PRÁCTICA V.7

AMINO ÁCIDOS EN LA SÍNTESIS DE TRIAZINOQUINAZOLINONAS
AMINO ACIDS IN THE SYNTHESIS OF TRIAZINOQUINAZOLINONES

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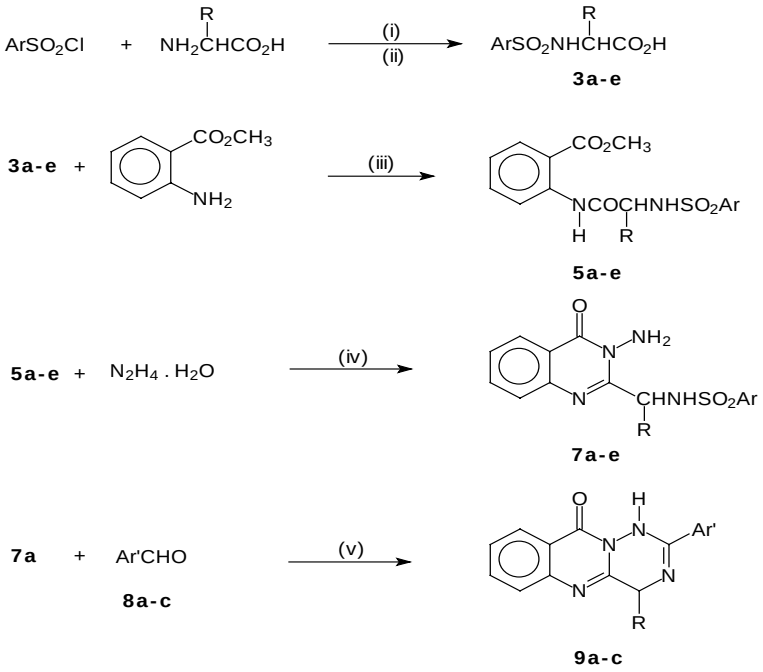
INTRODUCCIÓN

Las quinazolinas son compuestos que poseen una variedad de actividades biológicas, entre las que se incluyen la antiinflamatoria, antipirética[1-2], antimicrobial[3] y fungicidal[4] entre otras. En este trabajo se emplean amino ácidos como producto de partida para el diseño y la preparación de nuevos derivados de triazinoquinazolinonas.



(i): NaOH, (ii): HCl ; (iii): DCC, CH_2Cl_2, T.A. (iv): Δ, (v): DMF, Δ

3, 5, 7 R: a. $-CH(CH_3)_2$; b. $-C_6H_5$; c. $-CH_2C_6H_5$; d. $-H$; e. $-CH_2CH(CH_3)_2$
Ar: a. p-$CH_3C_6H_4$; b. p-$CH_3C_6H_4$; c. p-$CH_3C_6H_4$; d. $-C_6H_5$; e. p-$CH_3C_6H_4$;

9 R: a. =b. =c. $-CH(CH_3)_2$. Ar': a. p-FC_6H_4; b. p-$MeOC_6H_4$, c. p-ClC_6H_4

PARTE EXPERIMENTAL

PREPARACION DE AMINO ÁCIDOS TOSILADOS 3(a-e)

Procedimiento general:

La preparación de los derivados tosilados 3(a-e) se realiza siguiendo el procedimiento general reportado en la literatura[5]. Para convertir el amino ácido en su sal y obtener una solución transparente, 0.026 moles del respectivo amino ácido se disuelven en una solución de hidróxido de sodio (15 mL, 2M), se transfiere a un balón de 25 mL provisto de una barra magnética y se calienta en un baño por 1 minuto con agitación. El balón se remueve del baño caliente y se deja enfriar a temperatura ambiente. A la solución alcalina del amino ácido se añade 0.026 moles de cloruro de p-toluensulfonilo, cuidando que todo el cloruro de p-toluensulfonilo se asiente en el fondo del balón. El balón se coloca nuevamente en el baño caliente con agitación hasta que todo el cloruro de p-toluensulfonilo se disuelva y luego se continúa el calentamiento por 10 minutos a 70-80 ºC. El tiempo total de la reacción no debe exceder de 40 minutos. Se remueve el balón del baño caliente, se enfría a temperatura ambiente y luego se coloca en un baño con hielo. Se agrega ácido clorhídrico 2M gota a gota, hasta obtener un precipitado (pH~2). El balón se sumerge nuevamente en un baño de hielo por 5 minutos adicionales para obtener más precipitado. El producto crudo se filtra, se lava con agua y posteriormente se recristaliza utilizando el solvente apropiado. ^{1}HRMN δ: **a.** 1.02-1.13 (d, 6H, $2CH_3$), 2.25 (m, 1H, CH), 2.30 (s, 3H, CH_3), 7.21-7.44 (m, 4H, Ar-H´s), 7.43 (s, 1H, CO_2H); **b.** 2.28 (s, 3H, CH_3), 4.52 (d, 1H, CH), 7.41-7.82 (m, 4H, Ar-H´s), 8.44 (s, 1H, CO_2H). **c.** 2.31 (s, 3H, CH_3), 3.05-3.26 (m, 2H, CH_2), 3.99-4.22 (m, 1H, CH), 7.28 (s, 1H, CO_2H), 7.29-7.55 (m, 9H, Ar-H´s); **d.** 4.23 (d, 2H, CH), 7.33-7.61 (m, 5H, Ar-H´s); **e.** 0.25 (d, 6H, $2CH_3$), 0.98-1.10 (m, 1H, CH), 1.16-1.28 (m, 2H, CH_2), 2.32 (s, 3H, CH_3), 3.31-3.42 (m, 1H, CH), 7.26 (s, 1H, CO_2H), 7.43-7.50 (m, 4H, Ar-H´s).

SÍNTESIS DE AMIDAS 5(a-e)

Procedimiento general:

Los derivados 5(a-e) fueron obtenidos a partir de las condiciones reportadas en la literatura[6,7]. A 1mmol de los respectivos amino ácidos tosilados 3 (a-e) disueltos en dicloro metano (5 mL) se le añade 1 mmol de diciclohexilcarbodiimida (DCC) disuelta en dicloro metano (5 mL). La mezcla de reacción se agita por 10 minutos a temperatura ambiente. Posteriormente se añade 1 mmol de antranilato de metilo y se agita a temperatura ambiente por 3 a 6 horas. El curso de la reacción se sigue por TLC. Una vez terminada la reacción, la diciclohexilurea se separa por filtración. Al filtrado se le añade $MgSO_4$ y luego de trabajar de manera usual se obtiene el producto esperado. Rendimiento 80-90 %. **a.** ^{1}HRMN δ 0.85-0.95 (m, 6H, $2CH_3$), 2.21 (s, 1H, CH_3), 3.94 (s, 3H, OCH_3), 6.94-9.26 (m, 8H, Ar-H´s), 7.57 (2H, NH); **b.** ^{1}HRMN 2.21 (s, 3H, CH_3), 2.69-2.73 (m, 2H, CH_2), 3.92 (s, 3H, OCH_3), 4.25 (m, 1H, CH), 6.93-9.32 (m, 13H, Ar-H´s), 7.69 (s, 2H, NH); **c.** ^{1}HRMN 2.19 (s, 3H, CH_3), 2.69-2.72 (m, 2H, CH_2), 3.89 (s, 3H, OCH_3), 6.94-9.32 (m, 13H, Ar-H´s), 7.70 (2H, NH), **d.** ^{1}HRMN 3.90 (s, 3H, OCH_3), 6.93-9.22 (m, 9H, Ar-H´s), 8.12 (2H, NH); **e.** ^{1}HRMN 0.97 (d, 6H, $2CH_3$), 1.73-1.95 (m, 2H, CH_2), 1.97-2.19 (m, 1H, CH), 2.21 (s, 3H, CH_3), 3.42-3.55 (m, 1H, CH), 3.92 (s, 3H, OCH_3), 6.94-9.35 (m, 8H, Ar-H´s), 7.45 (s, 2H, NH).

SÍNTESIS DE N-AMINOQUINAZOLIN-4(3H)-ONAS 7(a-e)

Procedimiento general:

Las respectivas amidas 5(a-e) (0.01 mol) y la hidrazina hidratada (95 %) (0.05 mol) se disuelven en n-butanol (30 mL) y se reflujan por 6 a 8 horas[8,9]. Finalizada la reacción, la mezcla se enfría en un baño de hielo y el crudo obtenido se filtra y se recristaliza para dar el producto esperado. IR (cm^{-1}): 3312-3325 (NH_2), 3056-3060 (CH-Ar), 1660-1669 (CO). **a**. p.f 190 ºC, 76 %; ^{1}HRMN 6.82-8.02 (m, 8H, Ar-H´s), 5.51 (s, 2H, NH_2), 10.6 (s, 1H, NH); **b.** p.f 135 ºC, 65 %; **c.** p.f 170 ºC, 68 %; **d.** p.f 180 ºC, 74 %; **e.** p.f 170 ºC, 71 %; ^{1}HRMN 6.86-8.04 (m, 8H, Ar-H´s), 5.57 (s, 2H, NH_2), 10.2 (s, 1H, NH).

SÍNTESIS DE TRIAZINOQUINAZOLINONAS 9(a-c)

Procedimiento general:

El derivado **7a** (0.01 mol) y los aldehídos correspondientes **8a-c** (0.01 mol) disueltos en DMF (20 mL) y se reflujan por 6 a 8 horas en presencia de trietilamina (50 mg). Después de enfriar y acidificar con ácido

clorhídrico diluido, se obtiene un precipitado, se filtra, se lava con agua y se recristaliza para dar los compuestos 9 (a-c). IR (cm^{-1}) : 3196-3219 (NH), 1655-1663 (CO). **a.** p.f 180 ºC, 62 %, ^{1}HRMN 0.83-0.95 (m, 6H, $2CH_3$), 1.99 (m, 1H, CH), 7.35-8.30 (m, 8H, Ar-H´s), 9.21 (s, 1H, NH); **b.** p.f 170 ºC, 60 %, ^{1}HRMN 0.85-0.95 (m, 6H, $2CH_3$), 1.97 (m, 1H, CH), 3.78 (s, 3H, OCH_3), 6.75-8.24 (m, 8H, Ar-H´s), 9.21 (s, 1H, NH); **c.** ^{1}HRMN 0.83-0.95 (m, 6H, $2CH_3$), 1.99 (m, 1H, CH), 7.47-8.32 (m, 8H, Ar-H´s), 9.21 (s, 1H, NH).

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El trabajo en los laboratorios de Medicinal Chemistry debe mantener altos estándares de precaución y buen uso.
El manejo de instrumental eléctrico, la utilización del calor, el material de cristal y los disolventes no presentan un especial problema, si se siguen las instrucciones del supervisor.
Estabilidad: El *Boron trichloride* es inestable e incoloro (boron trichloride). Altamente inflamable; incompatible con metales. El *boron trichloride* reacciona violentamente con agua y fuertemente con “aniline, phosphine, dinitrogen tetroxide”. Produce vapores en presencia de aire húmedo.
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P-cloroanilina puede ser clasificado como un posible carcinógeno.
Diciclohexilcarbodiimida puede ser tóxico y abrasivo.

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Este documento ha sido supervisado por el Prof. José N. Domínguez (jdomingu@cantv.net) que informa que no existen problemas específicos de seguridad en la realización de este ejercicio, incluyendo toxicidad, inflamabilidad y explosión, ni cualquier otro destacable, dentro de lo usual en un laboratorio de Medicinal Chemistry.

Se agradecerá comunicar al Editor cualquier posible incidencia.

EXERCISE V.7

AMINO ACIDS IN THE SYNTHESIS OF TRIAZINOQUINAZOLINONES

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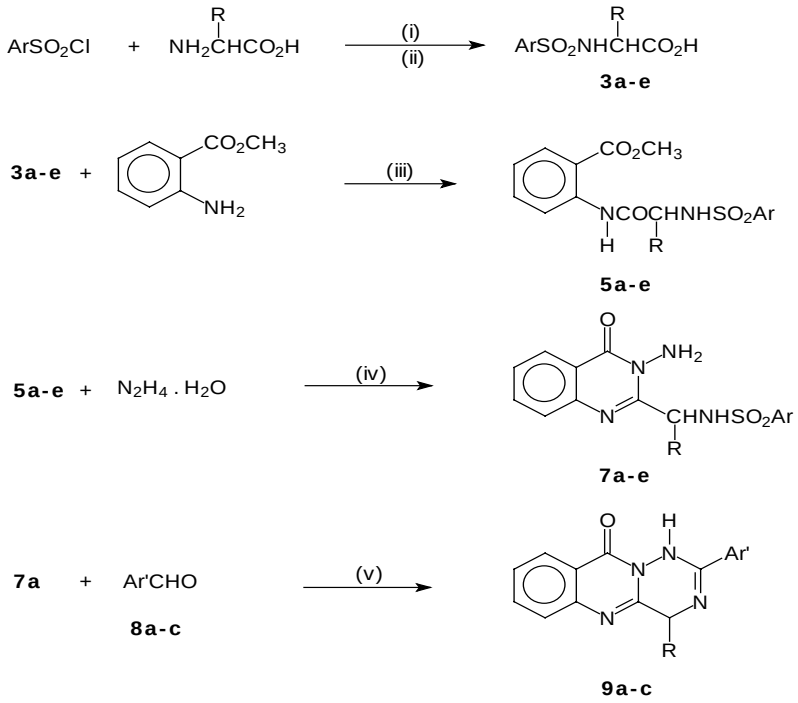
INTRODUCTION

Some biological activities have been attributed to quinazoline compounds, including anti-inflammatory, antipyretic[1–2], antimicrobial[3], and fungicidal[4] among others. In this work, we use amino acids as starting materials for the design and preparation of new triazinoquinazolinone compounds.



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3, **5**, **7** R: a. $-CH(CH_3)_2$; b. $-C_6H_5$; c. $-CH_2C_6H_5$; d. $-H$; e. $-CH_2CH(CH_3)_2$

Ar: a. p-$CH_3C_6H_4$; b. p-$CH_3C_6H_4$; c. p-$CH_3C_6H_4$; d. -C_6H_5; e. p-$CH_3C_6H_4$;

9 R: a. =b. =c. -CH $(CH_3)_2$. Ar': a. p-FC_6H_4; b. p-$MeOC_6H_4$, c. p-ClC_6H_4

EXPERIMENTAL

General procedure for synthesis of tosyl amino acids 3(a–e)

Preparation of derivatives 3(a–e) was performed according to the general procedure reported in the literature.[5] The unknown amino acids 0.026 mol were dissolved in sodium hydroxide solution (15 mL, 2 M). Transfer the sample into the 25-mL round-bottom flask with magnetic stirrer bar. Heat while stirring for at most 1 min. This converts the amino acid to its sodium salt, yielding a clear solution. Remove the flask from the water bath and cool it for 5 min at room temperature. Add 0.026 mol of *p*-toluenesulfonyl chloride (TsCl) to the alkaline amino acid solution and be sure all the TsCl sits on the bottom of the round-bottom flask. Clamp the flask into the water bath and start stirring. After all the TsCl has been dissolved, continue heating an additional 10 min at 70–80 °C. The total reaction time should not exceed 40 min. Remove the flask from the water bath and cool first at room temperature and finally in an ice bath. Add HCl (2 M) dropwise, and soon a white crystalline compound should start precipitating when the acidity has reached pH ~ 2, immerse the beaker for about 5 min in an ice bath. The crude product was filtered off, washed with water, and then recrystallized from appropriate solvent. ^{1}H NMR δ: **a.** 1.02–1.13 (d, 6H, $2CH_3$), 2.25 (m, 1H, CH), 2.30 (s, 3H, CH_3), 7.21–7.44 (m, 4H, Ar-H´s), 7.43 (s, 1H, CO_2H); **b.** 2.28 (s, 3H, CH_3), 4.52 (d, 1H, CH), 7.41–7.82 (m, 4H, Ar-H´s), 8.44 (s, 1H, CO_2H); **c.** 2.31 (s, 3H, CH_3), 3.05–3.26 (m, 2H, CH_2), 3.99–4.22 (m, 1H, CH), 7.28 (s, 1H, CO_2H), 7.29–7.55 (m, 9H, Ar-H´s); **d.** 4.23 (d, 2H, CH), 7.33–7.61 (m, 5H, Ar-H´s); **e.** 0.25 (d, 6H, $2CH_3$), 0.98–1.10 (m, 1H, CH), 1.16–1.28 (m, 2H, CH_2), 2.32 (s, 3H, CH_3), 3.31–3.42 (m, 1H, CH), 7.26 (s, 1H, CO_2H), 7.43–7.50 (m, 4H, Ar-H´s).

General procedure for synthesis of the amides 5(a–e)

Compounds 5(a–e) were obtained from known procedures.[6,7] To tosylated amino acids 3(a–e), 1 mmol dissolved in dichloromethane (5 mL) was added to 1 mmol dicyclohexylcarbodiimide (DCC) in dichloromethane (5 mL). The reaction mixture was stirred for 10 min at room temperature. Add 1 mmol of methyl anthranilate with

continuous stirring at room temperature (3–6 h). The reaction was monitored by thin-layer chromatography (TLC). Once the reaction ended, the dicyclohexylurea was separated by filtration and $MgSO_4$ was added to the filtrate portion, after the usual work-up the title products were obtained. Yield 80–90 %. **a.** ^{1}H NMR δ 0.85–0.95 (m, 6H, $2CH_3$), 2.21 (s, 1H, CH_3), 3.94 (s, 3H, OCH_3), 6.94–9.26 (m, 8H, Ar-H´s), 7.57 (2H, NH); **b.** ^{1}H NMR 2.21 (s, 3H, CH_3), 2.69–2.73 (m, 2H, CH_2), 3.92 (s, 3H, OCH_3), 4.25 (m, 1H, CH), 6.93–9.32 (m, 13H, Ar-H´s), 7.69 (s, 2H, NH); **c.** ^{1}H NMR 2.19 (s, 3H, CH_3), 2.69–2.72 (m, 2H, CH_2), 3.89 (s, 3H, OCH_3), 6.94-9.32 (m, 13H, Ar-H´s), 7.70 (2H, NH); **d.** ^{1}H NMR 3.90 (s, 3H, OCH_3), 6.93–9.22 (m, 9H, Ar-H´s), 8.12 (2H, NH); **e.** ^{1}H NMR 0.97 (d, 6H, $2CH_3$), 1.73–1.95 (m, 2H, CH_2), 1.97–2.19 (m, 1H, CH), 2.21 (s, 3H, CH_3), 3.42–3.55 (m, 1H, CH), 3.92 (s, 3H, OCH_3), 6.94–9.35 (m, 8H, Ar-H´s), 7.45 (s, 2H, NH).

General procedure for synthesis of *N*-amino quinazolin-4(3H)-one derivatives 7(a–e)

The corresponding amide 5 (a–e) (0.01 mol) and 95 % hydrazine hydrate (0.05 mol) were dissolved in *n*-butanol (30 mL) and refluxed for 6–8 h.[8,9] Cooling in an ice bath gave the crude product, which was filtered off and recrystallized to give compounds 7 (a–e). IR (cm^{-1}): 3312–3325 (NH_2), 3056–3060 (CH-Ar), 1660–1669 (CO). **a.** m.p. 190 ºC, 76 %; ^{1}H NMR δ 6.82-8.02 (m, 8H, Ar-H´s), 5.51 (s, 2H, NH_2), 10.6 (s, 1H, NH); **b.** m.p. 135 ºC, 65 %; **c.** m.p. 170 ºC, 68 %; **d.** m.p. 180 ºC, 74 %; **e.** m.p. 170 ºC, 71 %; ^{1}H NMR δ 6.86–8.04 (m, 8H, Ar-H´s), 5.57 (s, 2H, NH_2), 10.2 (s, 1H, NH).

General procedure for the synthesis of triazinoquinazolinones 9(a–c)

Compound 7a (0.01 mol) and the corresponding aldehyde derivatives 8(a–c) (0.01 mol) in DMF (20 mL) containing triethylamine (50 mg), and it was refluxed for 6–8 h; after cooling and acidification with dilute hydrochloric acid, a precipitate was formed, which was collected by filtration, washed with water, and recrystallized to give 9(a–c). IR (cm^{-1}): 3196–3219 (NH), 1655-1663 (CO). **a**. m.p. 180 ºC, 62 %, ^{1}H NMR δ 0.83–0.95 (m, 6H, $2CH_3$), 1.99 (m, 1H, CH), 7.35–8.30 (m, 8H, Ar-H´s), 9.21 (s, 1H, NH); **b.** m.p. 170 ºC, 60 %, ^{1}H NMR 0.85–0.95 (m, 6H, $2CH_3$), 1.97 (m, 1H, CH), 3.78 (s, 3H, OCH_3), 6.75–8.24 (m, 8H, Ar-H´s), 9.21 (s, 1H, NH); **c.** ^{1}H NMR 0.83–0.95 (m, 6H, $2CH_3$), 1.99 (m, 1H, CH), 7.47–8.32 (m, 8H, Ar-H´s), 9.21 (s, 1H, NH).

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P-chloroaniline should be labeled as a possible carcinogen.
Dicyclohexylcarbodiimide can be sensitizing and toxic.

Personal Protection:Wear suitable protective clothing, safety glasses and gloves.Keep container in a well-ventilated place.In case of contact with eyes, rinse immediately with plenty of water and seek medical advice.After contact with skin, wash immediately with plenty of water.
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