Synthesis of novel bis(nicotinecarbonitrile) derivatives
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Abstract
A series of bis(nicotinecarbonitriles) were prepared via the reaction of bis arylidenedmalononitriles with acetophenone in ethanolic potassium hydroxide solution. The isomeric bis(nicotinecarbonitriles) could also be obtained by the reaction of arylidenedmalononitriles with bis acetophenone under similar conditions. The reaction was assumed to take place via Michael addition followed by cyclization due to the alkoxide nucleophilic attack at one of the nitrile groups. Alternative syntheses of both isomeric derivatives were also reported.

Keywords: Bis(nicotinecarbonitriles), bis(arylidenemalononitriles), bis(chalcones), Michael addition, cyclization
Introduction

Pyridine derivatives are an important class of azaheterocycle found in many natural products. They have occupied a unique position in the field of medicinal chemistry (cf. Figure 1) due to their wide range of biological and pharmacological activities. In this respect, some pyridine derivatives have been reported to exhibit antibacterial, antimicrobial, antifungal, cardiotonic, analgesic, antiinflammatory and anti-lung cancer activities. Alternatively, some pyridine derivatives also represent the most interesting heterocyclic units in some agrochemical targets (cf. Figure 2).

Due to the continued importance of the pyridine core in both biological and chemical fields, different methodologies for pyridine synthesis have been developed. Among them, one-pot multicomponent reactions, remain the most interesting one in the synthesis of pyridine as well as different heterocycles and natural products. Modification of such strategies continues to be an interesting theme in literature. As a consequence of this interest and in continuation of our work on Michael addition, multicomponent reactions as well as on the synthesis of bis-heterocyclic with a suitable spacer, we report herein the results of our investigations concerning the synthesis of novel bis(nicotinecarbonitrile) derivatives.

![Figure 1]

**Figure 1**

![γ-Secretase modulator]

*Treatment of Alzheimer’s disease*

![Crizotinib (Xalkori, pfizer)]

*Treatment of lung cancer*

**Figure 2**

Antifungul  | Herbicide  | Insecticide
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![Antifungul](image1.png) | ![Herbicide](image2.png) | ![Insecticide](image3.png)

Results and Discussion

Firstly, we studied the attempted synthesis of bis pyridines via a four-component reaction of bis aldehydes, malononitrile, acetophene derivatives and NH$_4$OAc in refluxing ethanol (Scheme 1).
Unfortunately, under these conditions we could not isolate a pure sample of the corresponding bis pyridine 4. The reaction instead gave a product that was not easily handled and has not been characterized as yet. The reaction is assumed to proceed firstly via two-component reaction between the bis aldehyde 1 and malononitrile 2 to give a desired intermediate bis-arylidene-malononitrile 5 which then subsequently reacts with acetophenone 3 in the presence of ammonium acetate to give 4 (Scheme 2).

The reaction may also proceed via firstly formation of chalcone 6 by condensing 1 with acetophenone 3. The pyridine was assumed to be formed by the reacting of 6 with malononitrile in the presence of ammonium acetate (Scheme 3).

It is noteworthy to mention that attempts to carry out a stepwise reaction through the isolation of the bis-arylidenemalononitrile derivative 5 followed by reaction with acetophenone 3 in the presence of ammonium acetate were also unsuccessful. Compound 5 was obtained by Knoevenagel condensation of one mole of bis-aldehyde 1 with two moles of malononitrile 2 in ethanol in the presence of piperidine as a basic catalyst. The melting point as well as the $^1$H NMR spectral data of compound 5 were in agreement to the reported values. The $^1$H NMR spectrum of compound 5 indicated the presence of singlet signal integrated by two protons at $\delta$ 8.37 ppm assigned to vinyl hydrogens. In additions, it indicated quintet signal at $\delta$ 2.25 ppm and triplet signal at 4.29 ppm for methylene protons. The aromatic protons appeared as two doublet at $\delta$ 7.20 and 7.96 ppm with the same coupling constant ($J = 9$ Hz).
Moreover, the bis-chalcone 6a was also prepared as previously reported\textsuperscript{55}, by the reaction of bis-aldehyde 1a with two moles of acetophenone 3a in 4% ethanolic potassium hydroxide solution. Attempts to obtain the bis-pyridine 4a by the reaction of 6a with malononitrile 2 in the presence of ammonium acetate were also unsuccessful.

In search for an alternative pathway to prepare the target bis-pyridines, our attention turned to utilize KOH in ethanol as a basic catalyst instead of ammonium acetate. Thus, we studied the reaction of bis-arylidenemalononitrile 5a with acetophenone 3a in ethanolic potassium hydroxide solution at room temperature. The progress of the reaction was monitored on TLC. The reaction successfully afforded the corresponding bis-pyridine 7a in a 63% yield. The bis-chalcone 6a was also isolated from the reaction mixture as a minor product (Scheme 4).

Similarly, the bis-pyridines 7b,c were obtained by reaction of 5a with the corresponding ketone 3b and 3c. Although the \textsuperscript{1}H NMR of the reaction mixtures indicate the presence of few amount of the corresponding chalcones 6b and 6c, we were not able to isolate pure sample of these compounds (Scheme 4).

\textbf{Scheme 4}

The structure of 7a-c was confirmed by alternative synthesis via stirring a mixture of bis-aldehyde 1a and acetophenone derivatives 3a-c in ethanol-KOH mixture to give the corresponding bis-chalcones 6 in 65-80% yields. Subsequent reaction of 6 with malononitrile in ethanol at reflux leads to the formation of compounds 7 as sole products (Scheme 5).

\textbf{Scheme 5}

Similarly, the bis-pyridine 7d was obtained in 61% yield by the reaction of the appropriate bis aldehyde 1b with 4-methylacetophenone 3b and malononitrile in ethanolic potassium hydroxide solution (Scheme 6).
Moreover, the structure of 7 was confirmed by spectroscopic tools as well as elemental analyses data. The IR spectra of 7 reveal the presence of a nitrile stretching vibration band at 2213–2223 cm$^{-1}$ region and lack any band assignable for a carbonyl function. The $^1$H-NMR spectra of 7 exhibit the presence of the ethoxide moiety ($\delta =1.46–1.54$ “triplet of CH$_3$” , $\delta =4.55–4.66$ “quartet for OCH$_2$”) as well as the pyridine H-5 at $\delta =7.27–7.40$ confirming the cyclized form structure.

The reaction was assumed to take place through addition of 3 to the $\beta$-carbon of ylidene 5 affording the Michael adduct intermediate 8. The latter due to attack of the ethoxide anion at one of the nitrile groups gives intermediate 9 which underwent cyclization followed by dehydration and subsequent dehydrogenation giving finally the isolable product 7 (Scheme 7). The bis-chalcone 6 may be formed via decomposition of 8 through elimination of malononitrile.

Our study was extended to include the synthesis of novel isomeric bis- pyridines 12 by the reaction of bis acetophenone 10 with arylidemalononitriles 11 in ethanolic potassium hydroxide solution at room temperature. In some cases the bis-chalcones 13$^{55}$ were successfully isolated from the reaction mixture as a minor product (Scheme 8).
The reaction was assumed to take place through addition of 10 to the β-carbon of ylidene 11 affording the Michael adduct intermediate 14. The latter due to attack of the ethoxide anion at one of the nitrile groups gives 15 which underwent cyclization followed by dehydration and subsequent dehydrogenation gives finally the isolable product 12 (Scheme 9).

The bis-chalcone 13 may be formed via decomposition of 14 through elimination of malononitrile.

The structure of 17 was confirmed by authentication with samples prepared from bis-chalcones 13, obtained in situ from the reaction of bis-acetophenones 10 with the appropriate aldehydes 17, upon treatment with malononitrile in ethanolic solution containing KOH (Scheme 10).
Furthermore, the structure of 12 was established by spectroscopic and elemental analyses data. The IR spectra reveal a band attributed to the nitrile group at 2213–2223 cm\(^{-1}\) and the absence of a band assignable for the carbonyl group confirming the cyclized form structure. In addition, \(^1\)H NMR spectra display the ethoxide protons at δ 1.46–1.54 ("triplet of CH\(_3\)" and at δ 4.55– 4.66 ("quartet for OCH\(_2\)"") confirming the involvement of ethoxide function.

**Conclusions**

We have developed an efficient synthesis of novel bis(nicotines) which are linked to ether linkage via phenyl groups. Full characterization of these compounds is reported. The newly synthesized compounds were easily prepared in good yields under mild reaction conditions from readily available starting materials. The synthetic strategies used in this work should provide access for novel new bis(functionalized) heterocycles with promising pharmacological and biological activities.

**Experimental Section**

**General.** Melting points were measured with a Stuart melting point apparatus and are uncorrected. The IR spectra were recorded using an FTIR Bruker– vector 22 spectrophotometer as KBr pellets. The \(^1\)H NMR spectra were recorded in DMSO–d6 as solvent on Varian Gemini NMR spectrometer at 400 MHz using TMS as internal standard. Chemical shifts are reported as δ values in ppm. Mass spectra were recorded with a Shimadzu GCMS–QP–1000 EX mass spectrometer in EI (70 eV) model or on an AccuTOF-T100LP (JEOL) mass spectrometer in ESI. The elemental analyses were performed at the Micro analytical center, Cairo University. Analytical thin layer chromatography was performed using pre-coated silica gel 60.778 plates (Fluka), and the spots were visualized with UV light at 254 nm. Compounds 5\(^{33,39}\) and 6\(^{55}\) have been synthesized as previously reported.

**General procedure for 4,4′-((Alkane-1, n-diylbis(oxy))bis(phenylene))bis(2-ethoxy-6-arynicotinonitriles) (7a-d). Method A.** A mixture of bisaldehyde derivative (1) (1 mmol) and malononitrile (2 mmol) in absolute ethanol (20 ml) was heated at reflux for 30 min. in the presence of piperidine as a catalyst. The obtained solid was filtered, washed with ethanol and added to a solution of the appropriate acetonilone derivative (3a-c) (2 mmol) in ethanolic KOH (20 ml, 4%). The reaction mixture was stirred overnight at room temperature. The resulting solid was collected by filtration, and was separated from traces of compounds 6 by preparative thin-layer chromatography using DCM as an eluent where compounds 7a-d showed a value of R.F. equals to 0.92-0.98. Compounds 7a-d were further purified by recrystallization from DMF/EtOH.

**Method B.** The appropriate acetonilone derivative (3a-c) (2 mmol) was dissolved in ethanolic KOH solution (20 ml, 4%) and added to a solution of the corresponding bisaldehyde (1) (1 mmol) in ethanol (10 ml). The reaction mixture was then stirred overnight to afford compounds 6a-d which were filtered off and washed with ethanol. The solid product was added to malononitrile (2 mmol) in ethanolic KOH solution (20 ml, 4%). The reaction mixture was then heated at reflux for 2 hr. The solid products obtained upon cooling were purified as described in method A to give compounds 7.

4,4′-((Propane-1,3-diylbis(oxy))bis(4,1-phenylene))bis(2-ethoxy-6-phenylnicotinonitrile) (7a). (69% yield) as colorless crystals, mp 220°C; IR (cm\(^{-1}\)): 2214 (CN), 1587 (C=N), 1244 (C-O-C); ESI-MS: \(m/z\) 695[M+Na\(^+\)] and 673 [M+H\(^+\)]; \(^1\)H-NMR (300 MHz, DMSO): δ 141-1.46 (t, 6H, 2CH\(_3\), J 6.9 Hz), 2.25-2.29 (m, 2H, CH\(_2\), J 6 Hz), 4.26-4.30
(t, 4H, 2CH₂, J = 6.9 Hz), 4.59-4.66 (q, 4H, 2CH₂, J = 6.9 Hz), 7.16-8.24 (m, 18H, aromatic), 7.75 (s, 2H, H-5 pyridine); ¹³C-NMR: δ 14.32, 62.97, 94.23, 113.28, 114.80, 115.58, 121.45, 127.34, 128.83, 130.21, 160.02. Anal. Calcd for C₃₇H₃₆N₄O₄ (672.79): C, 76.77; H, 5.39; N, 8.33. Found: C, 77.05; H, 5.22; N, 8.45.

4,4’-((Propane-1,3-diylbis(oxy))bis(4,1-phenylene))bis(2-ethoxy-6-(p-toly)nicotinonitrile) (7b). (66% yield) as colorless crystals, mp 235°C; IR (cm⁻¹): 2210 (CN), 1589 (C=N), 1238 (C-O-C); EI-MS: m/z 702 (M⁺+2, 4.37%), 700 (M⁺, 19.25%), 386 (18.07%), 369 (27.81%), 267 (32.14%), 239 (63.03%)%, 105 (100.00%); ¹³H-NMR (300 MHz, DMSO): δ 140-1.44 (t, 6H, 2CH₃, J 7.2 Hz), 2.24-2.28 (m, 2H, CH₂, J 6 Hz), 2.36 (s, 6H, 2CH₃), 4.25-4.29 (t, 4H, 2CH₂, J 6 Hz), 4.56-4.63 (q, 4H, 2CH₂, J 7.2 Hz), 7.14-8.12 (m, 16H, aromatic), 7.67 (s, 2H, H-5 pyridine); ¹³C-NMR: δ 14.29, 20.88, 62.86, 64.45, 78.05, 112.80, 114.75, 120.44, 120.46, 127.24, 128.05, 129.41, 130.14, 140.44, 159.96. Anal. Calcd for C₄₅H₄₆N₄O₄ (700.82): C, 77.12; H, 5.75; N, 7.99. Found: C, 77.37; H, 5.95; N, 8.32.

General procedure for 6,6’-(alkane-1,3-diylbis(oxy))bis(2,1-phenylene))bis(2-ethoxy-4-Arylnicotinonitriles) (12a-e). Method A. Bis acetoephone derivative (10) (1 mmol) was dissolved in ethanolic KOH solution (20 ml, 4%) and added to a solution of the appropriate arylidenemalononitrile derivative (11a-c) (2 mmol). The reaction mixture was stirred overnight at room temperature. The solid products were collected by filtration, washed by water then by ethanol. The solid product were then separated from traces of compound 13 by thin layer chromatography using DCM as an eluent where compounds 12a-e showed a value of R.F. equals to 0.92-0.98. Compounds 12a-e were further purified by recrystallization from ethanol.

Method B. The appropriate bis acetoephone derivative (10) (1 mmol) was dissolved in ethanolic KOH solution (20 ml, 4%) and added to a solution of the corresponding aromatic aldehyde (17a-c) (2 mmol) in ethanol (10 ml). The reaction mixture was then stirred overnight to afford 13a-e. The solid product formed was collected by filtration, and added to malononitrile (2 mmol) in ethanolic KOH solution (20 ml, 4%). The reaction mixture was then heated at reflux with stirring for 2hr. The resulting solid products upon cooling were purified as described in method A to give compounds 12a-e.

6,6’-((Propane-1,3-diylbis(oxy))bis(2,1-phenylene))bis(2-ethoxy-4-phenylnicotinonitrile) (12a). (71% yield) as colorless crystals, mp 198°C; IR (cm⁻¹): 2215 (CN), 1589.02 (C=N), 1250 (C-O-C); ¹³H-NMR (300 MHz, DMSO): δ 135-1.40 (t, 6H, 2CH₃, J 6.9 Hz), 1.69 (t, 4H, 2CH₂), 2.34 (s, 6H, 2CH₃), 3.96 (t, 4H, 2CH₂), 4.51-4.58 (q, 4H, 2CH₂, J 6.9 Hz), 7.02-8.04 (m, 16H, aromatic), 7.60 (s, 2H, H-5 pyridine). Anal. Calcd for C₄₆H₄₂N₄O₄ (686.80): C, 77.29; H, 5.92; N, 7.84. Found: C, 77.48; H, 5.65; N, 7.53.

6,6’-((Propane-1,3-diylbis(oxy))bis(2,1-phenylene))bis(4-(4-chlorophenyl)-2-ethoxynicotinonitrile) (12b). (62% yield) as colorless crystals, mp 185°C; IR (cm⁻¹): 2218 (CN), 1589 (C=N), 1238 (C-O-C); ¹³H-NMR (300 MHz, DMSO): δ 1.38-1.43 (t, 6H, 2CH₃, J 6 Hz), 2.19 (m, 2H, CH₂), 4.15-4.15 (t, 4H, 2CH₂), 4.52-4.59 (q, 4H, 2CH₂, J 6
References


   https://doi.org/10.2165/00003495-200565160-00010

   https://doi.org/10.1124/pr.55.3.4

   https://doi.org/10.1016/0378-4274(96)03660-0

   https://doi.org/10.1021/jm100888d


   http://dx.doi.org/10.3998/ark.550190.010.e06


   https://doi.org/10.1016/S0960-894X(02)01046-6


   https://doi.org/10.1016/j.ejmech.2009.05.031

   https://doi.org/10.1021/cr100108k

   https://doi.org/10.1021/acs.lett.5b02903

   https://doi.org/10.1021/acs.orglett.7b00130

   https://doi.org/10.1021/cr100108k

   https://doi.org/10.1039/C0CS00013B


   https://doi.org/10.1080/00397910008087441
   https://doi.org/10.3998/ark.5550190.0017.324
   https://doi.org/10.1002/jhet.2373
   https://doi.org/10.1080/00397910008087441
   https://doi.org/10.1016/j.tet.2015.12.024
   https://doi.org/10.1080/17415993.2014.975131
   https://doi.org/10.2174/157017941106141023114039
   https://doi.org/10.1002/jhet.5570440636
   https://doi.org/10.1039/a904716f