}$), 7.42 t ($1H_{arom}$), 8.03 d ($1H_{arom}$), 8.92 s (1H, NH), 10.83 br.s (1H, NH). Found, %: C 61.79; H 7.03; N 24.24. $C_{12}H_{16}N_4O$. Calculated, %: C 62.05; H 6.94; N 24.12.

4-Imino-3-(2-morpholinoethyl)-3,4-dihydro-1*H*-quinazolin-2-one (IVc). Yield 85%, mp 207–208°C. IR spectrum, ν, cm^{-1}: 1695 (C=O), 3330 (NH). ^1H NMR spectrum, δ, ppm: 2.47–2.51 m (4H, $2CH_2$), 3.31–3.34 m (2H, CH_2), 3.52–3.55 m (4H, CH_2), 4.11–4.16 m (2H, CH_2), 7.05–7.12 m ($2H_{arom}$), 7.47 t ($1H_{arom}$), 8.06 d ($1H_{arom}$), 8.89 s (1H, NH), 10.73 s (1H, NH). Found, %: C 61.17; H 6.70; N 20.20. $C_{14}H_{18}N_4O_2$. Calculated, %: C 61.30; H 6.61; N 20.42.

3-(3-Hydroxypropyl)-4-imino-3,4-dihydro-1*H*-quinazolin-2-one (IVd). Yield 85%, mp 172–173°C. IR spectrum, ν, cm^{-1}: 1695 (C=O), 3305, 3390 (NH), 3530 (OH). ^1H NMR spectrum, δ, ppm: 1.74–1.78 m (2H, CH_2), 3.42 t (2H, CH_2), 4.08 t (2H, CH_2), 7.05–7.10 m ($2H_{arom}$), 7.44 d ($1H_{arom}$), 8.03 d ($1H_{arom}$), 8.86 br.s (1H, NH), 10.76 br.s (1H, NH). Found, %: C 60.39; H 6.09; N 19.26. $C_{11}H_{13}N_3O_2$. Calculated, %: C 60.26; H 5.98; N 19.17.

3-(3-Dimethylaminopropyl)-4-imino-3,4-dihydro-1*H*-quinazolin-2-one (IVe). Yield 83%, mp 146–147°C. IR spectrum, ν, cm^{-1}: 1695 (C=O), 3295, 3360 (NH). ^1H NMR spectrum, δ, ppm: 1.72–1.77 m (2H, CH_2), 2.19 s (6H, $2CH_3$), 2.31 t (2H, CH_2), 3.99 t (2H, CH_2), 7.01–7.08 m ($2H_{arom}$), 7.41 t ($1H_{arom}$), 8.03 d ($1H_{arom}$), 8.82 br.s (1H, NH), 10. 80 br.s (1H, NH). Found, %: C 63.61; H 7.25; N 22.91. $C_{13}H_{18}N_4O$. Calculated, %: C 63.39; H 7.37; N 22.75.

3-Butyl-4-imino-3,4-dihydro-1*H*-quinazolin-2-one (IVf). Yield 78%, mp 209–210°C. IR spectrum, ν, cm^{-1}: 1700 (C=O), 3295, 3310 (NH). ^1H NMR spectrum, δ, ppm: 0.94 t (3H, CH_3), 1.10–1.15 m (2H, CH_2), 1.56–1.60 m (2H, CH_2), 3.99 t (2H, CH_2), 7.01–7.06 m ($2H_{arom}$), 7.98 d ($1H_{arom}$), 8.74 br.s (1H, NH), 10.66 br.s (1H, NH). Found, %: C 66.20; H 6.88; N 19.47. $C_{12}H_{15}N_3O$. Calculated, %: C 66.34; H 6.96; N 19.34.

4-Imino-3-(3-methylbutyl)-3,4-dihydro-1*H*-quinazolin-2-one (IVg). Yield 77%, mp 204–205°C. IR spectrum, ν, cm^{-1}: 1700 (C=O), 3300 (NH). ^1H NMR spectrum, δ, ppm: 0.96 d (6H, $2CH_3$), 1.49–1.63 m (3H, CH_2 + CH), 4.01 t (2H, CH_2), 7.02–7.06 m ($2H_{arom}$), 7.42 t ($1H_{arom}$), 8.00 d ($1H_{arom}$), 8.74 br.s (1H, NH), 10.67 br.s (1H, NH). Found, %: C 67.77; H 7.39; N 18.12. $C_{13}H_{17}N_3O$. Calculated, %: C 67.51; H 7.41; N 18.17.

3-Hexyl-4-imino-3,4-dihydro-1*H*-quinazolin-2-one (IVh). Yield 75%, mp 161–162°C. IR spectrum, ν, cm^{-1}: 1695 (C=O), 3330 (NH). ^1H NMR spectrum, δ, ppm: 0.86 t (3H, CH_3), 1.23–1.28 m (6H, $3CH_2$), 1.56–1.59 m (2H, CH_2), 3.99 t (2H, CH_2), 7.03–7.10 m ($2H_{arom}$), 7.47 t ($1H_{arom}$), 8.05 d ($1H_{arom}$), 8.86 s (1H, NH), 10.71 s (1H, NH). Found, %: C 68.68; H 7.64; N 16.98. $C_{14}H_{19}N_3O$. Calculated, %: C 68.54; H 7.81; N 17.13.

4-Imino-3-[(1-pyrrolidin-2-yl)methyl]-3,4-dihydro-1*H*-quinazolin-2-one (IVi). Yield 83%, mp 217–218°C. IR spectrum, ν, cm^{-1}: 1690 (C=O), 3290 (NH). ^1H NMR spectrum, δ, ppm: 1.04 m (3H, CH_3), 1.60–1.68 m (4H, $2CH_2$), 2.12–2.32 m (2H, 2CH), 2.92–3.03 m (3H, CH_2, CH), 3.96–4.04 m (2H, 2CH), 7.04–7.12 m ($2H_{arom}$), 7.40–745 m ($1H_{arom}$), 8.03–8.07 m ($1H_{arom}$), 8.74 br.s (1H, NH), 10.87 br.s (1H, NH). Found, %: C 66.37; H 7.23; N 20.41. $C_{15}H_{20}N_4O$. Calculated, %: C 66.15; H 7.40; N 20.57.

IR spectra of compounds were recorded on UR-20 instrument from KBr pellets. ^1H NMR spectra were registered on a spectrometer Varian-Gemini (300 MHz) from solutions in $(CD_3)_2SO$, internal referencew TMS.

REFERENCES

1. Timmermaus, B.M. and Zwieten, P.A., *Drugs Future,* 1984, vol. 9, p. 41.
2. Campbell, S.F. and Davey, M., *J. Drug Delivery,* 1986, vol. 1, p. 83.
3. Imagawa, J. and Sakai, K., *Eur. J. Pharmakology*, 1986, vol. 131, p. 257.
4. Johne, S., *Pharmazie*, 1981, vol. 36, p. 583.
5. Menweil, N., Putz, H., Hagen, M., Colonno, R.J., and

Krystal, M., *Antiviral Chem. Chemother.,* 1996, vol. 7, p. 353.
6. Chern, J.-W., Tao, P.-L., Yen, M.-H., Lu, G.-Y., Shiau, C.-Y., Lai, Y.-J., Chien, S.-L., and Chan, C.-H., *J. Med. Chem.,* 1993, vol. 36, p. 2196.
7. Vasil'eva, M.V., Teleshov, E.I., and Pravednikov, A.I., *Izv. Akad. NaukSSSR, Ser. Khim.,* 1985, vol. 6, p. 1440.
8. Hassan, A.Y., Ghorob, M.M., and Nassar, O.M., *Phosphorus, Sulfur, Silicon. Relat. Elem.,* 1998, 1 vol. 34, p. 77.
9. Kamal, A. and Sattur, P.B., *Tetrahedron Lett*., 1989, vol. 30, p. 1133.
10. Kamal, A. and Sattur, P.B., *J. Chem. Soc. Chem. Commun*., 1989, vol. 13, p. 835.
11. Nomoto, Y., Haruki, T., Tensuji, O., and Kubo, K., *Chem. Pharm. Bull*., 1991, vol. 39, p. 900.
12. Ohshima, T., Masae, M., Yukihiko, T., and Motoyoshi, Y., *Chem. Pharm. Bull*., 1981, vol. 29, p. 1381.