Synthesis of Benzopyranophenazines via Isocyanide-Based Three-Component Reactions

AYOOB BAZGIR* AND ALI MOHAMMAD ASTARAKI

Department of Chemistry, Islamic Azad University, Doroud Branch, P.O. Box 133, Doroud,
Iran

a_bazgir@iau-doroud.ac.ir

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Abstract: Benzo[*a*]pyrano[2,3-*c*]phenazines were synthesized in good yields by a three-component reaction of benzo[*a*]phenazin-5-oles, isocyanides and dialkyl acetylendicarboxylates. In refluxing ethanol.

Keywords: Isocyanide, Benzo[*a*]pyrano[2,3-*c*]phenazines, Dialkyl acetylendicarboxylate.

Introduction

Multi-component reactions (MCRs) have been frequently used by synthetic chemists as a facile means to generate molecular diversity from bifunctional substrates that react sequentially in an intramolecular fashion.^{1,2} In recent years, isocyanide-based multicomponent condensation reactions (IMCRs) by virtue of their synthetic potential, their inherent atom efficiency, convergent nature, ease of implementation, and the generation of molecular diversity, have attracted much attention because of the advantages that they offer to the field of combinatorial chemistry.^{3,4}

It has been shown that isocyanides add to activated alkynes to generate zwitterionic species, which have been captured by CH-acids to produce various heterocycles.⁵⁻¹⁰ Although three-component reaction of isocyanide, activated alkynes and CH-acid has been applied to the synthesis of various heterocycles, to our knowledge, this synthetic strategy has not been applied to the synthesis of substituted benzo[*a*]pyrano[2,3-*c*]phenazine.

More than 6000 phenazine-containing compounds have been identified and reported during the past century.¹¹ Several hundreds of the known phenazines possess biological activities, including antimalarial,¹² trypanocidal,¹³ fungicidal,¹⁴ and antiplatelet¹⁵ effects, and are either isolated from natural sources or synthetically constructed. Also, the antitumor activity of pyridophenazinediones and pyridazinophenazinedione derivatives was reported.^{16,17} Due to

wide range of phenazines biological activity, research in this area is continuous to thrive and mostly is directed toward the synthesis of compounds with enhanced biological activity.^{11,18-}

²⁰ A literature survey reveals that limited number of synthetic routes for the preparation of benzopyranophenazines have been reported. Recently, the two-step synthesis of benzopyranophenazines under harsh conditions and long reaction time was described by Perez-Sacau and co-workers.²¹ To the best of our knowledge, there is only two reports on synthesis of benzopyranophenazines *via* a multicomponent reaction.²²

Due to the biological activity of phenazine derivatives, herein, we report an efficient isocyanide-based three-component method for the preparation of benzo[*a*]pyrano[2,3-*c*]phenazines.

Experimental

Melting points were measured on an Elecrtothermal 9100 apparatus. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. ¹H, ¹³C NMR were recorded on a BRUKER DRX-300 AVANCE spectrometer at 300.13 and 75.47 MHz, respectively. IR spectra were recorded using an FTIR apparatus. Elemental analyses were performed using a Heracus CHN-O-Rapid analyzer. The chemical used in this work were obtained from Fluka and Merck and were used without purification.

Typical procedure for the preparation of benzopyranophenazine (4)

A mixture of benzo[*a*]phenazin-5-oles (1 mmol), isocyanides (1 mmol) and dialkyl acetylenedicarboxylates (1 mmol) in refluxing etanole (5 mL) was stirred for 20 h. After completion of the reaction (TLC; ethyl acetate/n-hexane, 1/1), the reaction mixture was filtered and the precipitate washed with ethanol (5 mL) to afford the pure product.

*Dimethyl 3-(cyclohexylamino)-1H-benzo[*a*]pyrano[2,3-*c*]phenazine-1,2-dicarboxylate (4a)*

Yellow powder (86%); mp 225-227 °C. IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 3267, 1742, 1677. MS (EI, 70eV) *m/z*: 497 (*M*⁺). ¹H NMR (300 MHz, CDCl₃): δ_{H} 1.38-2.23 (10H, m, 5CH₂ of cyclohexyl), 3.63 (3H, s, OCH₃), 3.89 (3H, s, OCH₃), 4.10 (1H, bs, CH-N), 5.78 (1H, s, CH), 7.84-8.36 (7H, m, Ar-H), 8.85 (1H, d, *J* = 7.4 Hz, NH), 9.38-9.41 (1H, m, Ar-H). ¹³C NMR (75 MHz, CDCl₃): δ_{C} 24.6, 24.7, 25.6, 33.6, 33.9, 36.7, 50.6, 51.2, 52.3, 72.2, 112.7, 121.5, 125.6, 126.3, 128.6, 129.5, 129.6, 130.0, 130.1, 131.1, 141.1, 141.7, 142.6, 147.4, 160.1, 170.1, 174.1. Anal. Calcd for C₂₉H₂₇N₃O₅. C, 70.01; H, 5.47; N, 8.45. Found: C, 69.90; H, 5.41; N, 8.36.

*Diethyl 3-(cyclohexylamino)-1H-benzo[*a*]pyrano[2,3-*c*]phenazine-1,2-dicarboxylate (4b)*

Yellow powder (88%); mp 184-186 °C. IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 3240, 1720, 1669. MS (EI, 70eV) *m/z*: 525 (*M*⁺). ¹H NMR (300 MHz, CDCl₃): δ_{H} 1.21 (3H, t, *J* = 5.6 Hz, CH₃), 1.42-2.22 (13H, m, 5CH₂ of cyclohexyl and CH₃), 4.09 (3H, bs, CH-N of and OCH₂), 4.35 (2H, ABq, *J* = 5.6 Hz, OCH₂), 5.74 (1H, s, CH), 7.85-8.33 (7H, m, Ar-H), 8.87 (1H, bs, NH), 9.40 (1H, bs, Ar-H). ¹³C NMR (75 MHz, CDCl₃): δ_{C} 14.3, 14.8, 24.7, 25.6, 33.6, 33.9, 37.0, 50.5, 59.6, 60.8, 72.3, 112.7, 121.6, 125.5, 126.4, 128.6, 129.4, 129.5, 129.9, 130.1, 131.1, 140.5, 141.0, 141.9, 142.6, 147.4, 159.9, 169.8, 174.2. Anal. Calcd for C₃₁H₃₁N₃O₅. C, 70.84; H, 5.94; N, 7.99. Found: C, 70.72; H, 5.99; N, 7.93.

Dimethyl 3-(tert-butylamino)-1H-benzo[a]pyrano[2,3-c]phenazine-1,2-dicarboxylate (4c)

Yellow powder (80%); mp 237-239 °C. IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 3200, 1737, 1671. MS (EI, 70eV) m/z : 471 (M^+). ^1H NMR (300 MHz, DMSO- d_6): δ_{H} 1.60 (9H, s, CH_3), 3.49 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 5.64 (1H, s, CH), 7.97-8.37 (7H, m, Ar-H), 9.09 (1H, s, NH), 9.28-9.31 (1H, m, Ar-H). ^{13}C NMR (75 MHz, CDCl_3): δ_{C} 30.6, 36.4, 51.2, 51.3, 52.3, 52.5, 72.9, 112.7, 122.0, 125.7, 126.2, 128.4, 128.5, 129.2, 129.5, 129.6, 130.0, 131.1, 140.4, 141.1, 141.6, 142.6, 142.7, 147.7, 161.4, 170.3, 174.0. Anal. Calcd for $\text{C}_{27}\text{H}_{25}\text{N}_3\text{O}_5$. C, 68.78; H, 5.34; N, 8.91. Found: C, 68.85; H, 5.41; N, 8.84.

Diethyl 3-(tert-butylamino)-1H-benzo[a]pyrano[2,3-c]phenazine-1,2-dicarboxylate (4d)

Yellow powder (81%); mp 239-241 °C. IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 3200, 1721, 1669. MS (EI, 70eV) m/z : 499 (M^+). ^1H NMR (300 MHz, DMSO- d_6): δ_{H} 1.08 (3H, t, $J = 6.9$ Hz, CH_3), 1.31 (3H, t, $J = 6.4$ Hz, CH_3), 1.60 (9H, s, CH_3), 3.97 (2H, m, OCH_2), 4.25 (2H, ABq, $J = 6.4$ Hz, OCH_2), 5.60 (1H, s, CH), 8.00-8.38 (7H, m, Ar-H), 9.14 (1H, s, NH), 9.34-9.37 (1H, m, Ar-H). Anal. Calcd for $\text{C}_{29}\text{H}_{29}\text{N}_3\text{O}_5$. C, 69.72; H, 5.85; N, 8.41. Found: C, 69.63; H, 3.92; N, 8.50. (Due to very low solubility of the product 4d, we cannot report the ^{13}C NMR data for this product.)

Dimethyl 3-(2,4,4-trimethylpentan-2-ylamino)-1H-benzo[a]pyrano[2,3-c]phenazine-1,2-dicarboxylate (4e)

Yellow powder (83%); mp 197-199 °C. IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 3300, 1744, 1674. MS (EI, 70eV) m/z : 527 (M^+). ^1H NMR (300 MHz, DMSO- d_6): δ_{H} 0.96 (9H, s, CH_3), 1.62 (3H, s, CH_3), 1.65 (3H, s, CH_3), 2.02 (2H, s, CH_2), 3.47 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 5.65 (1H, bs, CH), 7.98-8.38 (7H, m, Ar-H), 9.20 (1H, s, NH), 9.27-9.30 (1H, m, Ar-H). ^{13}C NMR (75 MHz, CDCl_3): δ_{C} 31.1, 31.4, 31.6, 31.8, 36.4, 51.2, 52.2, 53.1, 56.1, 72.6, 113.0, 122.1, 125.8, 126.2, 128.6, 129.5, 129.5, 129.6, 130.0, 131.2, 140.4, 141.2, 141.6, 141.7, 147.8, 161.1, 161.4, 170.3, 173.9. Anal. Calcd for $\text{C}_{31}\text{H}_{33}\text{N}_3\text{O}_5$. C, 70.57; H, 6.30; N, 7.96. Found: C, 70.50; H, 6.36; N, 7.88.

Diethyl 3-(2,4,4-trimethylpentan-2-ylamino)-1H-benzo[a]pyrano[2,3-c]phenazine-1,2-dicarboxylate (4f)

Yellow powder (89%); mp 176-178 °C. IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 3400, 1731, 1666. MS (EI, 70eV) m/z : 555 (M^+). ^1H NMR (300 MHz, DMSO- d_6): δ_{H} 0.96 (9H, s, CH_3), 1.05 (3H, t, $J = 7$ Hz, CH_3), 1.30 (3H, t, $J = 7.1$ Hz, CH_3), 1.61 (3H, s, CH_3), 1.64 (3H, s, CH_3), 2.03 (2H, s, CH_2), 3.95 (2H, m, OCH_2), 4.24 (2H, ABq, $J = 7$ Hz, OCH_2), 5.62 (1H, s, CH), 7.99-8.39 (7H, m, Ar-H), 9.25 (1H, s, NH), 9.34-9.36 (1H, m, Ar-H). Anal. Calcd for $\text{C}_{33}\text{H}_{37}\text{N}_3\text{O}_5$. C, 71.33; H, 6.71; N, 7.56. Found: C, 71.44; H, 6.76; N, 7.49. (Due to very low solubility of the product 4f, we cannot report the ^{13}C NMR data for this product.)

Diethyl 3-(cyclohexylamino)-11,12-dimethyl-1H-benzo[a]pyrano[2,3-c]phenazine-1,2-dicarboxylate (4g)

Yellow powder (88%); mp 200-205 °C. IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 3400, 1721, 1671. MS (EI, 70eV) m/z : 553 (M^+). ^1H NMR (300 MHz, CDCl_3): δ_{H} 1.20 (3H, t, $J = 6.9$ Hz, CH_3), 1.42-2.23 (13H, m, 5CH_2 of cyclohexyl and CH_3), 4.09 (3H, bs, CH-N and OCH_2), 4.39 (2H,

ABq, $J = 6.9$ Hz, OCH₂), 5.75 (1H, s, CH), 7.84-8.21 (5H, m, Ar-H), 8.87 (1H, d, $J = 7.2$ Hz, NH), 9.38 (1H, bs, Ar-H). ¹³C NMR (75 MHz, CDCl₃): δ_C 14.3, 14.8, 20.6, 24.7, 25.6, 33.6, 33.9, 37.0, 50.5, 59.5, 60.7, 72.4, 112.8, 121.4, 125.3, 126.2, 128.1, 128.2, 128.3, 128.4, 129.6, 131.3, 139.8, 140.2, 140.4, 141.0, 141.1, 141.8, 146.8, 160.0, 169.8, 174.1. Anal. Calcd for C₃₃H₃₅N₃O₅. C, 71.59; H, 6.37; N, 7.59. Found: C, 71.51; H, 6.30; N, 7.53.

Dimethyl 3-(tert-butylamino)-11,12-dimethyl-1H-benzo[a]pyrano[2,3-c]phenazine-1,2-dicarboxylate (4h)

Yellow powder (83%); mp 223-227 °C. IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 3350, 1729, 1667. MS (EI, 70eV) m/z : 499 (M^+). ¹H NMR (300 MHz, DMSO-d₆): δ_H 1.68 (9H, s, CH₃), 2.57 (6H, s, CH₃), 3.61 (3H, s, OCH₃), 3.89 (3H, s, OCH₃), 5.84 (1H, s, CH), 7.28-8.42 (5H, m, Ar-H), 9.20 (1H, s, NH), 9.40 (1H, bs, Ar-H). ¹³C NMR (75 MHz, CDCl₃): δ_C 20.5, 20.6, 30.6, 36.5, 51.2, 52.2, 52.5, 73.0, 112.9, 121.9, 125.4, 126.0, 128.1, 128.2, 128.3, 129.6, 131.3, 140.4, 140.6, 140.9, 141.0, 141.9, 147.1, 161.6, 170.3, 174.0. Anal. Calcd for C₂₉H₂₉N₃O₅. C, 69.72; H, 5.85; N, 8.41. Found: C, 69.61; H, 5.92; N, 8.32.

Dimethyl 11,12-dichloro-3-(cyclohexylamino)-1H-benzo[a]pyrano[2,3-c]phenazine-1,2-dicarboxylate (4i)

Yellow powder (82%); mp 253-255 °C dec. IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 3200, 1730, 1668. MS (EI, 70eV) m/z : 566 (M^+). ¹H NMR (300 MHz, CDCl₃): δ_H 1.39-2.22 (10H, m, 5CH₂ of cyclohexyl), 3.62 (3H, s, OCH₃), 3.89 (3H, s, OCH₃), 4.09 (1H, bs, CH-N), 5.67 (1H, s, CH), 7.82-8.43 (5H, m, Ar-H), 8.83 (1H, d, $J = 7.5$ Hz, NH), 9.27 (1H, d, $J = 7.3$ Hz, Ar-H). ¹³C NMR (75 MHz, CDCl₃): δ_C 24.6, 25.5, 33.6, 33.8, 36.5, 50.6, 51.2, 52.4, 72.1, 121.6, 125.7, 126.5, 128.9, 129.7, 130.6, 134.0, 134.7, 139.5, 141.0, 141.1, 142.3, 148.2, 159.9, 169.9, 173.8. Anal. Calcd for C₂₉H₂₅Cl₂N₃O₅. C, 61.49; H, 4.45; N, 7.42. Found: C, 61.55; H, 4.31; N, 7.48.

Dimethyl 3-(tert-butylamino)-11,12-dichloro-1H-benzo[a]pyrano[2,3-c]phenazine-1,2-dicarboxylate (4j)

Yellow powder (86%); mp 237-239 °C. IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 3200, 1737, 1671. MS (EI, 70eV) m/z : 540 (M^+). ¹H NMR (300 MHz, DMSO-d₆): δ_H 1.59 (9H, s, CH₃), 3.50 (4H, bs, CH-N and OCH₃), 3.76 (3H, s, OCH₃), 5.54 (1H, s, CH), 7.95-8.52 (7H, m, Ar-H), 9.06 (1H, s, NH), 9.15 (1H, d, $J = 7.2$ Hz, Ar-H). Anal. Calcd for C₂₇H₂₃Cl₂N₃O₅. C, 60.01; H, 4.29; N, 7.78. Found: C, 60.11; H, 4.21; N, 7.86. (Due to very low solubility of the product 4j, we cannot report the ¹³C NMR data for this product).

Diethyl 11,12-dichloro-3-(2,4,4-trimethylpentan-2-ylamino)-1H-benzo[a]pyrano[2,3-c]phenazine-1,2-dicarboxylate (4k)

Yellow powder (90%); mp 195-205 °C. IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 3300, 1723, 1669. MS (EI, 70eV) m/z : 624 (M^+). ¹H NMR (300 MHz, CDCl₃): δ_H 1.03 (9H, s, CH₃), 1.18 (3H, s, CH₃), 1.43 (3H, s, CH₃), 1.66 (3H, s, CH₃), 1.71 (3H, s, CH₃), 2.06 (2H, s, CH₂), 4.06 (2H, bs, OCH₂), 4.27-4.39 (4H, m, OCH₂), 5.73 (1H, s, CH), 7.89-9.33 (7H, m, Ar-H and NH). ¹³C NMR (75 MHz, CDCl₃): δ_C 14.2, 14.8, 31.2, 31.6, 31.8, 36.5, 53.1, 56.1, 56.2, 59.7, 60.8, 72.6, 96.1, 122.3, 125.9, 128.9, 129.8, 130.6, 130.7, 134.0, 141.1, 169.7, 169.8, 173.6. Anal. Calcd for C₃₃H₃₅Cl₂N₃O₅. C, 63.46; H, 5.65; N, 6.73. Found: C, 63.55; H, 5.71; N, 6.68.

Results and Discussion

We found that a mixture of benzo[a]phenazin-5-oles **1a-c**, isocyanides **2a-c** and dialkyl acetylenedicarboxylates **3a,b** in refluxing ethanol, afforded corresponding 1H-

benzo[*a*]pyrano[2,3-*c*]phenazine-1,2-dicarboxylates **4a-k** in good yields for 20 h (Scheme 1). The results are summarized in Table 1.

Scheme 1

The good yield and purity of products and simplicity of the present procedure makes it an interesting, convenient and acceptable one-pot method for the preparation of 1*H*-benzo[*a*]pyrano[2,3-*c*]phenazine-1,2-dicarboxylates. The workup of these very clean reactions involves only a filtration and simple washing step with ethanol.

Table 1. Synthesis of benzopyranophenazine **4**.

Product 4	R	R ¹	R ²	Yield (%) ^a
A	H	Cyclohexyl	Me	86
B	H	Cyclohexyl	Et	88
C	H	<i>tert</i> -Butyl	Me	80
D	H	<i>tert</i> -Butyl	Et	81
E	H	1,1,3,3-Tetramethyl-butyl	Me	83
F	H	1,1,3,3-Tetramethyl-butyl	Et	89
G	Me	Cyclohexyl	Et	88
H	Me	<i>tert</i> -Butyl	Me	83
I	Cl	Cyclohexyl	Me	82
J	Cl	<i>tert</i> -Butyl	Me	86
K	Cl	1,1,3,3-Tetramethyl-butyl	Et	90

^aIsolated yields.

Although the mechanism of the reaction has not yet been established experimentally, a possible explanation is proposed in Scheme 2. The 1:1 zwitterionic ionic intermediate **5**, formed from the isocyanide **2** and the acetylenic ester **3**, is protonated by **1** to furnish intermediate **6**, which is attacked by the anion of the CH-acidic **7** in a Michael fashion to

produce ketenimine **8**. The latter then can undergo cyclization under the reaction conditions to afford the benzopyranophenazine **4**.⁵⁻¹⁰

Scheme 2

Compounds **4** are stable solids whose structures were established by IR, ¹H and ¹³C NMR spectroscopy, and elemental analysis.

Conclusion

In conclusion, we have described an efficient three-component method for the synthesis of benzo[*a*]pyrano[2,3-*c*]phenazines under neutral conditions without any activation or modifications. The products are of potential synthetic and pharmacological interest. Prominent among the advantages of this new method are operational simplicity, good yields and easy work-up procedures employed.

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