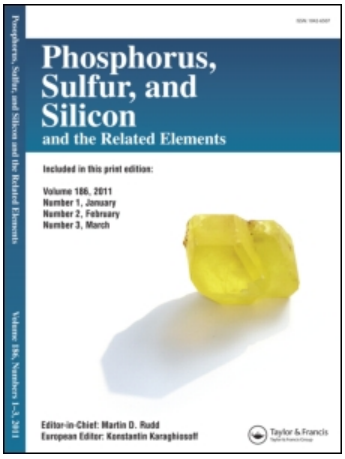

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Synthesis of Novel 1,2,3,4-Tetrahydrocarbazole Derivatives of Biological Interest

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SYNTHESIS OF NOVEL 1,2,3,4-TETRAHYDROCARBAZOLE DERIVATIVES OF BIOLOGICAL INTEREST

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2-Cyano-N-(tetrahydrocarbazole)acetamide (1) was utilized for the synthesis of several new arylazocarbazole derivatives (2a–e). Compound (1) reacted with phenyl isothiocyanate to yield the corresponding non-isolable intermediate (3), which gave, upon treatment with dilute hydrochloric acid, thiocarbamoyl derivative (4). Compound (3) reacted with chloroacetone, chloroacetic acid, chloroacetyl chloride, ethyl bromoacetate, and phenacyl bromide to afford thiazolone derivatives (6), (8), and (10), respectively. Compound (1) was heated in the presence of pyridine and/or hydrazine hydrate and/or isatine to give the corresponding tetrahydrocarbazole derivatives (13), (14), and (18), respectively.

Supplemental materials are available for this article. Go to the publisher's online edition of* Phosphorus, Sulfur, and Silicon and the Related Elements *to view the free supplemental file.

Keywords Aromatic amines; ethyl bromoacetate; phenacyl bromide; phenylisothiocyanate; 1,2,3,4-tetrahydrocarbazole

INTRODUCTION

The clinical need for therapeutic agents that restore or enhance an immune response in immunocompromised patients, such as that which occurs in viral infections, cancer, autoimmune diseases, and acquired immune deficiency syndrome (AIDS), has led to the search for novel immunostimulants.[1] Interferon-γ (IFN-γ) is a potent activator of the immune system and has been used in the treatment of infections in humans. A fused pyrrolo[2,3-c]carbazole-6-one (Figure 1) potentiates the INF-γ induction of MHC-class π molecules.[2] Other carbazole derivatives such as ellipticin, vincristine, and vinblastine alkaloids have a well established role in the treatment of cancer.[3–5] The present work is a part of our program aimed at developing new approaches for synthesis of fused heterocyclic systems containing carbazole moiety and evaluating their anticancer activity.

In addition, cyanoacetamides are highly reactive compounds. They are extensively utilized as reactants or reaction intermediates since the carbonyl and the cyano functions of these compounds are suitably situated to enable reactions with common bidentate reagents

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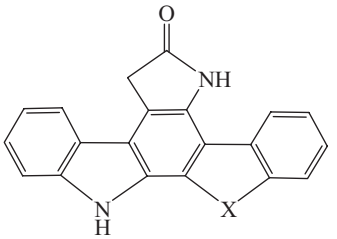


X= NH, O, S, CH_2

Figure 1

to form a variety of heterocyclic compounds. Moreover, the active hydrogen on the C-2 of these compounds can take part in a variety of condensation and substitution reactions.

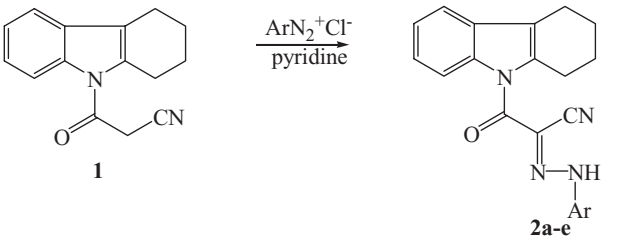
On the other hand, the diverse biological activities reported for many derivatives of cyanoacetamide have also drawn the attention of biochemists in the last decade. The literature covering the chemistry of cyanoacetamide derivatives has been limited. The main objective of the present work is to provide a comprehensive account of the synthetic utility of *N*-heteryl cyanoacetamides in building various organic heterocycles and to highlight their potential in evolving better chemotherapeutic agents.

In view of the above-mentioned findings, and as continuation of our efforts[6,7] to identify new candidates that may be of value in designing new, potent, selective, and less toxic antimicrobial agents, we report in this article the synthesis of some new heterocycles incorporating tetrahydrocarbazole moiety starting from *N*-tetrahydrocarbazolyl cyanoacetamide in order to investigate their antimicrobial activity.

RESULTS AND DISCUSSION

The synthetic procedures that were adopted to obtain the target compounds are depicted in Schemes 1–5 and the Supplemental Materials (available online). The starting compound 2-cyano-*N*-(tetrahydrocarbazole)acetamide (**1**) was prepared according to the previously reported procedure.[8] In continuation of our interest in the synthesis of a bridgehead nitrogen heterocyclic system,[9] we have found that diazotized aromatic amine is an excellent building block for the synthesis of the target compound. Thus, coupling of compound **1** with amine diazonium salts, mainly benzene diazonium salt, *p*-tolyl diazonium salt, *p*-anisyl diazonium salt, *p*-chlorophenyl diazonium salt, and *p*-nitrophenyl diazonium salt in pyridine at 0–5°C afforded the corresponding hydrazono compounds **2a–e**. The analytical and spectral data are in agreement with the proposed structure. Thus, the ^{1}H NMR spectrum of the reaction product **2b** showed signals at δ 1.77 (m, 4H, $2CH_2$-cyclo), a 1.91 singlet signal due to CH_3 protons, 2.49 (t, J = 6.8 Hz, 2H, CH_2-cyclo), 3.32 (t, J = 6.8 Hz, 2H, CH_2-cyclo), 6.87–7.66 ppm corresponding to aromatic protons, and finally a singlet signal at δ 12.30 ppm due to NH proton. Similarly, the ^{1}H NMR of compound **2c** showed the same ^{1}H NMR picture as for **2b**, except the OCH_3 protons appeared at δ 3.73 ppm. The IR spectrum of compounds **2a–e** in general showed the presence of a strong and broad band in the region 3100–3225 cm^{-1}, assigned to NH stretching of the hydrazone moiety, but a weak band at 1550–1580 cm^{-1}, also indicating their presence in the azo form and in a tautomeric mixture as well. The large shift and broadening of the NH band, as reported by Ramirez and Kerby,[10] for simple hydrazones can result only from

intramolecular hydrogen bonding as in **A**. The fact that the compounds **2a–e** show evidence for intramolecular hydrogen bonding is in favor of the hydrazone structure. Compounds **2a–e** exhibited bands in the region 1665–1669 cm^{-1} due to stretching vibration of the CO groups (Scheme 1).



2a, Ar = C_6H_5; **2b**, Ar = C_6H_4- CH_3-*p*; **2c**, Ar = C_6H_4-OCH_3-*p*;
2d, Ar = C_6H_4- Cl-*p*; **2e**, Ar = C_6H_4- NO_2-*p*

Scheme 1

Among the structural factors that lead to the lowering of the stretching vibration of the CO group are conjugation and hydrogen bonding. However, even if allowance is made for conjugation, the CO frequencies of the compounds studied are still much lower than those encountered in α,β-unsaturated ketones. This significant difference suggests that the CO group of these compounds should be involved in hydrogen bonding in the solid state, as shown in the proposed structure **A**. The UV spectra of the diazonium coupling products provided additional evidence that such compounds have the tautomeric relation with monohydrazones. Most of the dyes show four absorption bands in the region 196–438 nm. The relatively small difference in λ_{max} may be due to the polarity change of the absorption system caused by solvent interactions due to the general solvent effect.[11] It has been reported that the UV spectra of monophenylazo compounds differ from those of monophenylhydrazones. The azo compounds generally show two absorption bands at 400–410 and 290–300 nm corresponding to n–π^* and π–π^* transitions, respectively.[12]

On the other hand, monophenylhydrazones show three intense bands in 220–230, 250–280, and 330–390 nm regions.[11] The UV spectra of compounds **2a–e** can be interpreted in terms of the tautomeric mixture as well. It is clear that these dyes exhibit four bands; of these, the medium and high wavelength bands seem to be affected by the nature of the polar substituent in the arylazo group, and the low wavelength bands are unaffected. Table I shows that both electron-withdrawing and electron-donating groups cause the absorption to occur at higher wavelengths. Also from Table I, we can show that the presence of electron-donating or electron-withdrawing groups has not brought about any marked increase or decrease in λ_{max} in the visible region, and log ε has nearly remained constant. This does point towards the presence of the hydrazone structure where the resonance interactions with the substituents in the diazo component are minimal due to steric factors. Moreover, the structure of compounds **2a–e** was further confirmed by mass spectroscopic measurements, which showed the molecular ion peak at *m/z* for **2a** (342, 64%), **2b** (356, 80%), **2c** (372, 100%), **2d** (376, 75%), and **2e** (387, 76%), and in general showed the fragment at *m/z* 250 corresponding to $C_{15}H_{12}N_3O^+$.

Aryl isothiocyanates are versatile reagents, which have been used as synthetic intermediates to prepare biologically active heterocyclic compounds.[13] As a part of our program

Table I Spectral data of the newly prepared compounds

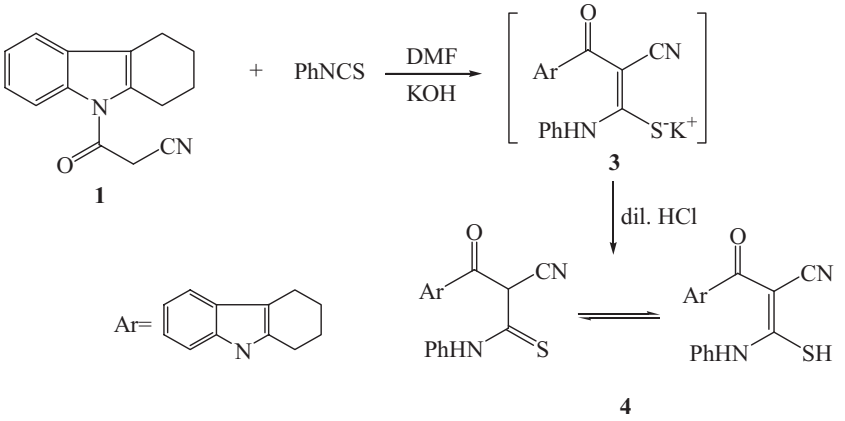
Compound	Spectral data
2a	IR (KBr)$\nu_{max.}$ cm^{-1}: 3225 (NH), 2220 (CN), 1665 (CO), 1600 (C=N), 1550 (N=N). ^{1}H NMR (DMSO) (δ, ppm), 1.77 (m, 4H, 2CH$_2$-cyclo), 2.49 (t, J = 6.8 Hz, 2H, CH$_2$-cyclo), 3.31 (t, J = 6.8 Hz, 2H, CH$_2$-cyclo), 6.87–7.66 (m, 9H, Ar−H), 12.32 (s, 1H, NH). MS: *m/z* (%), 342 (M$^+$, 64). UV: $\lambda_{max(nm)}$(log ε): 200 (2.32), 250 (2.86), 290 (3.3), 424 (4.03).
2b	IR (KBr)$\nu_{max.}$ cm^{-1}: 3200 (NH), 2220 (CN), 1665 (CO), 1600 (C=N), 1560 (N=N). ^{1}H NMR (DMSO) (δ, ppm), 1.77 (m, 4H, 2CH$_2$-cyclo), 1.91 (s, 3H, CH$_3$), 2.49 (t, J = 6.8 Hz, 2H, CH$_2$-cyclo), 3.32 (t, J = 6.8 Hz, 2H, CH$_2$-cyclo), 6.87–7.66 (m, 8H, Ar−H), 12.30 (s, 1H, NH). MS: *m/z* (%), 356 (M$^+$, 80). UV: $\lambda_{max(nm)}$(log ε): 196 (2.30), 260 (2.91), 305 (3.95), 438 (4.10).
2c	IR (KBr)$\nu_{max.}$ cm^{-1}: 3220 (NH), 2220 (CN), 1665 (CO), 1600 (C=N), 1565 (N=N). ^{1}H NMR (DMSO) (δ, ppm), 1.77 (m, 4H, 2CH$_2$-cyclo), 2.49 (t, J = 6.8 Hz, 2H, CH$_2$-cyclo), 3.30 (t, J = 6.8 Hz, 2H, CH$_2$-cyclo), 3.73 (s, 3H, OCH$_3$), 6.87–7.66 (m, 8H, Ar−H), 12.35 (s, 1H, NH). MS: *m/z* (%), 372 (M$^+$, 100). UV: $\lambda_{max(nm)}$(log ε): 203 (2.38), 250 (2.86), 295 (3.41), 424 (4.03).
2d	IR (KBr)$\nu_{max.}$ cm^{-1}: 3100 (NH), 2220 (CN), 1665 (CO), 1610 (C=N), 1580 (N=N). ^{1}H NMR (DMSO) (δ, ppm), 1.77 (m, 4H, 2CH$_2$-cyclo), 2.49 (t, J = 6.8 Hz, 2H, CH$_2$-cyclo), 3.32 (t, J = 6.8 Hz, 2H, CH$_2$-cyclo), 6.87–7.66 (m, 8H, Ar−H), 12.31 (s, 1H, NH). MS: *m/z* (%), 376 (M$^+$, 75). UV: $\lambda_{max(nm)}$(log ε): 198 (2.31), 250 (2.86), 290 (3.31), 428 (4.08).
2e	IR (KBr)$\nu_{max.}$ cm^{-1}: 3150 (NH), 2219 (CN), 1669 (CO), 1610 (C=N), 1580 (N=N), 1530, 1350 (NO$_2$). ^{1}H NMR (DMSO) (δ, ppm), 1.77 (m, 4H, 2CH$_2$-cyclo), 2.49 (t, J = 6.8 Hz, 2H, CH$_2$-cyclo), 3.31 (t, J = 6.8 Hz, 2H, CH$_2$-cyclo), 6.87–7.66 (m, 8H, Ar−H), 12.30 (s, 1H, NH). MS: *m/z* (%), 387 (M$^+$, 76). UV: $\lambda_{max(nm)}$(log ε): 198 (2.31), 248 (2.62), 280 (3.25), 420 (4.02).
4	IR (KBr)$\nu_{max.}$ cm^{-1}: 3205 (NH), 2200 (CN), 1625 (CO), 1305 (C=S). ^{1}H NMR (DMSO) (δ, ppm), 1.84 (m, 4H, 2CH$_2$-cyclo), 2.49 (t, J = 6.8 Hz, 2H, CH$_2$-cyclo), 3.41 (t, J = 6.8 Hz, 2H, CH$_2$-cyclo), 7.12–7.50 (m, 9H, Ar−H), 11.93 (s, 1H, NH).
5	IR (KBr)$\nu_{max.}$ cm^{-1}: 3405 (NH), 2191 (CN), 1697 (CO), 1615 (N−CO). ^{1}H NMR (DMSO) (δ, ppm), 1.85 (m, 4H, 2CH$_2$-cyclo), 1.95 (s, 3H, COCH$_3$), 2.83 (t, J = 6.8 Hz, 2H, CH$_2$-cyclo), 2.95 (t, J = 6.8 Hz, 2H, CH$_2$-cyclo), 4.75 (s, 2H, COCH$_2$), 7.24–7.65 (m, 9H, Ar−H).
6	IR (KBr)$\nu_{max.}$ cm^{-1}: 2190 (CN), 1615 (N−CO), 1597 (C=C). ^{1}H NMR (CDCl$_3$) (δ, ppm), 1.85 (m, 4H, 2CH$_2$-cyclo), 1.97 (s, 3H, CH$_3$), 2.83 (t, J = 6.8 Hz, 2H, CH$_2$-cyclo), 2.95 (t, J = 6.8 Hz, CH$_2$-cyclo), 6.61–7.65 (m, CH+9-Ar−H). MS: *m/z* (%), 411 (M$^+$, 12.8).
7	IR (KBr)$\nu_{max.}$ cm^{-1}: 3404 (NH), 2200 (CN), 1715 (CO), 1615 (N−CO). ^{1}H NMR (DMSO) (δ, ppm), 1.33 (t, 3H, CH$_3$), 1.86 (m, 4H, 2CH$_2$-cyclo), 2.81 (t, J = 6.8 Hz, 2H, CH$_2$-cyclo), 2.95 (t, J = 6.8 Hz, 2H, CH$_2$-cyclo), 4.34 (q, 2H, CH$_2$), 4.70 (s, 2H, COCH$_2$), 6.82–7.71 (m, 9H, Ar−H), 12.94 (s, 1H, NH).
8	IR (KBr)$\nu_{max.}$ cm^{-1}: 2210–2202 (CN), 1700 (CO), 1650 (N−CO). ^{1}H NMR (DMSO) (δ, ppm), 1.85 (m, 4H, 2CH$_2$-cyclo), 2.82 (t, J = 6.8 Hz, 2H, CH$_2$-cyclo), 2.95 (t, J = 6.8 Hz, 2H, CH$_2$-cyclo), 3.10 (s, 2H, SCH$_2$), 7.11–7.53 (m, 9H, Ar−H). MS: *m/z* (%), 413 (M$^+$, 45.0).
10	IR (KBr)$\nu_{max.}$ cm^{-1}: 2929 (CH), 2201 (CN), 1644 (CO), 1604 (C=C). ^{1}H NMR (CDCl$_3$) (δ, ppm), 1.83 (m, 4H, 2CH$_2$-cyclo), 2.65 (t, J = 6.8 Hz, 2H, CH$_2$-cyclo), 2.85 (t, J = 6.8 Hz, 2H, CH$_2$-cyclo), 4.85 (s, 1H, CH), 7.26–7.61 (m, 14H, Ar−H). MS (70 ev): *m/z* (%), 473 (M$^+$, 25).
13	IR (KBr)$\nu_{max.}$ cm^{-1}: 2930 (CH), 1600 (C=C).

(Continued on next page)

Table I Spectral data of the newly prepared compounds *(Continued)*

Compound	Spectral data
	^{1}H NMR (200 MH$_Z$, DMSO) (δ, ppm), 1.73 (m, 8H, 4CH$_2$), 2.64 (m, 4H, 2CH$_2$), 2.76 (m, 4H, 2CH$_2$), 6.93–7.51 (m, 8H, Ar—H).
	MS: *m/z* (%), 341 (M$^+$+1, 10.8), 340 (M$^+$, 29.6), 338 (15.1), 312 (5.4), 283 (12.4), 269 (10.8), 189 (6.5), 187 (20.4), 186 (11.3), 185 (15.6), 184 (23.7), 171 (30.1), 170 (100.0), 169 (39.2), 168 (45.7), 167 (31.2), 166 (18.3), 154 (14.5).
14	IR (KBr)$\nu_{max.}$cm^{-1}: 3400–3350 (NH$_2$, NH), 2925 (aliphatic CH$_2$), 1681 (amidic carbonyl), 1617 (C=N).
	^{1}H NMR (CDCl$_3$) (δ, ppm), 1.43, 1.72 (m, 2H, CH$_2$-cyclo), 1.72, 1.82 (m, 2H, CH$_2$-cyclo, J = 6.8 Hz), 2.67, 2.74 (m, 2H, CH$_2$-cyclo, J = 6.8 Hz), 2.81 (t, 1H, CH-pyridine ring), 6.91–7.70 (m, 4H, Ar—H), 8.58, 8.68 (d.d, 2H, CH$_2$-pyridine ring).
	MS: *m/z* (%), 242 (M$^+$+4, 55).
18	IR (KBr)$\nu_{max.}$cm^{-1}: 3365 (NH), 1721 (CO).
	^{1}H NMR (CDCl$_3$) (δ, ppm), 1.84 (m, 2H, CH$_2$-cyclo), 1.98 (t, 2H, CH$_2$-cyclo, J = 6.8 Hz), 3.01 (t, 2H, CH$_2$-cyclo, J = 6.8 Hz), 6.89–7.97 (m, 8H, Ar—H), 8.63 (s, 1H, NH).
	MS: *m/z* (%), 349 (M$^+$, 2.4), 243 (19.2), 242 (93.8), 214 (10.9), 198 (13.3), 171 (15.7), 170 (100.0), 169 (50.9), 168 (13.8), 145 (5.0), 144 (14.7), 143 (24.6), 142 (66.8), 141 (67.2), 140 (11.2), 115 (45.0), 114 (74.1), 113 (12.9), 100 (14.2), 88 (28.9), 62 (13.3).

to develop a new, simple, and efficient procedure for the synthesis of new aromatic compounds using readily available aryl isothiocyanates, we have recently affected recyclization of thiocarbamoyl in thiophenes, pyrazoles, and thiazoles.[14] Thus, the base-prompted reaction of the acidic methylene compound **1** with phenyl isothiocyanate in dry DMF at room temperature in basic medium led to the formation of the non-isolable intermediate **3**, which gave thiocarbamoyl derivative **4** upon treatment with dilute HCl (Scheme 2). Assignment of the product **4** was based on elemental analysis, IR, and ^{1}H NMR spectral data. The IR spectrum showed absorption bands at 3205, 2200, 1625, and 1305 cm^{-1} attributable to the NH, CN, CO, and C = S functions, respectively. The ^{1}H NMR spectrum of **4** displayed multiplet signals at δ 1.84, 2.49, and 3.41 ppm for CH$_2$ protons and multiplet signals at δ 7.12–7.50 ppm for aromatic protons besides an exchangeable proton at δ 11.93 ppm for NH proton.



1 **3** **4**

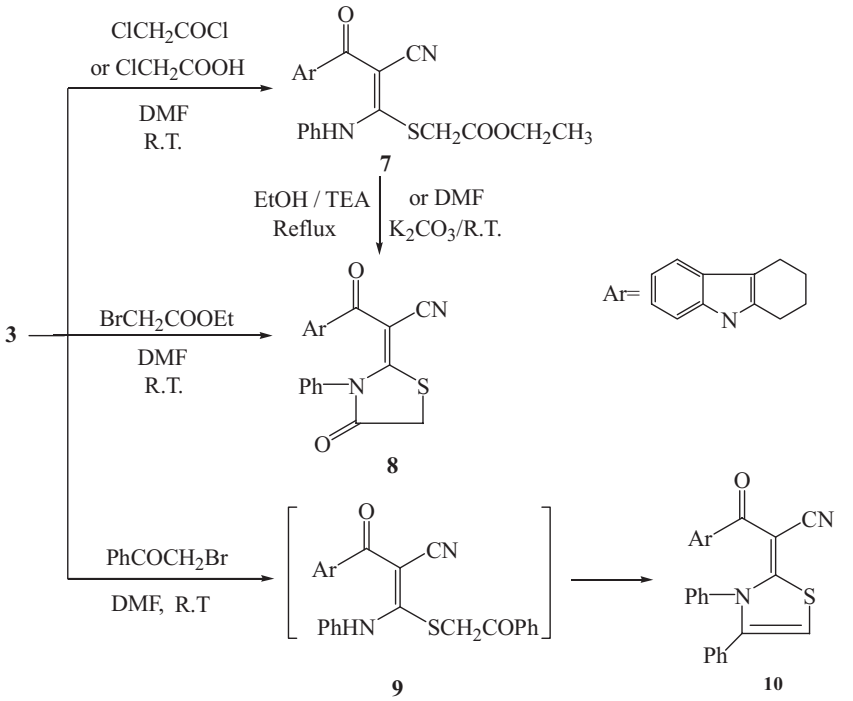
Scheme 2

On the other hand, it has been found that stirring of the intermediate **3** with chloroacetone in DMF for 2 h yielded a product **5**, which analyzed correctly for $C_{25}H_{23}N_3O_2S$. The structure **5** was inferred from its spectral data. Thus, the IR showed absorption bands at 3405, 2191, 1697, and 1615 cm^{-1} corresponding to NH, CN, CO, and N—CO functions. Its ^1H NMR spectrum showed signals at δ 1.85 (m, 4H, $2CH_2$-cyclo), 2.83 (t, J = 6.8 Hz, 2H, CH_2-cyclo), 2.95 (t, J = 6.8 Hz, 2H, CH_2-cyclo), and two singlet signals at δ 1.95 and 4.75 ppm corresponding to $COCH_3$ and $COCH_2$ protons, respectively, besides multiplet signals at δ 7.24–7.65 ppm due to aromatic protons and singlet signal at δ 8.25 ppm for NH proton. Upon shaking the compound with D_2O, the band signal at δ 8.22 ppm disappeared.

However, if the reaction was stirred overnight, it afforded a product **6**. The structure of **6** was inferred from its spectral data. Thus, the IR spectrum showed absorption bands at 2190, 1615, and 1597 cm^{-1} characteristic for CN, N—CO, and C=C functions. Its ^1H NMR spectrum showed, besides the normal and expected tetrahydrocarbazole protons, the presence of CH_3 protons at δ 1.97 ppm and CH proton at δ 6.61 ppm and the disappearance of the NH proton, indicating that the NH group was involved in the cyclization process, which lost one molecule of water. Moreover, the mass spectrum gave additional evidence for the structure **6**, which showed its molecular ion peak at *m/z* 411 (12.8%) and the base peak at *m/z* 241 corresponding to $C_{14}H_9NOS^+$ fragment. Based on the foregoing data, structure **6** was assigned to this product. The structure of **6** was further confirmed by alternative synthesis. Thus, it was found that refluxing of **5** in ethanol with a few drops of TEA led to the formation of a product identical in all respects (mp, mixed mp, IR) to **6**. (See Scheme S2, available online in the Supplemental Materials.)

Similarly, when the intermediate potassium salt **3** is stirred with an equimolar amount of chloroacetyl chloride or with chloroacetic acid in ethanol, a product that was analyzed for $C_{26}H_{25}N_3O_3S$ was isolated in each case in good yield. The acyclic structure of **7** was established on the basis of its IR spectrum, which shows bands related to NH and CO functions. Its ^1H NMR spectrum reveals multiplet signals at δ 6.82–7.71 ppm (9H, aromatic), a triplet signal at δ 1.33 (3H, CH_3), a singlet at δ 4.70 (2H, CH_2CO), a quartet at δ 4.34 (2H, CH_2), and a D_2O exchangeable NH at δ 12.92 ppm besides the normal tetrahydrocarbazol protons. Alternatively, treatment of the intermediate salt **3** with ethyl bromoacetate in ethanol gives a single product, which is identical in all respects to **7** (mp, mixed mp, and IR spectrum). The mass spectrum of **7** showed a molecular formula $C_{26}H_{25}N_3O_3S$ ($M^+ = 459$). Refluxing of **7** in ethanol with a catalytic amount of TEA or leaving it in DMF containing potassium carbonate at room temperature overnight afforded the corresponding thiazole derivative **8**.

In a similar manner, **8** was prepared by stirring ethyl bromoacetate with the intermediate **3** in the presence of DMF. The structure of **8** was proven on the basis of both spectral and analytical data. The IR spectrum showed absorption bands at 2210–2202 cm^{-1} due to CN, and 1650 and 1700 for two carbonyl groups. ^1H NMR spectrum showed signals at δ 1.85 as a multiplet for two CH_2 groups, 2.82 and 2.95 as triplet for two CH_2 groups, and δ 3.10 as a singlet for SCH_2. The mass spectroscopic measurements gave additional evidence for the correct structure of compound **8**, which showed the molecular ion peak at *m/z* 413 (45%). In addition, stirring of **3** with phenacyl bromide in DMF overnight yielded a product **10**, which analyzed correctly for $C_{30}H_{23}N_3OS$. The structure of **10** was inferred from its spectral data. See Scheme 3. Thus, the IR spectrum showed absorption bands at 2929, 2201, 1644, and 1604 cm^{-1} corresponding to CH, CN, CO, and C=C functions. Its ^1H NMR spectrum showed signals at δ 1.83, 2.65, and 2.85 ppm for 8H of $4CH_2$ protons, δ 4.85



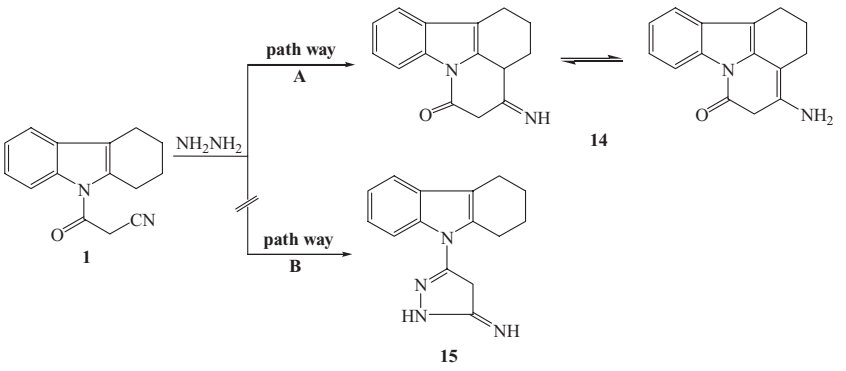
Scheme 3

(CH cyclic), and multiplet at δ 7.26–7.61 for (14H, aromatic). All attempts to synthesize the acyclic intermediate **9** failed.

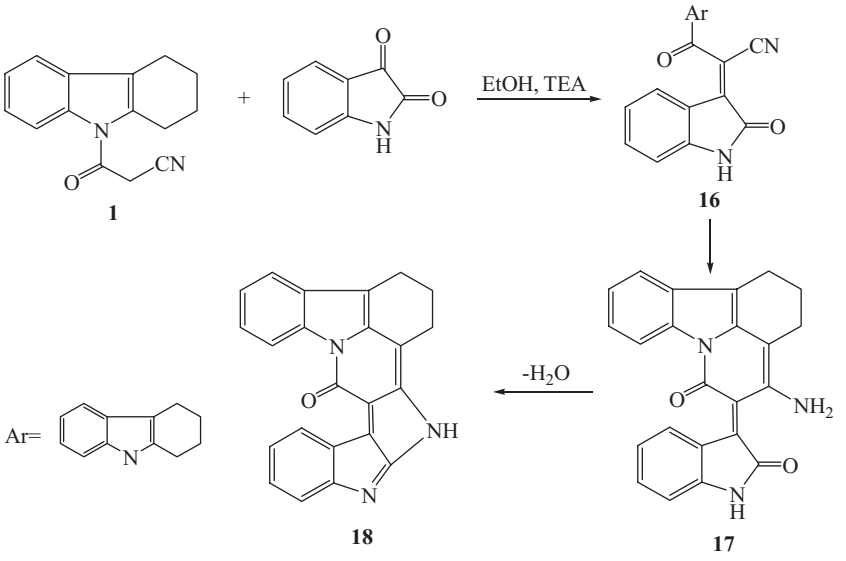
Moreover, by refluxing compound **1** in pyridine, we could isolate a dark yellow compound. Elgemeie et al.[15] claimed that refluxing phenacyl cyanide in pyridine afforded the so-called trimmer and assigned structure of **11**. However, our isolated product may be also the trimmer of compound **1** structure **12**, but the IR spectrum of this product did not show any absorption bands that can be attributed to amino or carbonyl or cyano functions (see the Experimental section). Furthermore, the ^{1}H NMR spectrum of this product showed only an aliphatic CH_2 proton and an aromatic multiplet. Mass spectrum measurements showed that this compound has a molecular weight of 341 (M^++1, 10.8%), which is consistent with two molecules of **1** losing 2H atom (see Figure S1 in the Supplemental Materials available online).

On the basis of these data, it was assumed that two molecules of **1** underwent dimerization with each other, maybe via a free radical reaction, to afford **13**. If the structure was **12**, a carbonyl signal would have appeared in the IR spectrum at 1700–1720 cm^{-1} (see Scheme S3 in the Supplemental Materials).

In continuation of our work, the pyridocarbazole derivative **14** was synthesized by refluxing an equimolar amount of compound **1** and hydrazine hydrate in ethanol in the presence of TEA. The formation of compound **14** was provided by the ^{1}H NMR spectrum, in particular the chemical shift of the H-2 proton. The ^{1}H NMR spectrum of compound **14** showed signals at δ 1.43, 1.72 (m, CH_2), 1.72, 1.82 (m, CH_2), 2.67, 2.74 (m, CH_2), 2.81 (t, CH-pyridine ring), 6.91–7.70 (m, Ar-ring), 8.85–8.68 (d.d, CH_2-pyridine ring). Alternatively, when structure **15** was the reaction product, it revealed the pyrazol ring CH_2



Scheme 4



Scheme 5

and the carbazol 2-H protons at δ 1.40 and 2.74 ppm, respectively, but they disappeared.[16] The formation of **14** is assumed to proceed via the nucleophilic attack of C_2 of carbazol to the cyano group, in which the hydrazine hydrate acts as base medium and is not involved in the cyclization process. The structure of **14** could be established for the reaction product based on its elemental and spectral data. The IR spectrum showed absorption frequencies at 3400–3350, 2925, 1681 and 1617 cm^{-1} corresponding to NH_2—NH, aliphatic CH_2, amidic carbonyl, and C=N functions.

Moreover, the mass spectroscopic measurements of the product **14** gave more confirmation for its correct structure, which showed the molecular ion peak at *m/z* 242 (M^++4, 55%) and the base peak at *m/z* 143 due to the loss of CH_2=CH_2 fragment. On the basis of these results, the structure of **15** for the reaction product **14** can be discarded (Scheme 4).

Interestingly, isatine reacts with **1** to give a single product that analyzed correctly for $C_{23}H_{15}N_3O$. This product was formulated as poly cyclic compound **18**. The structure of **18**

Table II Characterization data of the newly prepared compounds

Compound No.	Melting point, °C	Yield (%)	Mol. Formula (M. Wt.)	Calcd (Found)%		
				C	H	N
1	181	73	$C_{15}H_{14}N_2O$ (238.28)	75.61 (75.31)	5.92 (5.59)	11.76 (11.96)
2a	182	68	$C_{21}H_{18}N_4O$ (342.39)	73.67 (73.45)	5.30 (5.21)	16.36 (16.15)
2b	193	70	$C_{22}H_{20}N_4O$ (356.42)	74.14 (74.43)	5.66 (5.56)	15.72 (16.02)
2c	170	78	$C_{22}H_{20}N_4O_2$ (372.42)	70.95 (70.72)	5.41 (5.21)	15.04 (15.25)
2d	203	56	$C_{21}H_{17}ClN_4O$ (376.84)	66.93 (66.72)	4.55 (4.74)	14.87 (14.56)
2e	180	66	$C_{21}H_{17}N_5O_3$ (387.39)	65.11 (65.42)	4.42 (4.42)	18.08 (18.12)
4	85	70	$C_{22}H_{19}N_3OS$ (373.47)	70.75 (70.53)	5.13 (5.33)	11.25 (11.33)
5	164	68	$C_{25}H_{23}N_3O_2S$ (429.53)	69.91 (69.78)	5.40 (5.64)	9.78 (9.74)
6	259	74	$C_{25}H_{21}N_3OS$ (411.52)	72.97 (72.75)	5.14 (5.34)	10.21 (10.31)
7	264	69	$C_{26}H_{25}N_3O_3S$ (459.56)	67.95 (67.72)	5.48 (5.17)	9.14 (9.11)
8	112	66	$C_{24}H_{19}N_3O_2S$ (413.49)	69.71 (69.91)	4.63 (4.43)	10.16 (10.46)
10	153	72	$C_{30}H_{23}N_3OS$ (473.59)	76.08 (76.26)	4.90 (4.90)	8.87 (8.67)
13	118	73	$C_{24}H_{24}N_2$ (340.46)	84.67 (84.43)	7.11 (7.32)	8.23 (8.51)
14	115	69	$C_{15}H_{14}N_2O$ (238.28)	75.61 (75.82)	5.92 (5.71)	11.76 (11.52)
18	206	68	$C_{23}H_{15}N_3O$ (349.38)	79.07 (79.26)	4.33 (4.12)	12.03 (12.03)

was proven by IR, ^{1}H NMR, and mass spectra. Its mass spectrum showed the molecular ion peak at *m/z* 349 (2.4%) and the base peak at *m/z* 170. The IR spectrum showed absorption bands at 3365 cm^{-1} and 1721 cm^{-1} due to the NH and CO functions. For the ^{1}H NMR spectrum, see the Experimental section and Table II). The reaction gave the condensation product intermediate **16**, which was followed by nucleophilic attack of the active methylene group to the cyano group to afford the second intermediate **17**, which lost a water molecule to give the final product **18** (Scheme 5).

EXPERIMENTAL

All melting points were recorded on Gallenkamp electric melting point apparatus and are uncorrected. The IR spectra υ cm^{-1} (KBr) were recorded on a Perkin Elmer Infrared Spectrophotometer Model 157, Grating. The ^{1}H NMR spectra were run on a Varian Spectrophotometer at 200 MHz using TMS as an internal reference and DMSO-d_6 as solvent. The mass spectra (EI) were recorded on 70 eV with Kratos MS equipment and/or a Varian MAT 311 A Spectrometer. Elemental analyses (C, H, and N) were carried out at the Microanalytical Center of Cairo University, Giza, Egypt. The results were found to be in good agreement ($\pm$ 0.3%) with the calculated values.

Synthesis of 3-(5,6,7,8-Tetrahydrocarbazol-9-yl)-3-oxopropanenitrile (1)

It has been prepared according to the previously reported work.[8]

Coupling of (1) with Aromatic Diazonium Salts: Synthesis of Aryl Hydrazono Tetrahydrocarbazolyl Propionitrile (2a–e)

A well-stirred solution of aromatic amines (20 mmol) in concentrated HCl (6 mL) and water (4 mL) was cooled in an ice bath and diazotized with a solution of sodium nitrite (1.39 g, 20 mmol) in water (5 mL).

The cooled diazonium solution was added dropwise to a well-stirred cooled solution of **1** in ethanol (10 mL) containing sodium acetate (1.75 g, 20 mmol). The reaction mixture was stirred for 1–2 h until it reached complete coupling reaction. The crude product was filtered off, dried well, and recrystallized from ethanol. The results are given in Table II.

Synthesis of 3-Mercapto-3-phenylamino-2-(1,2,3,4-tetrahydro-carbazole-9-carbonyl)-acrylonitrile (4)

To a cold suspension of potassium hydroxide (1.4 g, 25 mmol) in DMF (30 mL), cyanotetrahydro-carbazoloacetamide (6.0 g, 25 mmol) was added followed by phenyl isothiocyanate (2.99 mL, 25 mmol). The mixture was stirred overnight at room temperature and then poured onto ice-cold water. Acidification using dilute HCl until the medium became acidic gave solid product **4**, which was filtered off, washed with water, dried, and crystallized from aqueous ethanol to give compound **4** (see Tables I and II).

Synthesis of the Acyclic Intermediate (5)

Equimolar quantities of **4** (3.37 g, 10 mmol) in ethanol containing potassium carbonate (1.39 g, 10 mmol) and chloroacetone (0.798 mL, 10 mmol) were stirred for 2 h at room temperature, then left to stand at the same temperature for 24 h. The separated solid product was washed with water, dried, and crystallized from ethanol to give **5** (see Tables I and II).

Synthesis of 2-(4-Methyl-3-phenyl-3*H*-thiazol-2-ylidene)-3-oxo-3-(1,2,3,4-tetrahydro-carbazol-9-yl)-propionitrile (6), 3-Oxo-2-(4-oxo-3-phenyl-thiazolidin-2-ylidene)-3-(1,2,3,4-tetrahydro-carbazol-9-yl)-propionitrile (8), and 2-(3,4-Diphenyl-3*H*-thiazol-2-ylidene)-3-oxo-3-(1,2,3,4-tetrahydro-carbazol-9-yl)-propionitrile (10)

Pathway 1. A mixture of equimolar amounts of **3** and α-halo compounds (10 mmol) was stirred in DMF (20 mL) containing potassium carbonate (1.39 g, 10 mmol) overnight. The reaction mixture was poured onto ice-cold water, acidified by dilute HCl, filtered off, and recrystallized from ethanol to give the corresponding thiazole derivatives (see Tables I and II).

Pathway 2. Refluxing the acyclic intermediates **5** and **7** in ethanol (20 mL) containing a catalytic amount of TEA for 3 h afforded the corresponding thiazole derivatives **6** and **8**.

Synthesis of 6,7,8,9-Tetrahydro-9-(5,6,7,8-tetrahydrocarbazol-9-yl)-5*H*-carbazole (13)

Compound **1** (2.38 g, 10 mmol) was refluxed in dry pyridine for 2 h and then left to cool at room temperature, where a yellow crystalline product appeared. This product was collected by filtration, washed thoroughly with ethanol, and recrystallized from ethanol/DMF to afford compound **13** (see Tables I and II).

Synthesis of 4-Amino-2,3-dihydro-1*H*-pyrido[3,2,1-jk]carbazol-6(5*H*)-one (14)

A mixture of **1** (2.38 g, 10 mmol) and hydrazine hydrate (0.49 mL, 10 mmol) in ethanol (25 mL) in the presence of TEA (4 drops) was refluxed for 3 h. The reaction mixture was then cooled to room temperature, and the obtainable solid material was filtered off, dried, and recrystallized from ethanol to give compound **14** (see Tables I and II).

Synthesis of Pyrrolopyridocarbazol Derivative (18)

Equimolar amounts of **1** (2.38 g, 10 mmol) and isatine (1.47 g, 10 mmol) in ethanol (25 mL) in presence of few drops of pyridine were refluxed for 4 h. The reaction mixture was left to cool at room temperature overnight. The formed precipitate was filtered off, dried, and recrystallized from ethanol to give compound **18** (see Tables I and II).

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