UDC 547.8561:547.583.5:542.957.2

STUDYING THE GRIGNARD REACTION OF QUNAZOLINONE DERIVATIVES CONTAINING AN ESTER GROUP

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Key words: anthranilamide; quinazolinone; glycine; heterocyclisation; Grignard reagent

The transformation of 4-oxo-3,4- dihydroquinazolinone derivatives containing an ester group under the conditions of the Grignard reaction has been investigated. It has been found that the reaction of 2-carbethoxy-4-oxo-3,4-dihydroquinazoline and (4-oxo-3,4-dihydroquinazolin-3-yl)-, (2-carbethoxy-4-oxo-3,4-dihydro-quinazolin-3-yl)acetic acid esters proceeds involving the ester group and the excess of the reagent does not influence on its result.

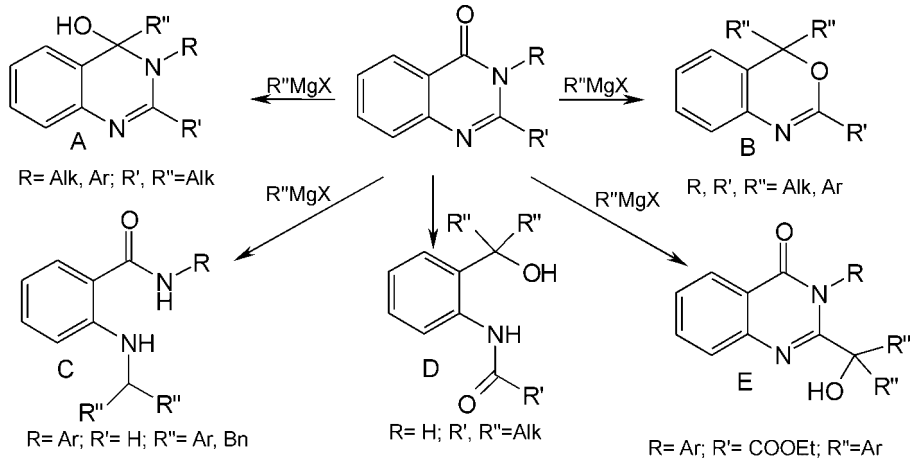
ДОСЛІДЖЕННЯ РЕАКЦІЇ ГРИНЬЯРА ПОХІДНИХ ХІНАЗОЛІНОНУ, ЩО МІСТЯТЬ СКЛАДНОЕСТЕРНУ ГРУПУ
Л.А.Шемчук, Д.В.Левашов, М.Аль-Асрі Джаміль, Ю.О.Шенгоф, П.С.Арзуманов, В.П.Черних
Досліджено перетворення похідних 4-оксо-3,4-дигідрохіназоліну, які містять естерну групу, в умовах реакції Гриньяра. Встановлено, що реакція 2-карбетокси-4-оксо-3,4-дигідрохізоліну та естерів (4-оксо-3,4-дигідрохіназоліл)-, (2-карбетокси-4-оксо-3,4-дигідрохіназоліл)оцтової кислоти перебігає по естерній групі, надлишок реагента не впливає на перебіг реакції.

ИЗУЧЕНИЕ РЕАКЦИИ ГРИНЬЯРА ПРОИЗВОДНЫХ ХИНАЗОЛИНОНА, СОДЕРЖАЩИХ СЛОЖНОЭФИРНУЮ ГРУППУ
Л.А.Шемчук, Д.В.Левашов, М.Аль-Асри Джамиль, Ю.А.Шенгоф, П.С.Арзуманов, В.П.Черных
Изучено превращение производных 4-оксо-3,4-дигидрохиназолина, содержащих сложноэфирную группу, в условиях реакции Гриньяра. Установлено, что реакция 2-карбэтокси-4-оксо-3,4-дигидрохиназолина и эфиров (4-оксо-3,4-дигидрохиназолил)-, (2-карбэтокси-4-оксо-3,4-дигидрохиназолил)уксусной кислоты протекает по сложноэфирной группе, избыток реагента не влияет на протекание реакции.

This work is devoted to the evaluation of interaction of quinazolinone derivatives and Grignard reagents. Total number of such publications is insignificant and they concern only to unfunctionalized alkyl (aryl) substituted in positions 2 and 3 derivatives of 4-oxo-3,4-dihydroquinazolines, or substituted on one of these positions. The generalized information according to the literature research made by Beilshtein Inst. database is cited below, on the scheme 1. 2,3-Disubsituted derivatives react with an alkyl (aryl) magnesiumhalides by carbonyl group in position 4 of the quinazoline kernel [1, 2], herewith, the rearrangement in 1,3-benzoxazinones (products A and B) is also possible [3]. 4-Oxo-3,4-dihydroquinazoline derivatives which don't contain a substituent in the second position interact with R-magnesiumhalides by this position that is accompanied by the quinazoline cycle opening (product C) [4]. Not substituted in position 3 derivatives react with Grignard reagents by an oxo-group, thus decyclization is also observed (product D) [5, 6]. Together with this, it has been shown by us that the presence of functional group, in particular ester group, can affect the reaction passing. Thus interaction of 3-aryl-2-carbethoxy-4-oxo-3,4-dihydroquinazolines with arylmagnesiumhalides proceeds only on an ester group and not touches dihydropyrimidine kernel, even under the significant excess of Grignard reagent (product E) [7].

In addition to work on research of Grignard reaction among 4-oxo-3,4-dihydroquinazolines derivatives, containing an ester group a series of researches have been made. Since, in agreement with the resulted literature data, the interaction direction depends on the presence of substituents in position 2 and 3 of the quinazoline kernel, the transformation under Grignard reaction of the derivatives containing an ester group in position 2 or 3 and not substituted on other position has been investigated. As a substrates the 2-carbethoxy-4-oxo-3,4-dihydro-quinazoline and esters of (4-oxo-3,4-dihydroquinazolin-3-yl)acetic acid were chosen (not substituted on the third and second positions responsibly), and also esters of (2-carbethoxy-4-oxo-3,4-dihydroquinazolin-3-yl)acetic acid which contain the ester group in both the second, and in the third positions.

By carrying out the reaction of not substituted in the third position 2-carbethoxy-4-oxo-3,4-dihydro-quinazoline (1) with arylmagnesiumhalides correspon-



Scheme 1

ding derivatives (2) were received. Esters of (4-oxo-3,4-dihydro-quinazoline-3-yl)acetic acid (4) were received by heating of compounds (3) with formic acid, also reacted with Grignard reagents by ester group (Scheme 2). In both cases reaction stopped on the stage of interaction with ester group and excess of a reagent (1:7) did not influence its result. Most likely, such result is possible to explain by spatial availability and delocalization of electron density as a result of diaryl hydroxymethyl group formation.

We obtained *N*-(*o*-ethyloxalylaminobenzoyl)alkyl glycinates (7) by two different methods. In method A: benzoxazin-4-one (6) was treated with alkyl glycinates hydrochloride resulting in compounds (7). In method B: *N*-(*o*-amino benzoyl)alkyl glycinates (3) were acylated by ethyloxalylchloride affording compounds (7).

A comparison between this two methods shows: method A is less economic, consuming time and with fewer yields while method B is more economic preserving time and with excellent yields.

Besides, alkyl-(2-carbethoxy-4-oxo-3,4-dihydro-3-quinazolinyl) acetates (10) were obtained by two different methods. Method I: compounds (7) were boiled in acetic anhydride leading to intramolecular condensation and obtaining compounds (10). In method II: quinazolinone (9) was alkylated by the alkyl chloroacetates resulting in compounds (10) with excellent yields (Scheme 3).

Interesting reactions have been done between Grignard reagents which were prepared according to [8] and compounds (7) and (10) to obtain diaryl hydroxymethyl fragments which have pharmacophoric properties resulting in the desired products *N*-(1,1-diaryl-1-hydroxyeth-2-yl)-*N'*-diarylhydroxyacetyl anthranil-amides (8) and 2-(diarylhydroxymethyl)-3-(1,1-diaryl-1-hydroxyeth-2-yl)-4-oxo-3,4-dihydroquinazolines (11).

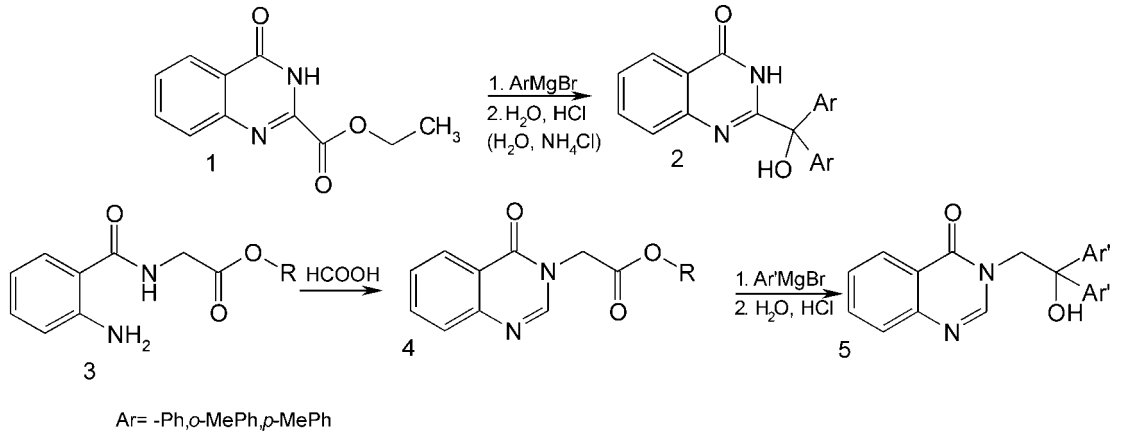
Conclusions

The interaction of not substituted in the position 3 2-carbethoxy-4-oxo-3,4-dihydroquinazoline, not substituted in the position 2 esters of (4-oxo-3,4-dihydro-quinazolin-3-yl)acetic acid and also disubstituted (2-carbethoxy-4-oxo-3,4-dihydroquinazolin-3-yl)acetic acid with Grignard reagent stopped on the stage of interaction with ester group and excess of a reagent did not influence its result.

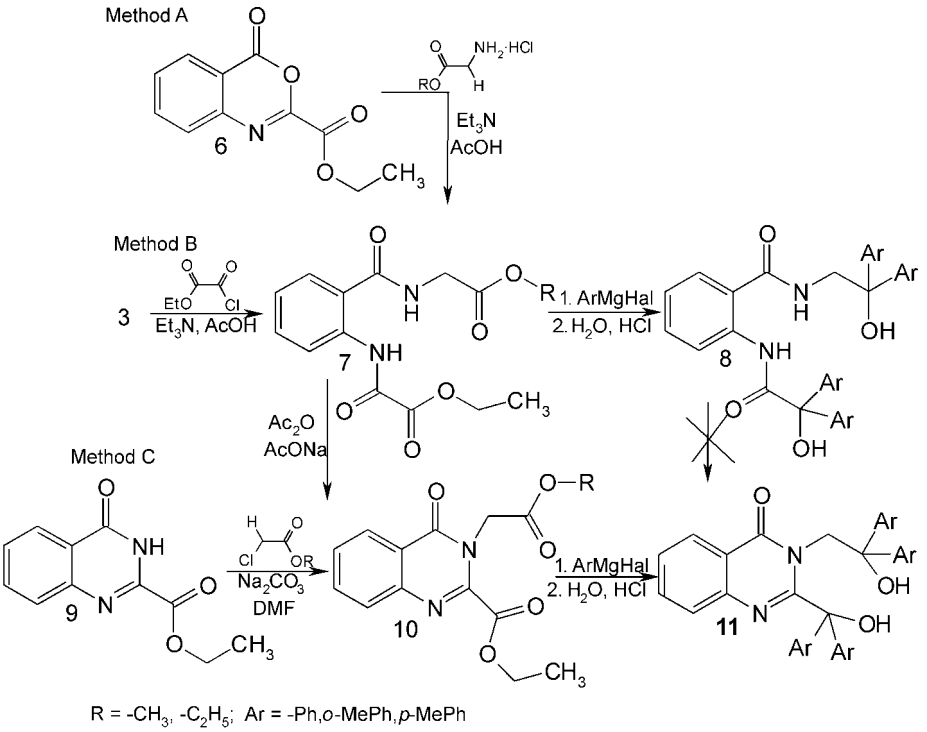
Experimental Methods

^{1}H NMR spectra were registered on a spectrophotometer Varian M200, operating frequency 200 MHz, from solutions in DMSO-d_6 with TMS as internal reference.

2-(Diphenylhydroxymethyl)-4-oxo-3,4-dihydro-3-quinazoline (2a). 3.28 g (0.01 mole) of 2-carbethoxy-4-oxo-3,4-dihydroquinazoline (3.10) was dissolved in tetrahydrofurane to the solution of phenylmagnesium



Scheme 2



Scheme 3

bromide in tetrahydrofurane. The reaction mixture was stirred for 1 hour, hydrolyzed by a saturated solution of NH_4Cl, the organic layer was separated, the solvent was evaporated. The residue was recrystallized from methanol. Yield — 75%. M.p. — 196-198°C. NMR ^{1}H, δ, ppm: 6.60 м (5H, Ar), 7.10 м (2H, Ar), 7.40 м (4H, Ar, OH), 7.60 м (2H, 6-CH, 8-CH), 8.10 т (1H, 7-CH), 8.30 д (1H, 5-CH), 11.40 с (1H, NH).

Compounds (2b,c) were obtained similarly.

2-(Di(*o*-tolyl)hydroxymethyl)-4-ox-3,4-dihydroquinazoline (2b). Yield — 60%. M.p. — 222-224°C. NMR ^{1}H, δ, ppm.: 2.40 с (6H, CH_3), 6.80-7.20 м (5H, Ar), 7.40 м (4H, Ar), 7.60 м (2H, 6-CH, 8-CH), 8.10 т (1H, 7-CH), 8.30 д (1H, 5-CH) , 11.40 с (1H, NH).

2-(Di(*p*-tolyl)hydroxymethyl)-4-oxo-3,4-dihydroquinazoline (2c). Yield — 75%. M.p. — 240-242°C. NMR ^{1}H, δ, ppm: 2.10 с (6H, CH_3), 7.00-7.30 м (5H, Ar), 7.40 м (4H, Ar), 7.60 м (2H, 6-CH, 8-CH), 8.10 т (1H, 7-CH), 8.30 д (1H, 5-CH), 11.40 с (1H, NH).

Alkyl-(4-oxo-3, 4-dihydro-3-quinazolinyl) acetates (4a,b). A mixture of 0.01 mole N-(*o*-amino benzoyl) alkyl glycinates (2.08 g of methyl ester or 2.22 g of ethyl ester) (3) and 5 ml of formic acid was bolied for 45-60 minutes, cooled and diluted with 50 ml of water with good scratching to initiate the formation of crystals. The mixture was left to the next day, filtered, washed by water, dried. The products were recrystallized from ethanol. Yield of methyl ester (4a) was 68% and of ethyl ester (4b) was 64%. M.p. — 144-146°C (4a) and 168-170°C (4b); ^{1}H NMR, δ, ppm: for (4a): 3.70 s (3H, OCH_3), 4.85 s (2H, CH_2), 7.55 t (1H, ArH), 7.70 d (1H, ArH), 7.85 t (1H, ArH), 8.10 d (1H, ArH), 8.35 s (1H, C-2 H quinazolinone); for (4b): 1.15 t (3H, $CH_2\underline{CH_3}$), 4.25 q (2H, $\underline{CH_2}CH_3$), 4.9 s (2H, CH_2CO), 7.4 t (1H,ArH),7.55 d (1H,ArH), 7.7 t (1H,ArH), 8.15 d (1H,ArH), 8.35 s (1H, C-2 H quinazolinone).

3-(1,1-Diaryl-1-hydroxyeth-2-yl)-4-oxo-3,4-dihydroquinazolines (5a,b). 0.01 mole (2.18 g of methyl ester and 2.32 g of ethyl ester) of alkyl-(4-oxo-3,4-dihydro-3-quinazolinyl) acetates (4a, b) were heated in 15 ml of anhydrous THF for dissolution. The mixtures were evaporated directly and the precipitates were crystallized from anhydrous methanol and filtered within hot. The products were filtered, cooled. Yields of products were 45% for (5a) and 53% for (5b) in case of C_6H_5MgBr and *p*- MeC_6H_4MgBr respectively. M.p. — 105-107°C (5a) and 200-202°C (5b); ^{1}H NMR, δ, ppm: for (5a): 4.75 s (2H, CH_2), 5.75 s (1H,OH), 7.5 m (14H,ArH), 8.35 s (1H,C-2 H quinazolinone); for (5b): 2.25 s (6H,CH_3+CH_3), 4.80 s (2H, CH_2), 5.55 s (1H, OH), 6.40 d (2H, ArH), 6.80 d (2H, ArH), 7.00-8.00 m (8H, ArH), 8.15 s (1H, C-2 H quinazolinone).

N-(o-Ethyl oxalyl aminobenzoyl) alkyl glycinates (7a,b). *Method A:* a mixture of 0.01 mole of alkyl glycinates hydrochlorides (1.25 g of methyl ester or 1.4 g of ethyl ester) and 0.01 mole (1.44 ml) of triethylamine in 15 ml of ethanol was heated for dissolution then 0.01 mole (2.19 g) of 2-carbethoxy-4H-3,1-benzoxazin-4-one (6) was added and heated for 5-10 minutes leading to formation of red color in the mixture. The mixture was cooled, diluted with 50 ml of water with good scratching, left for 24 hours, filtered, dried and recrystallized from ethanol. Yield of methyl ester (III.7a) was 75% and of ethyl ester (III.7b) was 77%.

Method B: To a mixture of 0.01 mole of N-(o-amino benzoyl) alkyl glycinate (2.08 g of methyl ester or 2.22 g of ethyl ester) (3) and 15 ml of acetic acid, 0.01 mole (1.44 ml) of triethylamine was added drobly

with mixing. To that mixture, 0.01 mole (1.2 ml) of ethyl oxalyl chloride was added gradually then stirred for 5 hours. The mixture was diluted with 50 ml water with scratching. The mixture was left for 24. The formed products were filtered, washed by water, dried, recrystallized from ethanol. Yield of methyl ester (7a) was 85-88% and of ethyl ester (7b) was 80-83%. M.p. — 125°C (7a) and 100°C (7b); ^{1}H NMR, δ, ppm: for (7a): 1.30 t (3H, $CH_2\underline{CH_3}$), 3.65 s (3H, OCH_3), 4.00 d (2H, $NH\underline{CH_2}$), 4.20 q (2H, $\underline{CH_2}CH_3$), 7.20 t (1H, ArH), 7.60 t (1H, ArH), 7.90 d (1H, ArH), 8.50 d (1H, ArH), 9.30 t (H, $\underline{NH}CH_2$), 12.60 s (NHCO); for (7b): 1.30 m (6H, $2CH_2\underline{CH_3}$), 3.90 d (2H, $NH\underline{CH_2}$), 4.30 m (4H, $2\underline{CH_2}CH_3$), 7.25 t (1H, ArH), 7.55 t (1H, ArH), 7.85 d (1H, ArH), 8.55 d (1H, ArH), 9.30 t (H, $\underline{NH}CH_2$), 12.65 s (NHCO).

N-(1,1-Diaryl-1-hydroxyeth-2-yl)-N′-diarylhydroxyacetyl anthranilamides (8a,b). 0.01 mole (3.08 g of methyl ester or 3.22 g of ethyl ester) of *N*-(*o*-ethyl oxalyl aminobenzoyl) alkyl glycinates (7) were heated in 15 ml of anhydrous THF for dissolution. In portions with 20 minute-intervals, the mixture was added to and stirred with freshly prepared Grignard reagents with a ratio (1:7) with gentle heating. Stirring was kept for 30 minutes after last addition. To the mixture, we poured a solution for hydrolysis with mixing. Product was crystallized from ethanol. Yield of (8a) was 65% and of (8b) — 60-63%. M.p. — 90°C (8a) and 120°C (8b); ^{1}H NMR, δ, ppm: for (8a): 4.00 d (2H, CH_2), 7.20-7.70 m (26H, ArH+2OH), 8.55 d ($\underline{NH}CH_2$), 11.95 s (NHCO); for (8b): 2.20 m (12H, CH_3), 3.20 d (2H,CH_2), 7.10 m (20H,ArH +2OH), 7.50 m (1H,ArH), 8.50 d (1H,ArH), 9.75 d ($\underline{NH}CH_2$), 11.85 s (NHCO).

Alkyl-(2-carbethoxy-4-oxo-3,4-dihydro-3-quinazolinyl) acetates (10a,b). *Method A:* a mixture of 0.01 mole (3.08 g of methyl ester or or 3.22 g of ethyl ester) of *N*-(*o*-ethyl oxalyl aminobenzoyl) alkyl glycinates (7a,b) and 0.01 mole (0.82 g) of anhydrous sodium acetate was heated in 5 ml of acetic anhydride for 60 minutes. Mixture was cooled and diluted with 2-3 ml of water then scratched and left to next day. Ethanol was added and the product was filtered off and recrystallized from ethanol. The product was collected as pale yellowish white crystals. Yield was 60%.

Method B: a mixture of 0.01 mole (2.18 g) 2-carboethoxy-quinazoline-4(3H)-one (9) and 0.012 mole (1.27 g) of sodium carbonate was mixed well in 10 ml of anhydrous DMF for 8 hours. To that mixture, 0.012 mole (1.28 ml) of ethyl chloroacetate was added slowly with continuous stirring for 4 hours. The solvent was evaporated, water was added and the precipitate was formed then filtered off, dried. Yields were 88-91%. M.p. — 95°C (10a) and 88°C (10b); ^{1}H NMR, δ, ppm: for (10a): 1.35 t (3H, $CH_2\underline{CH_3}$), 2.50 s (3H,OCH_3), 4.45 q (2H, $\underline{CH_2}CH_3$), 4.9 s (2H, CH_2CO), 7.35 t (1H, ArH), 7.45 d (1H, ArH), 7.65 t (1H, ArH), 8.00 d (1H, ArH); for (10b); 1.15 t (3H, $CH_2\underline{CH_3}$ at N-3), 1.30 t (3H, $CH_2\underline{CH_3}$ at C-2), 4.25 q (2H, $\underline{CH_2}CH_3$ at N-3), 4.4 q (2H, $\underline{CH_2}CH_3$ at C-2), 4.9 s (2H,CH_2CO), 7.4 t (1H, ArH), 7.55 d (1H, ArH), 7.7 t (1H, ArH), 8.15 d (1H, ArH).

2-(Diarylhydroxymethyl)-3-(1,1-diaryl-1-hydroxyeth-2-yl)-4-oxo-3,4-dihydroquinazolines (11a,b). 0.01 mole of (2.90 g of methyl ester and 3.04 g of ethyl ester) of alkyl-(2-carbethoxy-4-oxo-3,4-dihydro-3-quinazolinyl) acetates (10a, b) were dissolved in 15 ml of THF and proceeded as explained in preparation of compounds (8) with ratio of ArMgHal as (1:5). Yields were 50-60%. M.p. — 288-290°C (11a) and 166-168°C (11b); ^{1}H NMR, δ, ppm: for (11a): 4.35 s (2H, CH_2), 6.90-7.10 m (24H, ArH+2OH), 7.5 m (1H, ArH), 7.90 d (1H, ArH); for (11b): 2.20 m (12H,CH_3), 3.35 s (2H, CH_2), 7.15 m (6H, ArH), 7.4 m (12H.Ar +2OH), 7.55 m (2H, ArH), 7.70 t (1H, ArH), 8.15 d (1H, ArH).

References

1. *Upadhyaya M.J. // J. Ind. Chem. Soc. — 1950. — Vol. 27. — 40 p.*
2. *Sen Sidhu. // J. Ind. Chem. Soc. — 1948. — Vol. 25. — 437 p.*
3. *Elkashef A.-F.M. // Collection of Czechoslovak. Chem. Communications. — 1974. — Vol. 39. — 287 p.*
4. *Essawya A., El-Hashash M.A., El-Behdy A.M. et al. // Ind. J. Chem. — 1982. — Vol. 6. — 593 p.*
5. *Koelsch C.F. // J. Am. Chem. Soc. — 1945. — Vol. 67. — 1718 p.*
6. *Kacker I.K., Zaheer S.H. // J. Chem. Soc. — 1956. — 415 p.*
7. *Shemchuk L.A., Chernykh V.P., Levashov D.V. et al. // Russ. J. of Org. Chem. — 2010. — Vol. 46(8). — 1243 p.*
8. *Титце Л., Айхер Т. Препаративная органическая химия. — М.: Мир, 1999. — 704 с.*

Надійшла до редакції 17.05.2011 р.