Indian Journal of Chemistry
Vol. 65, May 2026, pp. 520-522
DOI: 10.56042/ijc.v65i5.18162

Note

Catalyst-free synthesis of 2-amino-3-cyanopyridine

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Received 22 March 2025; accepted (revised) 11 May 2026

A new compound, 2-amino-4-(4-bromophenyl)-6-(phenylamino)pyridine-3,5-dicarbonitrile, has been synthesized by the catalyst-free reaction of 2-(4-bromobenzylidene)malononitrile with malononitrile and benzylamine. The structure of the reaction product has been determined by NMR spectroscopy and X-ray diffraction analysis. A probable reaction mechanism and intramolecular rearrangement has been proposed.

Keywords: Catalyst-free, Cyanopyridine, Malononitrile, Benzylamine, Rearrangement

The pyridine, dihydropyridine, tetrahydropyridine and piperidine rings, as a significant structural fragment, play key roles in metabolism and are present in different natural sources, such as nicotinamide, nicotinic acid and vitamin B$_6$. These compounds are also used as intermediates in organic synthesis for obtaining synthetic analogs, with a wide range of pharmaceutical applications. Chemical compounds such as nifedipine, felodipine and nicardipine are known medicinal drugs for the clinical treatment of cardiovascular, brain and hypertension diseases, *etc.*[1–10] (Fig. 1).

As noted, pyridines as six-membered heterocyclic compounds that can be obtained from natural sources or synthesized synthetically. Indicated classes are reduced forms of dihydropyridines and have pharmacological activities, making them a target for drug discovery research in chemistry[11-13].

Results and Discussion

As a result of the catalyst-free multicomponent reaction, 2-amino-4-(4-bromophenyl)-6-(phenylamino)pyridine-3,5-dicarbonitrile was synthesized based on 2-(4-bromobenzylidene) malononitrile, malononitrile and benzylamine in methanol solvent. After purifying and identifying the structure of the compound by NMR spectroscopy and X-ray diffraction, its intramolecular regrouping was observed. The reaction and regrouping mechanism routes are given in Scheme 1.

As can be seen from the scheme, first the addition of malononitrile to benzylidene malononitrile, then of benzylamine to the intermediate, as well as the attack of the benzylamine nitrogen, results in the formation of the cycle. Then, with intramolecular oxidation and redistribution of electron density, a rearrangement reaction occurs.

Experimental Section

All commercially available compounds (Aldrich) were used as received. The purity of compound was checked by TLC (silica gel 60 F254) using hexane–ethyl acetate (5:3) as eluent. The NMR spectra were recorded on a Bruker Avance 300 spectrometer (UltraShield TM Magnet; Germany) equipped with a BVT 3200 temperature control unit at 300.130 MHz for ^{1}H and 75.468 MHz for ^{13}C using 5 mL NMR ampules; the chemical shifts were referenced to tetramethylsilane as internal standard. The data were acquired and processed using Bruker Standard TopSpin 3 software. Experimental NMR parameters: ^{1}H digital resolution 0.23 Hz, SWH = 7530 Hz, TD = 32 K, SI = 16 K, 90° pulse duration 10 µs, PL1 = 3 dB, ns = 1, ds = 0, d1 = 1 s; ^{13}C digital resolution 0.27 Hz, SWH = 17985 Hz, TD = 64 K, SI = 32 K, 90° pulse duration 9 µs, PL1 = 1,5 dB, ns = 100, ds = 2, d1 = 3 s. Sample was dissolved in deuterated dimethyl sulfoxide (DMSO-d$_6$; 99.7%, 0.3% H$_2$O).

The X-ray diffraction data for compound were obtained on a Bruker Smart Apex II CCD diffractometer (Germany) at 100(2) K (Mo Kα radiation (λ = 0.71073 Å). A single crystal was immersed in cryo oil and mounted in a nylon loop. The data were collected and processed using SHELXTL (measurement of reflection intensities, indexing and determination of unit cell parameters), SAINTP (integration of reflection intensities and scaling), SADABS

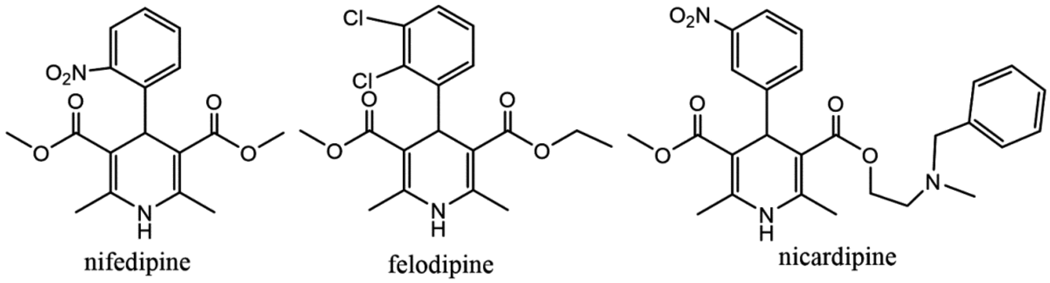
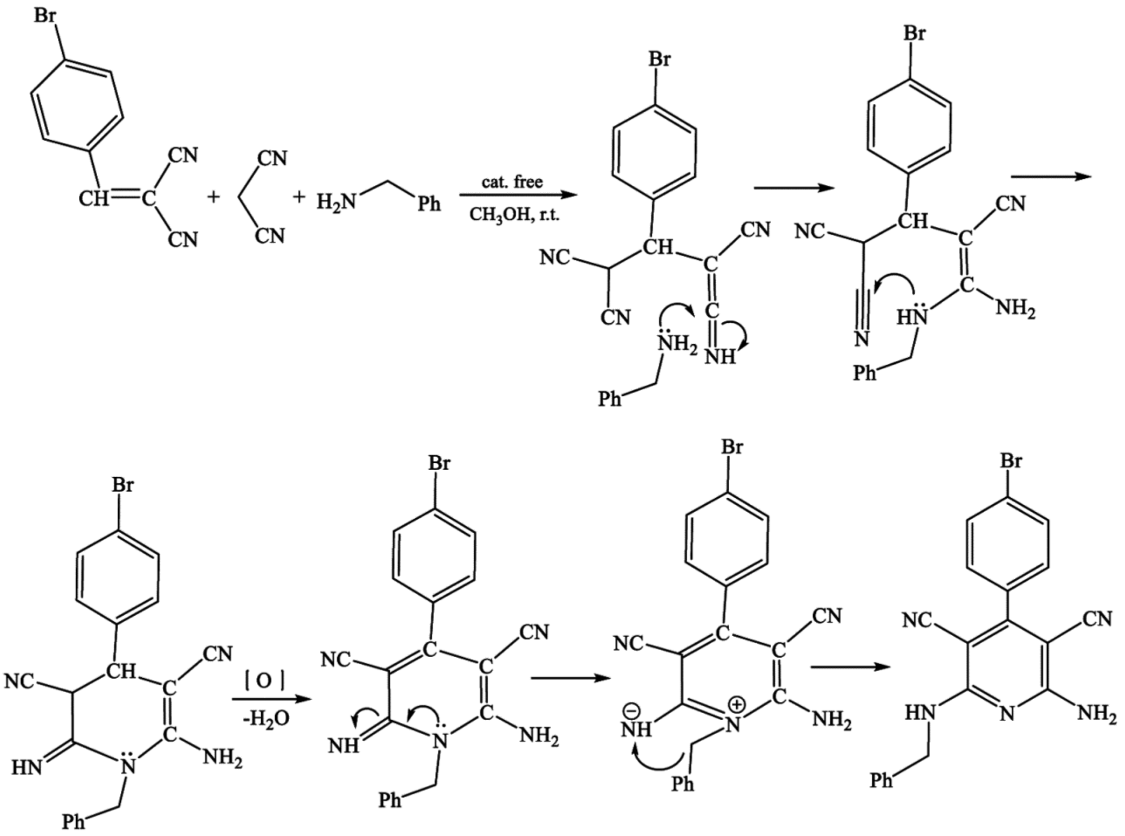


Fig. 1 — A few known medicinal drugs for the clinical treatment of cardiovascular, brain and hypertension diseases



Scheme 1 — Synthesis route of the pyridine derivative

(correction for absorption) and SHELXTL (space group identification and structure solution). The structure was refined against F2 by the least squares method. The structure of molecule is shown in Fig. 2.

The purity of the synthesized compound was confirmed by thin-layer chromatography (TLC) on commercial aluminum-backed plates of silica gel (60 F254), and iodine vapor was used as visualizing agent, eluent- 5:2 hexane/ethyl acetate. The melting point was measured on an Electrothermal 9100 apparatus and is uncorrected.

General procedure for the synthesis of 2-amino-4-(4-bromophenyl)-6-(phenylamino)pyridine-3,5-dicarbonitrile

A mixture of 2-(4-bromobenzylidene)malononitrile (0.0051 mol) and malononitrile (0.0052 mol) was dissolved in MeOH (40 mL) and was stirred for 10 min. The benzylamine (0.0052 mol) was added under vigorous stirring. The reaction was allowed to proceed for 48 h. Upon evaporation of the solvent, the product crystallized. The crystals were filtered and recrystallized from a 3:2 EtOH/H_2O mixture: Yield 70.8%. m.p. 219°C. ^{1}H NMR (300 MHz, DMSO-d_6):

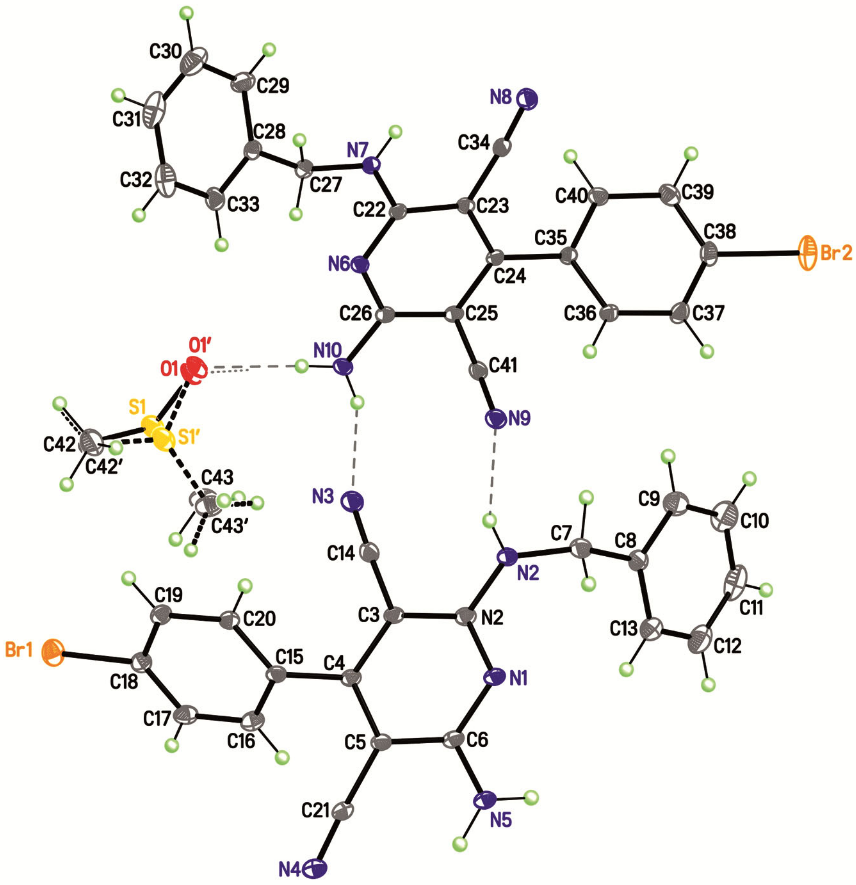


Fig. 2 — Molecular structure of compound according to the X-ray diffraction data

δ 4.3 (s, 2H, CH_2), 6.6 (s, 3H, NH and NH_2), 7.2–7.5 (m, 9H, arom.).

$C_{20}H_{14}BrN_5$: Mr 404.77; crystal dimensions 0.15×0.15×0.12 mm^3; triclinic crystal system, space group P-1: a = 10.8824, b = 12.2289, c = 14.9459Å; α = 96.317°, β = 95.499°, γ = 98.128°; Z = 2; dcalc = 1.514 g/cm^3; $\mu = 2.187$ mm^{-1}.

As can be seen from the Fig. 2, the two molecules interact head-to-toe *via* hydrogen bonding to form a dimer and contain two molecules of DMSO.

Conclusion

Synthesis of a new compound, 2-amino-4-(4-bromophenyl)-6-(phenylamino)pyridine-3,5-dicarbonitrile, was carried out as a result of a catalyst-free multicomponent reaction. The structure of the reaction product was determined using NMR and X-ray diffraction. A probable mechanism of the reaction and intramolecular rearrangement was also proposed.

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