SYNTHESIS OF CONDENSED PYRIMIDINES IN ONE-POT REACTION FROM PYRANOQUINOLINES AND BMMAs

Nariman M. Nahas
Department of Chemistry, Faculty of Applied Science, Umm Al-Qura University,
Makkah, P.O.Box 16222, Saudi Arabia

Abstract: New pentacyclic heterocycles of the type 3a-e -5a-e were synthesized by one - pot reaction of the amino-cyano pyrano[3,2-h]quinolines 1a-e with BMMAs (e.g. Ethyl N-[bis (methylsulfanyl) methylene] glycinate, ethyl 2[bis (methylsulfanyl) methylene]-1-methylhydrazine carboxylate and / or ethyl N[bis(methylsulfanyl) methylene]- β-alaninate). All the synthesized derivatives were identified by conventional methods (IR, ^{1}HNMR, MS) and elemental analysis.
Antifungal tests were also performed.

Introduction

Literature survey has revealed that pyran and pyrimidine rings are interesting class of heterocycles and were found to posses wide biological activities (1-6). On the other hand, the synthesis of pyranoquinolins has gained very important goals to be used as antibacterial activities (7-10). Recently, the use of new reagents for heterocyclic annelation containing an N-[bis (methylthio) methylene]amino moiety (=BMMA) was reported and allowed to synthesize condensed pyrimidines in a one-pot reaction from heteroaromatic ortho-aminocarbonyl type compounds (11). Some authors showed the use of BMMA in combination with electron-rich pentatomic heterocycles (12-15) and their condensed homologues, but nothing has been reported so far on their employment in reaction with pyran derivatives. Therefore in this paper we report the efficient one-pot synthesis of new pentacyclic heterocyclic systems obtained from the reaction of substituted pyranoquinolines with several BMMA reagents.

Experimental

Chemicals were purchase from Merck, Fluka, and Aldrich chemical companies. The reaction was monitored by TLC. The products were isolated and identified by comparison of their physical and spectral data for those in literature, and all of compounds 2a-c (BMMAs) were synthesized by the reported procedure (15). IR spectra were recorded on Nicolet Jeol FT-IR and the ^{1}HNMR were measured on an EM-360 200MHz instrument. Microanalyses were determined on a Perkin-Elmer 240C microanalyser, and Mass spectra were recorded on a Jeol JMS 600 spectrometer.

General procedure for the synthesis of 2-amino-3-cyanopyrano[3, 2-h]quinolines 1_{a-e} with BMMAs

A mixture of 1a-e (0.01 mol), and BMMA (0.01 mol) in glacial acetic acid (20 ml) was heated under reflux for 3-5 h, with stirring. The reaction mixture was allowed to cool, poured on ice/ cold water and neutralized with sodium carbonate. The precipitate was filtered off and recrystallized from ethanol.

14-Aryl-12-chloro-5-(methylsulfanyl)-2-oxo-imidazo[1,2-c]pyrimido[4`,5`: 6,5]pyrano[3,2-h]quinolines 3a-e.

These compounds were prepared by the reaction of 1a-e with ethyl N-[bis(methylsulfanyl)methylene]glycinate 2a for 4 h

Compound 3a: (61% yield); Mp (°C) = 292 dec.; IR (v cm^{-1}) = 1700 (C=O); Ms (m/z) = 4-46; ^{1}HNMR ($CDCl_3$) = 2.65 (s, 3H, CH_3), 4.26 (s, 2H, CH_2), 4.95 (s, 1H, pyran), 7.18-8.70 (m, 9H, arom); Anal. Calcd. For $C_{23}H_{15}N_4O_2SCl$: C 61.81%, H 3.38%, N 12.54%, S 7.18%, Cl 7.93%. Found: C 61.72%, H 3.41%, N 12.49%, S 7.26%, Cl 7.84%.

Compound 3b: (55% yield); Mp (°C) = 276-79 dec.; IR (ν cm^{-1}) = 1700 (C=O); ^{1}HNMR ($CDCl_3$) = 2.60 (s, 3H, CH_3), 3.70 (s, 3H, CH_3), 4.25 (s, 2H, CH_2), 4.95 (s, 1H, pyran), 7.20-8.80 (m, 8H, arom). Anal. Calcd. For $C_{24}H_{17}N_4O_3SCl$: C 60.44%, H 3.59%, N 11.75%, S 6.72%, Cl 7.43%. Found: C 60.52%, H 3.52%, N 11.66%, S 6.65%, Cl 7.51%.

Compound 3c: (51% yield); Mp (°C) = 287-89 dec.; IR (ν cm^{-1}) = 1720 (C=O); ^{1}HNMR ($CDCl_3$) = 2.65 (s, 3H, CH_3), 4.30 (s, 2H, CH_2), 5.00 (s, 1H, pyran), 7.18-8.76 (m, 8H, arom). Anal. Calcd. For $C_{23}H_{14}N_5O_4SCl$: C 56.16%, H 2.87%, N 14.24%, S 6.52%, Cl 7.21%. Found: C 56.23%, H 2.81%, N 14.29%, S 6.47%, Cl 7.15%.

Compound 3d: (56% yield); Mp (°C) > 300; IR (ν cm^{-1}) = 1710 (C=O); MS (m/z) = 436; ^{1}HNMR ($CDCl_3$) = 2.60 (s, 3H, CH_3), 4.35 (s, 2H, CH_2), 4.90 (s, 1H, pyran), 6.38-8.70 (m, 7H, arom). Anal. Calcd. For $C_{21}H_{13}N_4O_3SCl$: C 57.73, H 3.00%, N 12.83%, S 7.34%, Cl 8.11%. Found: C 57.64%, H 2.95%, N 12.77%, S 7.40%, Cl 8.20%.

Compound 3e: (53% yield); Mp (°C) > 300; IR (ν cm^{-1}) = 1710 (C=O); ^{1}HNMR ($CDCl_3$) = 2.60 (s, 3H, CH_3), 4.32 (s, 2H, CH_2), 4.90 (s, 1H, pyran), 7.12-8.80 (m, 7H, arom). Anal. Calcd. For $C_{21}H_{13}N_4O_2S_2Cl$: C 55.68, H 2.89%, N 12.37%, S 14.16%, Cl 7.83%. Found: C 55.76%, H 2.81%, N 12.42%, S 14.42%, Cl 7.90%.

14-Aryl-12-chloro-3-methyl-5-(methylsulfanyl)-2-oxo-3H-[1,2,4]triazolo[1,2-c]pyrimido[4`,5`: 6,5]pyrano[3,2-h]quinolines 4a-e:

These compounds were prepared by the reaction of 1a-e with ethyl 2-[bis(methylsulfanyl)methylene]-1-methylhydrazine carboxylate 2b in glacial acetic acid for 3 h.

Compound 4a: (58% yield), Mp (°C) = 266-68dec.; IR (ν cm^{-1}) = 1715 (C=O); ^{1}HNMR ($CDCl_3$) = 2.80 (s, 3H, CH_3), 3.60 (s, 3H, CH_3), 4.95 (s, 1H, pyran), 7.20-8.70 (m, 8H, arom). Anal. Calcd. For $C_{23}H_{16}N_5O_2SCl$: C 59.80, H 3.49%, N 15.17%, S 6.94%, Cl 7.67%. Found: C 59.74%, H 3.43%, N 15.10%, S 6.88%, Cl 7.73%.

Compound 4b: (52% yield); Mp (°C) > 300; IR (ν cm^{-1}) = 1705 (C=O); ^{1}HNMR ($CDCl_3$) = 2.65 (s, 3H, CH_3), 3.70 (s, 3H, CH_3), 3.40 (s, 3H, CH_3), 4.90 (s, 1H, pyran), 7.22-8.78 (m, 8H, arom). Anal. Calcd. For $C_{24}H_{18}N_5O_3SCl$: C 58.59, H 3.69%, N 14.24%, S 6.52%, Cl 7.21%. Found: C 58.68%, H 3.61%, N 14.17%, S 6.45%, Cl 7.29%.

Compound 4c: (57% yield); Mp (°C) > 300; IR (ν cm^{-1}) =1370, 1570 (NO_2), 1720 (C=O); ^{1}HNMR ($CDCl_3$) = 2.75 (s, 3H, CH_3), 3.50 (s, 3H, CH_3), 5.00 (s, 1H, pyran), 7.18-8.80 (m, 8H, arom). Anal. Calcd. For $C_{23}H_{15}N_6O_4SCl$: C 54.49, H 2.98%, N 16.58%, S 6.33%, Cl 6.99%. Found: C 54.54%, H 2.93%, N 16.52%, S 6.26%, Cl 6.90%.

Compound 4d: (50% yield); Mp (°C) = 258-60dec.; IR (ν cm^{-1}) = 1710 (C=O); MS (mz) = 451; ^{1}HNMR ($CDCl_3$) = 2.60 (s, 3H, CH_3), 3.40 (s, 3H, CH_3), 4.90 (s, 1H, pyran), 6.40-8.75 (m, 7H, arom). Anal. Calcd. For $C_{21}H_{14}N_5O_3SCl$: C 55.81%, H 3.12%, N 15.50%, S 7.10%, Cl 7.85%. Found: C 55.75%, H 3.16%, N 15.46%, S 7.16%, Cl 7.91%.

Compound 4e: (54% yield), Mp (°C) > 300; IR (ν cm^{-1}) 1710 (C=O); ^{1}HNMR ($CDCl_3$) = 2.60 (s, 3H, CH_3), 3.40 (s, 3H, CH_3), 4.90 (s, 1H, pyran), 7.10-8.65 (m, 7H, arom). Anal. Calcd. For $C_{21}H_{14}N_5O_2S_2Cl$: C 53.90, H 3.02%, N 14.97%, S 13.71%, Cl 7.58%. Found: C 53.83%, H 2.97%, N 14.93%, S 13.97%, Cl 7.63%.

15-Aryl-13-chloro-3,4-dihydro-6-(methylsulfanyl)-2-oxo-pyrimido[1,2-c] pyrimido[4`,5`: 6,5]pyrano[3,2-h]quinolines 5a-e:

These compounds were prepared by the reaction of 1a-e with ethyl N-[bis(methylsulfanyl)methylene]-β-alaninate 2c in glacial acetic acid for 5 h.

Compound 5a: (40% yield); Mp (°C) > 300; IR (ν cm^{-1}) 1690 (C=O); ^{1}HNMR ($CDCl_3$) = 2.50 (s, 3H, CH_3), 2.60 (t, 2H, CH_2, J = 6.30 Hz), 4.30 (t, 2H, CH_2, J = 6.30 Hz), 4.95 (s, 1H, pyran), 7.18-8.76 (m, 9H, arom). Anal. Calcd. For $C_{24}H_{17}N_4O_2SCl$: C 62.53, H 3.72%, N 12.16%, S 6.96%, Cl 7.69%. Found: C 62.61%, H 3.66%, N 12.22%, S 7.01%, Cl 7.77%.

Compound 5b: (43% yield); Mp (°C) = 298-300dec.; IR (ν cm^{-1}) 1960 (C=O); ^{1}HNMR ($CDCl_3$) = 2.50 (s, 3H, CH_3), 2.65 (t, 2H, CH_2, J = 6.35 Hz), 3.70 (s,3H,CH_3), 4.27 (t, 2H, CH_2, J = 6.35 Hz), 4.90 (s, 1H, pyran), 6.88-8.70 (m, 8H, arom). Anal. Calcd. For $C_{25}H_{19}N_4O_3SCl$: C 61.16, H 3.90%, N 11.41%, S 6.53%, Cl 7.22%. Found: C 61.22%, H 3.85%, N 11.37%, S 6.81%, Cl 7.27%.

Compound 5c: (38% yield); Mp (°C) > 300; IR (ν cm^{-1}) 1700 (C=O); ^{1}HNMR ($CDCl_3$) = 2.60 (s, 3H, CH_3), 2.70 (t, 2H, CH_2, J = 6.80 Hz), 4.35 (t, 2H, CH_2, J = 6.80 Hz), 5.00 (s, 1H, pyran), 7.18-8.78 (m, 8H, arom). Anal. Calcd. For $C_{24}H_{16}N_5O_4SCl$: C 56.97, H 3.19%, N 13.85%, S 6.34%, Cl 7.01%. Found: C 56.89%, H 3.22%, N 13.77%, S 6.29%, Cl 7.10%.

Compound 5d: (35% yield); Mp (°C) = 263-65dec.; IR (ν cm^{-1}) 1695 (C=O); ^{1}HNMR ($CDCl_3$) = 2.55 (s, 3H, CH_3), 2.67 (t, 2H, CH_2, J = 6.60 Hz), 4.28 (t, 2H, CH_2, J = 6.60 Hz), 4.90 (s, 1H, pyran), 6.38-8.75 (m, 7H, arom). Anal. Calcd. For $C_{22}H_{15}N_4O_3SCl$: C 58.60, H 3.35%, N 12.43%, S 7.11%, Cl 7.86%. Found: C 58.54%, H 3.30%, N 12.50%, S 7.05%, Cl 7.92%.

Compound 5e: (30% yield); Mp (°C) > 300; IR (ν cm^{-1}) 1690 (C=O); ^{1}HNMR ($CDCl_3$) = 2.55 (s, 3H, CH_3), 2.67 (t, 2H, CH_2, J = 6.60 Hz), 4.28 (t, 2H, CH_2, J = 6.60 Hz), 4.95 (s, 1H, pyran), 7.15-8.70 (m, 7H, arom). Anal. Calcd. For $C_{22}H_{15}N_4O_2S_2Cl$: C 56.58, H 3.24%, N 12.00%, S 13.74%, Cl 7.59%. Found: C 56.66%, H 3.27%, N 11.92%, S 13.69%, Cl 7.50%.

Antifungal Activity

The newly synthesized compounds were screened for their antifungal activity against three of fungi, namely, Fusarium moniliforme, Rhizopus stalonifer and Aspergillus terreus, using the disk diffusion method (16, 17). The results of the biological activity showed that only compounds 3c; 4a, 4c; 5c, 5d showed weak activity and the remaining compound exhibited moderate activity with respect to tetracyclin as a standard.

Results and Discussions

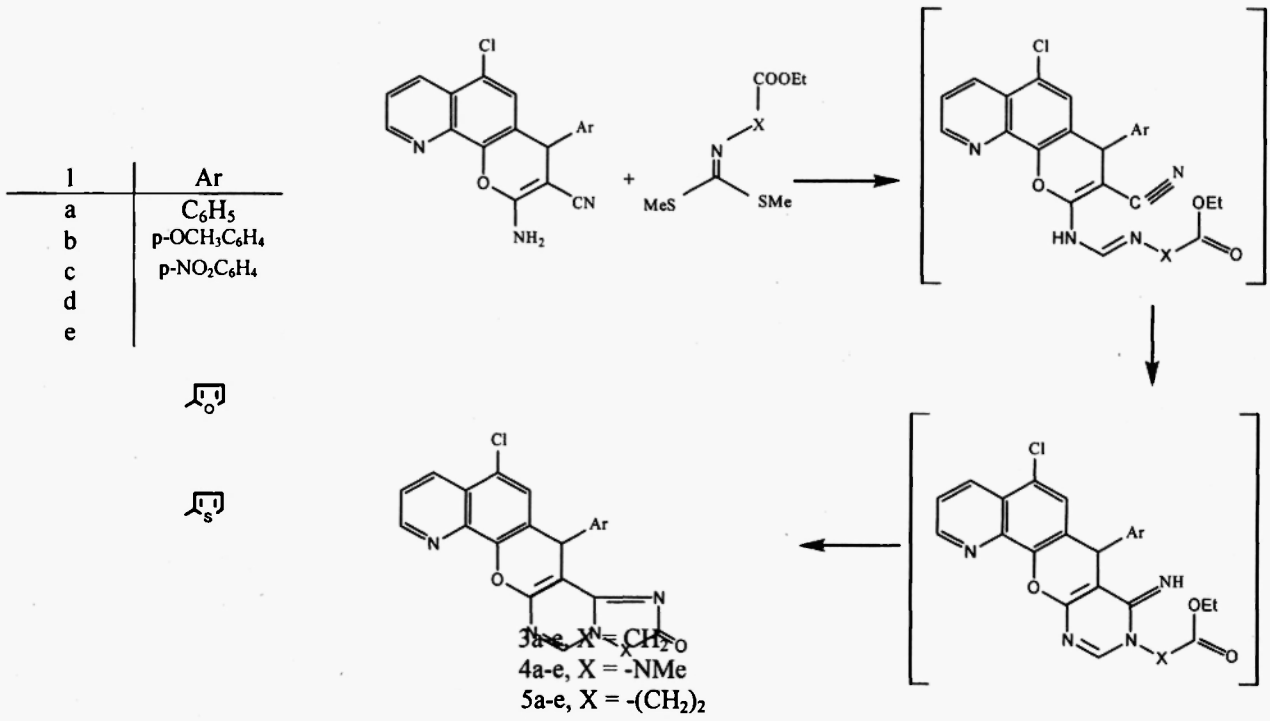
The starting BMMA reagents 2a-c were prepared in good yields by reacting adequate amino ester with CS_2/ MeI/ NEt_3 and subsequently accomplishing the alkylation of the intermediate thus obtained with methyl iodide and potassium carbonate (15). As mentioned before, some authors showed the use of BMMA in combination with electron-rich pentatomic heterocycles (furan and thiophene) and their condensed homologues (13, 14) and recently with pyrroles (15), but nothing had been reported so far on their employment in reactions with pyran derivatives. For this purpose the amino-cyanopyrano[3,2-h]quinolines were allowed to react with ethyl N-[bis(methylsulfanyl)methylene]glycinate 2a, ethyl 2-[bis(methylsulfanyl)methylene]-1-methylhydrazine carboxylate 2b and/ or ethyl N-[bis(methylsulfanyl)methylene]-β-alaninate 2c to produce the expected pentacyclic heterocycles namely, 14-Aryl-12-chloro-5-(methylsulfanyl)-2-oxo-imidazo[1,2-c]pyrimido[4`,5`: 6,5]pyrano[3,2-h]quinolines 3a-e; 14-Aryl-12-chloro-3-methyl-5-(methylsulfanyl)-2-oxo-3H-[1,2,4]triazolo[1,2-c]pyrimido[4`,5`: 6,5]pyrano[3,2-h]quinolines 4a-e and/ or 15-Aryl-13-chloro-3,4-dihydro-6-(methylsulfanyl)-2-oxo-pyrimido[1,2-c] pyrimido[4`,5`: 6,5]pyrano[3,2-h]quinolines 5a-e respectively. The spectral data and the elemental analysis proved the formation of these pentacyclic heterocycles 3a-e – 5a-e, so the use of BMMA reagent to prepare a condensed pyrimidine in one-pot reaction from (hetero) aromatic ortho-amino-carbonyl-type compounds (COOEt and CN) was succeeded not only for pentatomic heterocycles (furan, thiophene and pyrrole) (12-15), but also for hexatomic heterocycles pyrans.

The mechanism of formation of pentacyclic heterocycles was suggested to proceed as follows: (Scheme-1):

Conclusions

This work reports a facile one-pot synthesis of pentacyclic heterocycles using BMMA and amino-cyano pyran derivatives

1	Ar
a	C_6H_5
b	p-$OCH_3C_6H_4$
c	p-$NO_2C_6H_4$
d	
e	



Scheme-1

References

1. S.J. Mohr, M. A. Chirigos and F.S. Fuhrman, J.W. *Pryor, Cancer Res.* **35**, 3750 (1975).
2. F.Eiden and F. Denk, *Arch -Pharm. Weinnheim Ger.* **324**, 353 (1991).
3. V. K. Tandon, M. Vaish, S. Jain, D.S. Bhakuni and R. C. Srimal, *Indian J. Pharm Sci.* **53**, 22 (1991).
4. A. Richardson and F. J. McCarry, *J. Med. Chem.* **15, 1203** (1972).
5. V. J. Ram, *J. Prakt, Chem.* **331, 893** (1989).
6. S. Mehrota, J. P. Barthcal, B. R. Pandey, K. P. Bharagava and S. S. Parmar, *J. Heterocyclic Chem.* **17, 1213** (1980).
7. K. C. Majumdar, S. K. Ghosh and P. Biswas, *Monatshefte Fur Chemie.* **131, 967** (2000).
8. A. A. Abdel Hafez, *J. Chem. Tech. Biotechnol.* **55, 95** (1992).
9. M. S. Al-Thebite, *Afinidad*, **489, 365** (2000).
10. N. M. Nahas and A. A. Abdel Hafez, *Heterocyclic Commun.* **11 (3-4), 263** (2005).
11. F. Sauter, J. Frohlich, K. Blasl and K. Gewald, *Heterocycles* **40, 851** (1995).
12. A. Z. M. J. Shaifullah Chowdhury, *J. Bangladesh Acad. Sci* **23, 59, (1999)**; *Chem. Abstr.* **132, 93275** (1999).
13. F. Sauter, J. Frohlich and E. K. Ahmed, *Monatsh Chem.* **127, 319** (1996).
14. F. Sauter, J. Frohlich and A. Z. M. Shaifullah Chowdhury, *Sci Pharm.* **64, 647** (1996); *Chem. Abstr.* **125, 275796** (1996).
15. L. Antonino, B. Marcella, D. Patrizia, B. Paola, M. Alessandra, C. Girolamo, D. Gaetano and A.M. Anna, *Bioorganic & Medicinal Chemistry* **13, 1545** (2005).
16. L. P. Carrod and P. D. Grady, *Antibiotic and Chemotherapy*, 3rd ed., Churchill Livingstone Edinburgh P. **477** (1927).
17. A. Cremer, *Antibiotic Sensitivity and Assay Tests*, 4th ed. Butterworth, London, P. **521** (1980).

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