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2-Aryl-1,1-dicyano-3-phenylsulfonylpropenes in Heterocyclic Synthesis: A Synthetic Strategy Towards Heterocyclic Sulfones

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Summary. The applicability and synthetic potency of the novel reagent 1-aryl-1,1-dicyano-3-phenylsulfonylpropene for the development of an expeditious synthetic approach to unique polyfunctionally substituted heterocyclic sulfone systems is reported. Chemical and spectroscopic evidences for the structures of the new compounds are presented.

Keywords. Sulfonylheterocycles; Pyridines; Pyridazines; Pyridopyrimidines.

2-Aryl-1,1-dicyano-3-phenylsulfonylpropen in der Heterocyclensynthese: Eine Synthesestrategie für heterocyclische Sulfone

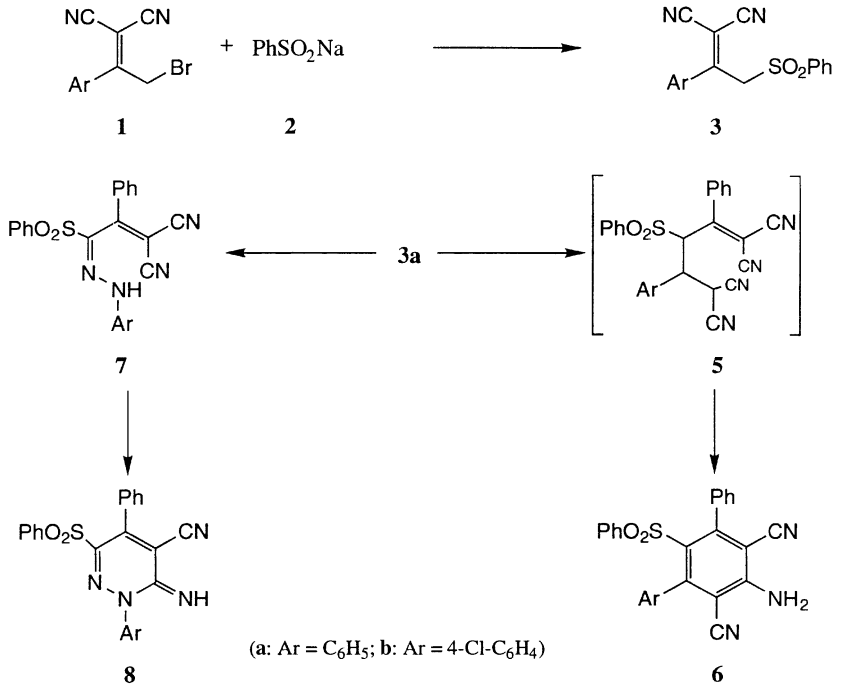
Zusammenfassung. Die Anwendbarkeit und synthetische Brauchbarkeit des neuen Reagens 1-Aryl-1,1-dicyano-3-phenylsulfonylpropen für eine rasch durchführbare Synthese von polyfunktionell substiuierten heterocyclischen Sulfonen wird vorgestellt. Die chemischen und spektroskopischen Daten werden als Evidenz für die Stukturen der neuen Verbindungen präsentiert.

Introduction

Sulfones have proven to be valuable synthons for the synthesis of a wide variety of biologically active heterocyclic systems [1–6]. As an extension of our efforts directed towards the development of convenient synthetic approaches for the construction of biological active heterocycles [7–10], I wanted to accentuate the synthetic scope of the novel reagent 2-aryl-1,1-dicyano-3-phenylsulfonylpropene (**3**) as a key precursor for the synthesis of some hitherto unreported polyfunctionally substituted sulfonylheterocycles and their fused systems with an expected broad spectrum of bioresponses.

Results and Discussion

The reaction of equimolar amounts of each of the β-bromomethyl-α-cyanocinnamonitriles **1a**,**b** [11] with sodium benzenesulfinate (**2**) in boiling ethanol furnished exclusively the corresponding 2-aryl-1,1-dicyano-3-phenylsulfonylpropenes **3a**,**b**

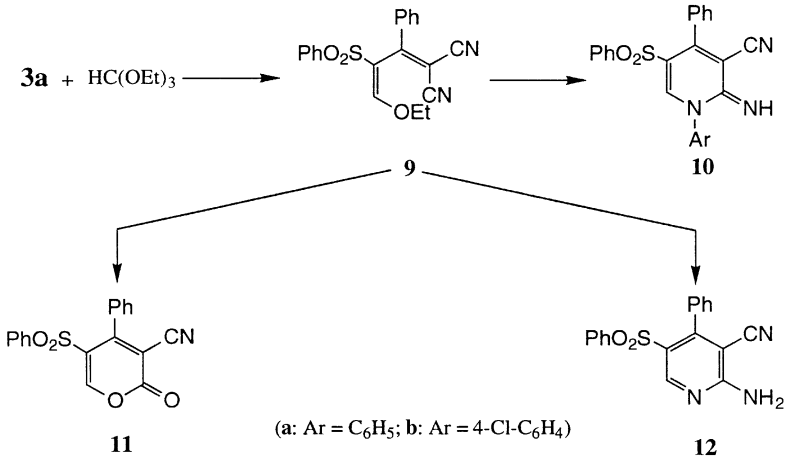


Scheme 1

in excellent yield (Scheme 1). The elemental and spectroscopic data of **3** are consistent with the assigned structure.

Compound **3** is established as a versatile reagent for the construction of several unique heterocyclic systems. The methylene group of **3** proved to be highly reactive towards electrophilic reagents. Thus, **3a** reacted with an equimolar amount of arylidenemalonitriles **4** to yield the corresponding fully substituted benzene derivatives **6**. Formation of **6** is believed to proceed *via* a *Michael* addition of the activated methylene group in **3** to the electron deficient carbon in the α,β-unsaturated system in **4**, intramolecular cyclization, and autoaromatizations *via* loss of HCN under the experimental reaction conditions (Scheme 1). Similar autoaromatizations have been reported previously [11–13].

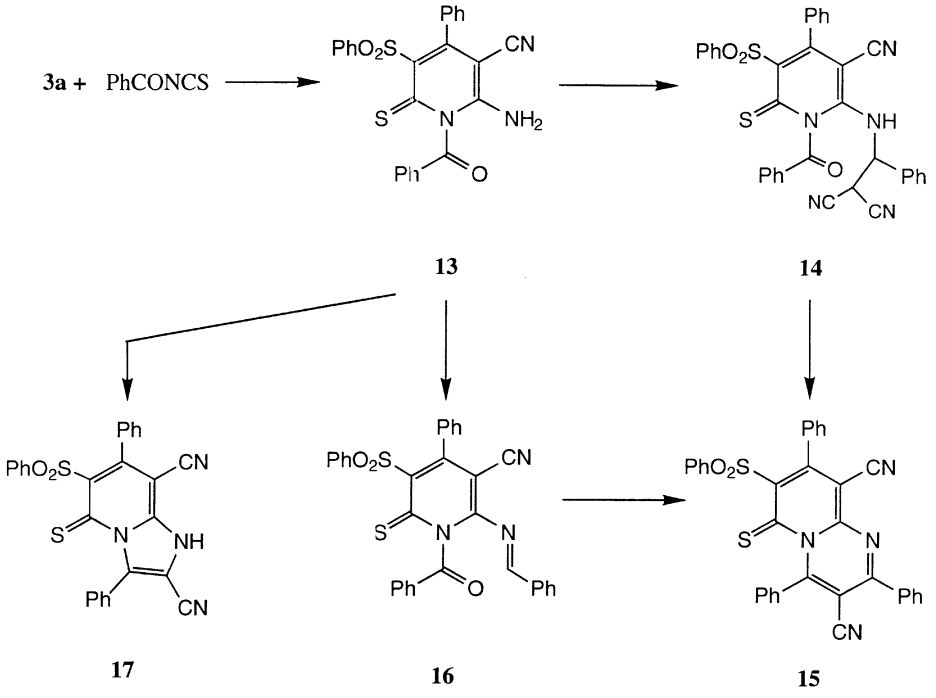
Compound **3a** readily coupled with equimolar amounts of arenediazonium chlorides to yield the corresponding coupling products which may be formulated as the acyclic hydrazone form **7** or its cyclic pyridazine form **8**. However, the hydrazone structure was tentatively preferred over **8** for the reaction products on the basis of spectroscopic data. Thus, as a representative example, the IR spectrum of **7a** reveals the presence of two absorption peaks at $\nu = 2222$ and $2218\,\mathrm{cm}^{-1}$ which are attributed to two CN functions. Its ^{13}C NMR spectrum (*DMSO*-d_6) shows, in addition to the expected signals at $\delta = 162.63$ (C-3), 143.9 (C-2), 136.9-126.0 (aromatic carbons), and 69.67 (C-1) ppm, two signals at $\delta = 116.76$ and 114.31 ppm attributed to the presence of two CN carbons. Furthermore, pyridazine **8** could be obtained upon heating hydrazone **7** in glacial acetic acid.



Scheme 2

Compound **3a** reacted with an equimolar amount of triethyl orthoformate in refluxing dioxane in the presence of acetic anhydride to provide the corresponding ethoxymethylene derivative **9** in acceptable yield. Compound **9** exhibits a high reactivity towards nucleophilic reagents. Thus, the reaction of **9** with equimolar amounts of primary aromatic amines in refluxing dioxane solutions afforded the corresponding N-arylpyridine derivatives **10** *via* EtOH elimination and spontaneous intramolecular heterocyclization (Scheme 2). The analytical and spectroscopic data are in accordance with the proposed structure. The 2-pyranone derivative **11** was obtained in 55% yield upon boiling **9** with $Ba(OH)_2$ in EtOH solution. Likewise, the 2-aminopyridine-3-carbonitrile derivative **12** was obtained by the action of an excess of ammonia on **9** at room temperature. Formation of **12** is assumed to proceed *via* EtOH elimination and spontaneous heterocyclization *via* a *Michael* type nucleophilic addition of the NH_2 protons to the neighbouring $C \equiv N$ function. Structure **12** was established by a correct elemental analysis and compatible spectra. Thus, its IR spectrum (KBr) revealed absorption peaks corresponding to the presence of only one CN and of NH_2 functions.

The 1-benzoyl-2-aminopyridine derivative **13** was obtained in 75% yield from the reaction of **3a** with an equimolar amount of benzoyl isothiocyanate in refluxing acetonitrile solution (Scheme 3). Compound **13** could be annelated into fused heterocyclic ring systems of an expected wide spectrum of biological activities. Thus, compound **13** reacted with an equimolar amount of benzylidenemalononitrile (**4a**) to afford a single product with a pyrido[1,2-*a*]pyrimidine structure (**15**). Formation of **15** was assumed to proceed *via* a *Michael* type addition of the NH_2 group of **13** to the electron deficient carbon atom in the α,β-unsaturated cinnamonitrile system in **4a** to form the intermediate acyclic 1:1 *Michael* adduct **14**, spontaneous intramolecular cyclization *via* loss of H_2O from the amide carbonyl group, and autoaromatization by loss of HCN to yield the final product **15**. Both elemental and spectroscopic data of **15** are consistent with the assigned structure. Thus, its mass spectrum revealed a molecular ion peak at $m/z = 580$ corresponding to the molecular formula $C_{34}H_{20}N_4O_2S_2$. Its IR spectrum showed absorption peaks corresponding to the presence of two CN and C=S functions at $\nu = 2225$, 2220, and



Scheme 3

1200 cm^{-1}. Alternatively, product **15** could be obtained *via* an independent stepwise synthetic route involving the condensation of **13** with an equimolar amount of benzaldehyde in the presence of a catalytic amount of Et_3N to afford the corresponding *Schiff* base **16**. The latter, in turn, reacted with malononitrile in dioxane containing a catalytic amount of Et_3N under reflux to afford a single product found to be identical with **15**.

Finally, our methodology was applied to the synthesis of polyfunctionally substituted fused pyridines accessible only with difficulty otherwise. Thus, compound **14** reacted with an equimolar amount of chloroacetonitrile in ethanol in the presence of K_2CO_3 to afford the corresponding imidazo[1,2-*a*]pyridine derivative **17** (Scheme 3).

In conclusion, it seems that the results extend and broaden the knowledge in the area of heterocyclic sulfone systems obtainable only with difficulty otherwise and demonstrate a general applicable methodology for the construction of such ring systems with reasonable yields.

Experimental

Melting points are uncorrected; IR spectra (KBr): Pye Unicam SP-1000, ν in cm^{-1}; ^1H and ^{13}C NMR spectra (*DMSO*-d_6): Varian Gemini 200 MHz spectrometer, *TMS* as internal standard, chemical shifts in δ (ppm); mass spectra: AEI MS 30 mass spectrometer operating at 70 eV; elemental analysis: Microanalytical Data Unit at Cairo University, their results agreed with the calculated values. β-Bromomethyl-(α-cyanocinnamonitriles) **1a**,**b** [11] were prepared according to the literature.

General procedure for the synthesis of 2-aryl-1,1-dicyano-3-phenyl-sulfonylpropenes

A mixture of **1a**,**b** (0.01 mol) and sodium benzenesulfinate (**2**, 0.015 mol) in EtOH (30 ml) was boiled under reflux for 4 h. The reaction mixture was left to cool at room temperature and poured onto cold H_2O. The solid product precipitated was collected by filtration, washed thoroughly with H_2O, dried, and crystallized.

1,1-Dicyano-2-phenyl-3-phenylsulfonylpropene (**3a**; $C_{17}H_{12}N_2O_2S$)

Yield: 2.59 g (84%); m.p.: 125°C (EtOH); IR: 3010 (CH_2), 2220, 2218 (2 CN), 1630 (C=C); ^{1}H NMR: 4.25 (s, 2H, CH_2), 6.81–7.20 (m, 5H, arom. protons), 7.42–7.80 (m, 5H, arom. protons); MS: *m/z* (%) = 308 (M^+, 12%).

2-(4′-Chlorophenyl)-1,1-dicyano-3-phenylsulfonylpropene (**3b**; $C_{17}H_{11}ClN_2O_2S$)

Yield: 3.02 g (88%); m.p.: 136°C (EtOH); IR: 3018 (CH_2), 2222, 2215 (2 CN), 1635 (C=C).

2-Amino-4-(4′-chlorophenyl)-3-cyano-6-phenyl-5-phenylsulfonylbenzonitrile (**6b**; $C_{26}H_{16}ClN_3O_2S$)

To a suspension of **3a** (0.003 mol) in dry dioxane (25 ml) containing Et_3N (5 drops), arylidenemalononitrile **4b** (0.003 mol) was added. The reaction mixture was heated under reflux for 4 h, poured into an ice/H_2O mixture (30 ml), and neutralized with dilute HCl. The solid product was filtered off and crystallized.

Yield: 1.03 g (73%); m.p.: 223°C (EtOH); IR: 3445–3310 (NH_2), 2220, 2218 (2 CN), 1645 (C=C); 4.35 (br s, 2H, NH_2, exchangeable), 6.78–7.21 (m, 5H, arom. protons), 7.34–7.82 (m, 9H, arom. protons).

General procedure for the synthesis of 3-arylhydrazono-1,1-dicyano-2-phenyl-3-phenylsulfonylpropenes

To a stirred solution of **3a** (0.004 mol) in EtOH (50 ml) containing AcONa (3 g), the appropriate arenediazonium chloride (prepared by adding $NaNO_2$ (0.004 mol) to the primary aromatic amine (0.004 mol) in concentrated HCl (3 ml) at 0–5°C with stirring). The reaction mixture was then left at room temperature for 6 h, triturated with cold H_2O (15 ml) where the solid product formed was filtered off, washed thoroughly with H_2O, dried, and crystallized.

1,1-Dicyano-2-phenyl-3-phenylhydrazono-3-phenylsulfonylpropene (**7a**; $C_{23}H_{16}N_4O_2S$)

Yield: 1.15 g (70%); m.p.: 196°C ($CHCl_3$); IR: 3200 (NH), 2222, 2218 (2 CN), 1660 (C=C); ^{1}H NMR: 6.76–7.80 (m, 15H, arom. protons), 9.81 (br s, 1H, NH, exchangeable); ^{13}C NMR: 162.63 (C-3), 143.9 (C-2), 136.9–126.0 (arom. carbons), 116.76, 114.13, (2 CN), 69.67 (C-1); MS: *m/z* (%) = 412 (M^+, 24%).

3-(4′-Chlorophenylhydrazono)-1,1-dicyano-2-phenyl-3-phenylsulfonylpropene (**7b**; $C_{23}H_{15}ClN_4O_2S$)

Yield: 1.32 g (74%); m.p.: 180°C ($CHCl_3$); IR: 3200 (NH), 2222, 2219 (2 CN).

General procedure for the synthesis of 2-aryl-3-imino-5-phenyl-6-phenylsulfonylpyridazine-4-carbonitriles

A solution of **7a**,**b** (0.002 mol) in glacial acetic acid (25 ml) was boiled under reflux for 1 h and the solvent was evaporated *in vacuo*. The reaction mixture was triturated with cold H_2O; the solid product was filtered off, washed with cold H_2O, dried, and crystallized.

1,4-Diphenyl-6-imino-3-phenylsulfonylpyridazine-5-carbonitrile (**8a**; $C_{23}H_{16}N_4O_2S$)

Yield: 0.54 g (66%); m.p.: 242°C (AcOH); IR: 3250 (NH), 2222 (CN), 1660 (C=C); ^{1}H NMR: 6.95–7.81 (m, 15H, arom. protons), 12.80 (br s, 1H, NH, exchangeable); ^{13}C NMR: 173.23 (C-3), 160.41 (C-6), 147.32 (C-5), 139.30–126.86 (arom. carbons), 122.51 (C-4), 116.76 (CN carbon); MS: *m*/*z* (%) = 412 (M^+, 28%).

1-(4′-Chlorophenyl)-6-imino-4-phenyl-3-phenylsulfonylpyridazine-5-carbonitrile (**8b**; $C_{23}H_{15}ClN_4O_2S$)

Yield: 0.62 g (70%); m.p.: 230°C (AcOH); IR: 3250 (NH), 2220 (CN), 1630 (C=C).

1,1-Dicyano-3-ethoxymethylene-3-phenyl-3-phenylsulfonylpropene (**9**; $C_{20}H_{16}N_2O_3S$)

A mixture of **3a** (0.01 mol) and triethyl orthoformate (0.01 mol) in dioxane (30 ml) containing Ac_2O (15 ml) was boiled under reflux for 3 h. The reaction mixture was cooled at room temperature and poured into cold H_2O. The solid product that separated was filtered off, washed thoroughly with H_2O, dried, and crystallized from dioxane.

Yield: 2.22 g (61%); m.p.: 110°C; IR: 3020 (CH_2), 2225, 2219 (2 CN), 1660 (C=C); ^{1}H NMR: 0.91 (t, 3H, $J = 8.0$ Hz, CH_3), 3.71 (q, 2H, $J = 8.3$ Hz, CH_2), 6.85–7.31 (m, 5H, arom. protons), 7.40–7.82 (m, 6H, arom. protons + olefinic CH); MS: *m*/*z* (%) = 364 (M^+, 16%).

General procedure for the synthesis of 1-aryl-1,2-dihydro-2-imino-4-phenyl-5-phenylsulfonylpyridine-3-carbonitriles

A solution of **9** (0.002 mol) and the appropriate primary aromatic amine (0.002 mol) in dry dioxane (30 ml) was boiled under reflux for 3 h. The reaction mixture was evaporated *in vacuo* and triturated with cold H_2O. The solid product was filtered off, dried, and crystallized from an appropriate solvent.

1,2-Dihydro-1,4-diphenyl-2-imino-5-phenylsulfonylpyridine-3-carbonitrile (**10a**; $C_{24}H_{17}N_3O_2S$)

Yield: 0.53 g (64%); m.p.: 188°C (EtOH); IR: 3220 (NH), 2225 (CN); ^{1}H NMR: 6.71–7.82 (m, 16H, arom. protons + pyridine H-6), 11.93 (br s, 1H, NH, exchangeable); MS: *m*/*z* (%) = 411 (M^+, 28%).

1-(4′-Chlorophenyl)-1,2-dihydro-2-imino-4-phenyl-5-phenylsulfonylpyridine-3-carbonitrile (**10b**; $C_{24}H_{16}ClN_3O_2S$)

Yield: 0.59 g (66%); m.p.: 185°C (dioxane); IR: 3250 (NH), 2222 (CN).

2-Oxo-4-phenyl-5-phenylsulfonyl-2H-pyran-3-carbonitrile (**11**; $C_{18}H_{11}NO_4S$)

A mixture of **9** (0.002 mol) and $Ba(OH)_2$ (0.002 mol) in EtOH (25 ml) was boiled under reflux for 2 h. The reaction mixture was poured into cold H_2O; the solid product that separated was filtered off and crystallized from EtOH.

Yield: 0.37 g (55%); m.p.: 135°C; IR: 2220 (CN), 1675 (C=O), 1650 (C=C); ^{1}H NMR: 6.71–7.82 (m, 11H, arom. protons + pyran H-6); MS: *m/z* (%) = 337 (M^+, 16%).

2-Amino-4-phenyl-5-phenylsulfonylpyridine-3-carbonitrile (**12**; $C_{18}H_{13}N_3O_2S$)

A suspension of **9** (0.003 mol) in NH_2OH (30 ml) was stirred at room temperature for 4 days. The reaction mixture was evaporated *in vacuo* and triturated with cold H_2O. The solid product was filtered off, washed thoroughly with H_2O, dried, and crystallized from ethanol.

Yield: 0.56 g (56%); m.p.: 200°C; IR: 3450–3400 (NH_2), 2222 (CN); ^{1}H NMR: 4.75 (br s, 2H, NH_2, exchangeable), 6.75–7.35 (m, 6H, arom. protons + pyridine H-6), 7.41–7.80 (m, 5H, arom. protons).

2-Amino-1,6-dihydro-1-benzoyl-4-phenyl-5-phenylsulfonyl-6-thioxopyridine-3-carbonitrile (**13**; $C_{25}H_{17}N_3O_3S_2$)

To a suspension of NH_4SCN (0.005 mol) in acetonitrile (30 ml), benzoyl chloride (0.005 mol) was added. The reaction mixture was boiled under reflux for 5 min and then treated with **3a** (0.005 mol). The mixture was boiled under reflux for 1 h, left aside to cool at room temperature, poured onto ice/H_2O mixture, and neutralized with NaOH (0.01 *N*). The solid product was collected by filtration, washed thoroughly with H_2O, dried, and crystallized from EtOH.

Yield: 1.77 g (75%); m.p.: 175°C; IR: 3400–3350 (NH_2), 2220 (CN), 1710 (C=O), 1200–1140 (C=S); ^{1}H NMR: 7.52–7.65 (m, 11H, arom. protons), 8.16–8.36 (m, 4H, arom. protons), 9.71 (br s, 2H, NH_2, exchangeable); MS: *m/z* (%) = 471 (M^+, 21%).

1,8a-Dihydro-2-phenylsulfonyl-1-thioxo-3,6,8-triphenylpyrido[1,2-a] pyrimidine-4,7-dicarbonitrile (**15**; $C_{34}H_{20}N_4O_2S_2$)

Method A. To a solution of **13** (0.002 mol) in dry dioxane (30 ml) containing piperidine (5 drops), benzylidenemalononitrile (**4a**, 0.002 mol) was added. The reaction mixture was boiled under reflux for 4 h,left to cool at room temperature, triturated with cold H_2O, and neutralized with dilute HCl. The solid product precipitated was collected by filtration and crystallized from EtOH.

Yield: 0.68 g (59%); m.p.: 245°C; IR: 2225, 2219 (2 CN), 1200 (C=S); ^{1}H NMR: 7.38–7.80 (m, 12H, arom. protons), 7.91–8.26 (m, 8H, arom. protons); MS: *m/z* (%) = 580 (M^+, 14%).

Method B via Schiff base (**16**; $C_{32}H_{21}N_3O_3S_2$)

To a solution of **13** (0.004 mol) in dioxane (30 ml) containing Et_3N (5 drops), benzaldehyde (0.004 mol) was added. The reaction mixture was boiled under reflux for 3 h, poured onto cold H_2O, and neutralized with dilute HCl. The solid product obtained was filtered off, dried, and crystallized from EtOH.

Yield: 1.34 g (60%); m.p.: 222°C; IR: 2222 (CN), 1710 (C=O), 1200 (C=S); ^{1}H NMR: 7.33–7.66 (m, 10H, arom. protons + methylenic CH), 7.82–8.30 (m, 11H, arom. protons).

To a solution of **16** (0.002 mol) in dioxane (30 ml) containing Et_3N (5 drops), malononitrile (0.002 mol) was added. The reaction mixture was boiled under reflux for 4 h, poured onto cold H_2O, and neutralized with dilute HCl. The solid product precipitated was collected by filtration and neutralized from EtOH. Yield: 0.68 g (59%); identical (m.p., mixed m.p., IR spectrum) with authentic sample prepared according to method A.

1,7a-Dihydro-5-H-3,7-diphenyl-2-phenylsulfonyl-1-thioxoimidazo[1,2-a] pyridine-4,6-dicarbonitrile (**17**; $C_{27}H_{16}N_4O_2S_2$)

To a warm solution of **13** (0.002 mol) in EtOH (30 ml) containing K_2CO_3 (0.002 mol), chloroacetonitrile (0.002 mol) was added. The reaction mixture was boiled under reflux for 3 h and then

poured onto cold H_2O. The solid product was collected by filtration, washed thoroughly with H_2O, dried, and crystallized from EtOH.

Yield: 0.54 g (55%); m.p.: 275°C; IR: 3320 (NH), 2222, 2216 (2 CN), 1200 (C=S); ^{1}H NMR: 7.38–7.80 (m, 9H, arom. protons), 7.90–8.18 (m, 6H, arom. protons), 11.69 (br s, 1H, NH, exchangeable); MS: m/z (%) = 492 (M^+, 19%).

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