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NEW EASY ONE-POT SYNTHETIC ROUTES OF 2-ARYLBENZIMIDAZOLES

Ahmad Q. Hussein[a,*] and Mervat S. Sammor[b]

[a] *Chemistry Department, School of Science, The University of Jordan, Amman, Jordan*
[b] *Al-Balqa' Applied University, Zarqa, Jordan*
[*]*Corresponding author Email: aqhussein@ju.edu.jo*

ABSTRACT: One-pot condensation of 1,2-phenylenediamine with phenacyl cyanides affords high yields of the corresponding 2-arylbenzimidazoles. The same products are also obtained through similar condensation of phenylenediamine either with phenacyl thiocyanates or with benzylidenemalononitriles.

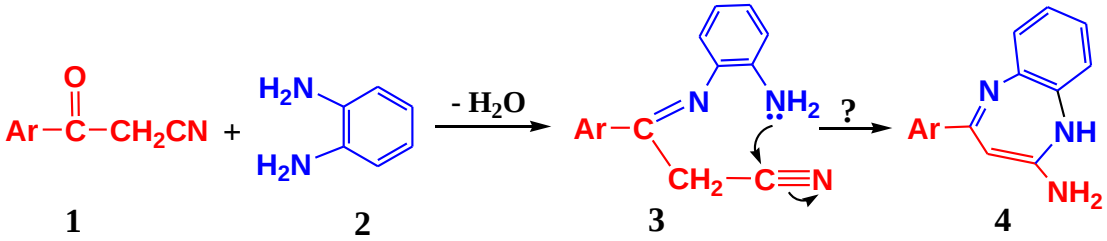
KEY WORDS: 2-Arylbenzimidazole; 1,2-Phenylenediamine; Phenacyl cyanide; Phenacyl thiocyanate; Benzylidenemalononitrile; 2-Amino1,5-benzodiazepine.

INTRODUCTION:

Phenacyl cyanides **1**, also known as aroyl acetonitriles, are privileged organic synthons, as they incorporate, in addition to an active methylene, two electrophilic functionalities, a carbonyl and a cyano group. Furthermore, these compounds are readily accessible either by α-acylation of acetonitrile[i] or through treatment of phenacyl halides with alkali metal cyanides[ii]. In consequence, phenacyl cyanides are favorable starting materials which are widely employed in the field of organic and heterocyclic synthesis through reactions with appropriate reaction partners. Condensation of phenacyl cyanides with hydrazines[iii-viii], functionalized amines[ix-xiii], alkynes[xiv], 1,3-dicarbonyls[xv-xvi], and diazo[xvii], compounds are only few among numerous examples which demonstrate the synthetic potential of these compounds.

As a continuation of our search towards new synthesis of the diazepine ring system[xviii], we have, in this study, investigated the unreported condensation reaction of compounds **1** with 1,2-phenylenediamine **2**. We envisaged that this reaction would ultimately afford 2-amino-1,5-benzodiazepine ring system **4** (Scheme 1). It may be anticipated that the reaction would be initiated through a nucleophilic addition of one amino group of phenylenediamine to the carbonyl carbon of phenacyl cyanide, thus leading to the intermediate imine **3**. Subsequent intramolecular attack of the second amino group at the electrophilic cyano-

functionality would eventually lead to the target compounds **4** as final reaction products. In such event, this one-pot reaction would then offer a new facile synthetic method for 2-amino-1,5-benzodiazepines. It is worth noting, in this context, that a lot of chemical research is being devoted to the benzodiazepine ring system (BZD) and towards exploring new synthetic strategies towards BZD[xix]. The benzodiazepine system encompasses a large number of derivatives which exhibit diverse pharmacological activities, and a significant number of them are approved prescription drugs[xx-xxi].

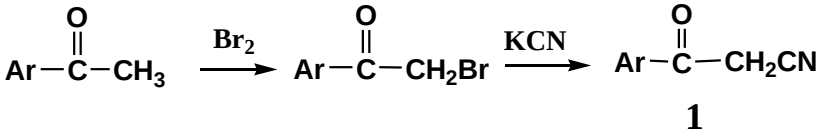


Scheme 1: Possible pathway of the reaction between compound **1** and **2**.

RESULTS AND DISCUSSION:

Synthesis of Phenacyl Cyanides

Phenacyl cyanides **1** were obtained in high yields from the corresponding phenacyl bromides **5** by substitution of the bromide ion with sodium cyanide, following a literature procedure[ii] (Scheme 2). The phenacyl bromides were freshly prepared through α-bromination of the corresponding acetophenones[x] (experimental section). The prepared phenacyl cyanides were identified through their spectral data and by comparison of their melting points (experimental section) with the corresponding reported value [xxiv-xxix].



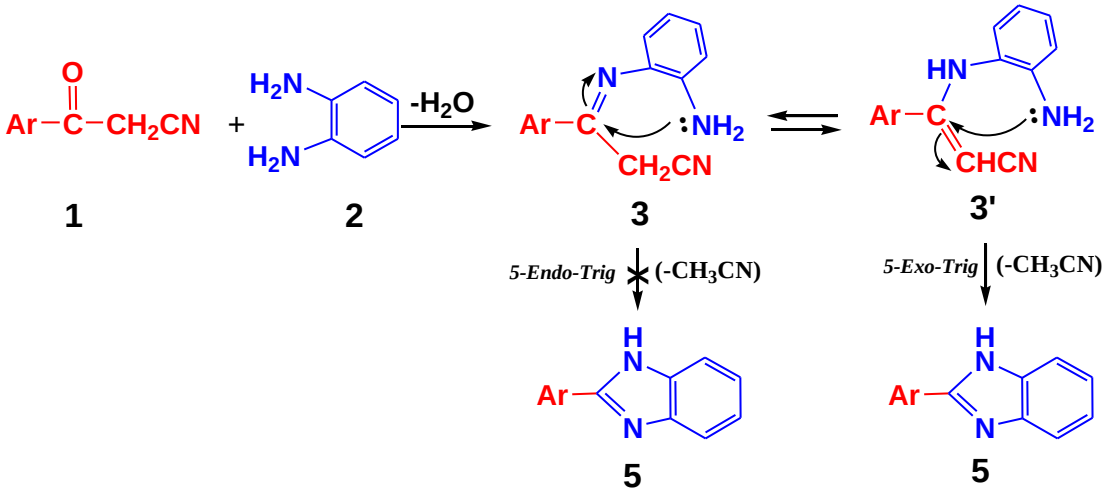
Scheme 2: Synthesis of phenacyl cyanides from acetophenones

Reaction of Phenacyl Cyanides with 1,2-Phenylenediamine

Upon heating a solution of the phenacyl cyanide **1a** with a slight excess of 1,2-phenylenediamine in acetic acid at 80 ^{o}C, a smooth reaction soon ensued, as evidenced by the brownish color acquired by the mixture. Thin-layer chromatographic examination revealed the presence of a new product in addition to the starting materials, which were completely consumed within few hours of heating. Workup of the reaction mixtures (experimental section) afforded crystalline products, which were isolated, purified by recrystallization, and finally identified through their IR, ^{1}H- and ^{13}C-NMR, and HRMS spectral data.

To our surprise, however, the spectral data of the products were unequivocally consistent with the 2-arylbenzimidazole structure **5** , rather than the presumed 1,5-benzodiazepine structure **4** (Scheme 3). Thus, in the infrared spectra of the products, an N-H absorption was observed in the range 3100-3250 cm^{-1}, but no absorption corresponding to the cyano

group could be detected. The ^{1}H-NMR spectrum of compound **5c**, as a representative example of these products, exhibited two doublets at 8.02 and 7.33 ppm for the p-substituted Ar protons, two distinct multiplets at 7.55 and 7.18 ppm for the protons of the fused phenyl group, a broad signal at 3.52 for the NH, and a singlet at 2.34 for the methyl protons. In the ^{13}C-NMR spectra, each of compounds **5** exhibited a signal at 151- 153 ppm, which is characteristic of the heteroring carbon C(2)[xxx]. In the spectrum of compound **5c**, this carbon appeared at 151.6 ppm, while the methyl carbon occurred at 21.4 ppm, and signals corresponding to the remaining aromatic carbon atoms were observed in the range between 115.2 and 140.5 ppm. The high resolution molecular mass measurement (HRMS) of compound **5c** gave a value of *m/z* = 207.0923 (M-1), which matches the correct molecular formula (calc. for $C_{14}H_{11}N_2$, *m/z* = 207.0922). The remaining members of the series all gave HRMS results which agree with the corresponding calculated values (within ± 1-2 ppm).



Scheme 3: Condensation reaction of phenacyl cyanides with 1,2-phenylenediamine

Table 1: Physical data of the synthesized benzimidazoles **5**.

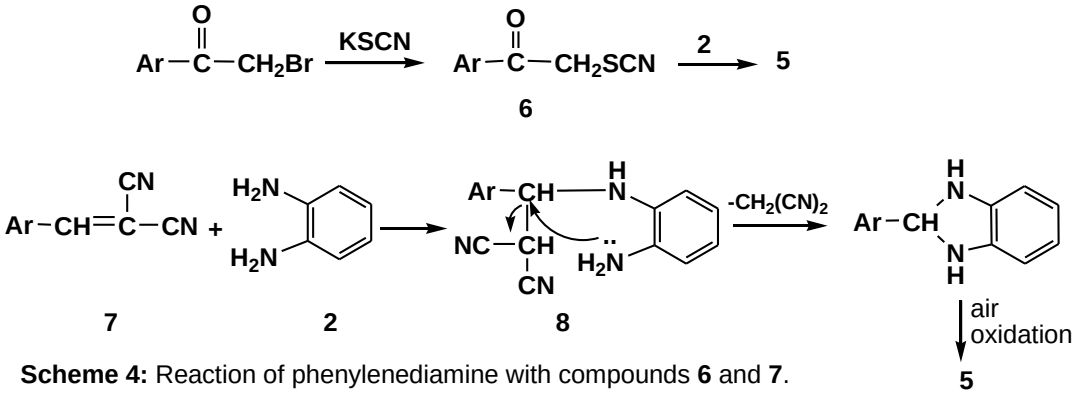
Compd	Ar	%Yield (method)	m.p. (^{o}C) (Lit.)	δ ^{13}C (ppm) (C2) / (Me)	HRMS; m/z found (calc.)
5a	4-BrC_6H_4	86 (A) 81 (B)	292-294 298 [xxi]	150.8	[M-1]: 270.98763 (270.98709)
5b	4-ClC_6H_4	82 (A) 68 (C)	282-285 289 [xxxii]	150.3	[M+1]: 229.05270 (229.05325)
5c	4-MeC_6H_4	74 (A) 70 (B)	256-258 261-263 [xxxiii]	151.6 / 21.4	[M-1]: 207.09237 (207.09223)
5d	2-MeC_6H_4	74 (A)	196-198 199-202 [xxxiv]	151.9 / 19.8	[M+1]: 209.10768 (209.10788)

5e	C_6H_5	69 (A) 75 (B) 54 (C)	287-289 292 [xxxv]	152.2	[M+1]: 195.09229 (195.09222)
5f	3- $MeOC_6H_4$	78 (A)	198-200 205-206 [xxxvi]	151.6 / 54.6	[M+1]: 225.10318 (225.10279)
5g	4- $MeOC_6H_4$	82 (A)	218-220 222-225 [xxxvii]	151.0 / 55.4	[M+1]: 225.10226 (225.10279)

A plausible reaction pathway for the formation of benzimidazoles in this reaction is depicted in scheme 3 . Obviously , the reaction proceeds *via* the initial condensation involving one amino group of 1,2-phenylenediamine and the carbonyl carbon of **1** with the ultimate formation of the intermediate imine **3**, which may equilibrate[xxxviii] with the alternative tautomeric form **3'.** Through a conjugate Michael addition via the amino group to the vinylic nitrile (C=CH-CN) moiety, this latter tautomer (**3')** undergoes intramolecular cyclization in an allowed "*5-Exo-Trig*" process[xxxix-xl]. Eventually, the resulting adduct suffers elimination of a molecule of acetonitrile to furnish the final benzimidazole product **5**. An alternative addition-elimination via the other tautomeric form **3** is excluded, since it would involve a disfavored "*5-Endo-Trig*" process.

Reaction of 1,2-phenylenediamine with Phenacyl Thiocyanates and 2-Benzylidenemalononitriles

We furthermore found that, under the same reaction conditions described above for the condensation of phenacyl cyanides with 1,2-phenylenediamine, the closely related phenacyl thiocyanates **6**, as well as 2-benzylidenemalononitriles **7**, react in a similar manner with 1,2-phenylenediamine to yield the same products **5**. Presumably, the condensation of phenylenediamine with 2-Benzylidenemalononitriles **7** occurs through initial Michael-type addition which results in the formation of the corresponding adduct **8** (Scheme 4). Subsequent intramolecular cyclization of the latter adduct, through an S_N2-type displacement of the malononitrile moiety by the amino group, followed by aromatization of the resulting imidazolidine ring through air oxidation, would furnish the corresponding 2-arylbenzimidazoles **5**.



Scheme 4: Reaction of phenylenediamine with compounds **6** and **7**.

III. EXPERIMENTAL SECTION:

General procedure for preparation of phenacyl bromides

General procedure: 8.0 g of bromine (0.05 mol) in 15 mL acetic acid were slowly added to the desired substituted acetophenone (0.05 mol) in 15 mL acetic acid with shaking at room temperature inside a fume hood. After the red color of bromine disappeared, ice water (50-60 mL) was added to the reaction mixture, and the precipitate was collected by filtration, which was dried and purified by recrystallization from ethanol-water. Following this procedure, the following phenacyl bromides were synthesized:

4-Bromophenacyl bromide: Yield 82%, m.p. 111-112 oC, Lit.[xxii] m.p. 107-110 ºC.

4-Chlorophenacyl bromide: Yield 86 %; m.p. 95-96 oC; Lit.[xxiii] m.p. 96-97 ºC.

4-Methylphenacyl bromide **5c**: Yield 77 %; m.p. 48-49 ºC; Lit.[xxiii] m.p. 51 ºC.

2-Methylphenacyl bromide: Yield 72 %; oil, it was used without further purification.

Phenacyl bromide: Yield 75 %; m.p. 51-52 ºC, Lit.[xxii] m.p. 50-51 ºC.

3-Methoxyphenacyl bromide: Yield 88 %; m.p. 58-60 ºC; Lit.[xxiii] m.p. 61-62 ºC.

4-Methoxyphenacyl bromide: Yield 92 %; m.p. 66-67; Lit. [xxiii] m.p. 68 ºC;

General procedure for the preparation of phenacyl cyanides (1)

1.3 g potassium cyanide (0.02 mol) in 5 mL water were dropwise added to an ice-cooled solution of the appropriate phenacyl halide (0.01 mol) in ethanol (15 mL) under magnetic stirring. The mixture was left stirring for 3 h, then poured over ice-water (50 mL) containing 5 mL conc. HCl. The precipitate was collected , dried and recrystallized from ethanol-water. The pure compounds were identified through their NMR spectral data, and by melting points. The ^{1}H-NMR spectrum of compound **1c**, as a representative example, shows two doublets at 7.83 (2H) and 7.34 (2H) ppm for the aromatic hydrogens, and two singlets at 4.06 (2H) and 2.46 (3H), which correspond to the methylene and the methyl hydrogens, respectively. In addition to signals of the aromatic ring carbon atoms, the ^{13}C-NMR spectrum of each of these compounds exhibits two characteristic signals at about 114 and at 30 ppm, assigned to the CN and CH_2 carbon atoms, respectively.

4-Bromolphenacyl cyanide **1a**: Yield 88 %; m.p. 159-160 ºC; Lit.[xxiv] m.p 161-162 ºC.

4-Chlorophenacyl cyanide **1b**: Yield 78 %, m.p. 129-130 ºC; Lit.[xxii] m.p. 126-128 ºC.

4-Methylphenacyl cyanide **1c**: Yield 84 %; m.p.104-105 ºC; Lit.[xxv] m.p. 106-108 ºC.

2-Methylphenacyl cyanide **1d**: Yield 70%; m.p.83-84; Lit.[xxvii] m.p. 81-82 ºC.

Phenacyl cyanide **1e**: Yield 72 %; m.p. 82-83 ºC; Lit.[xxviiiI] m.p. 79-81 ºC.

3-Methoxyphenacyl cyanide **1f**: Yield 86 %; m.p. 84-85 ºC; Lit.[xxvi] m.p. 87-88 ºC.

4-Methoxyphenacyl cyanide **1g**: Yield 88 %; m.p. 131-133 ºC; Lit.[xxix] m.p. 135-136 ºC.

General procedure for the preparation of phenacyl thiocyanates (6)

These compounds were prepared by reaction of phenacyl bromides with potassium thiocyanate according to known procedure:

4-Bromophenacyl thiocyanate: Yield 92%; m.p. 150-151 ºC; Lit.[xli] m.p. 148-9 ºC.

4-Methylphenacyl thiocyanate: Yield 86%; m.p. 100-101 ºC; Lit.[xlii] m.p. 102-103 ºC.

Phenacyl thiocyanate: Yield 80%; m.p. 67-69 ºC; Lit.[xlii] m.p. 70-72 ºC.

General procedure for the preparation of benzylidenemalononitriles (7)

These compounds were prepared by condensation of malononitrile with the appropriate substituted benzaldehyde according to Lit.[xxxxiii] procedure.

Benzylidenemalononitrile: Yield 74%; m.p. 84-86 ^{o}C; Lit.[xliii] m.p. 83-85 ^{o}C.
4-Chlorobenzylidenemalononitrile: Yield 78%; m.p 92-93 ^{o}C; Lit.[xliii] m.p. 90-91 ^{o}C.

General procedure for the preparation of 2-arylbenzimidazoles (5)

Method A: A mixture of 10 mmol of the appropriate phenacyl cyanide (**1)** and 1.52 g of phenylenediamine (14 mmol) and an equivalent amount of either in 10 mL acetic acid were stirred at 80^{o}C for 2-4 hours, until completion of the reaction as indicated by consumption of 1 by thin-layer chromatographic examination. The mixture was then allowed to cool, and was then diluted with 30 mL of ice-cold water. The crude product, which precipitated, was collected by suction filtration, and finally purified by recrystallization from ethanol-water. The same procedure was followed in case of method B and C, while replacing phenacyl cyanide with phenacyl thiocyanate, or with benzylidenemalononitrile, respectively.

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