Synthesis of Arylcyanomethylenequinone Oximes

Subjects: Chemistry, Organic

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Quinone methides are a class of biologically active compounds that can be used in medicine as antibacterial, antifungal, antiviral, antioxidant, and anti-inflammatory agents. In addition, quinone methides have the potential to be used as pesticides, dyes, and additives for rubber and plastics.

quinonemethide   arylcyanomethylenequinone oximes   quinone

## 1. The Condensation of (Hetero) Arylacetonitriles with Nitro (Hetero) Arenes

There are not many methods applicable to the synthesis of both arylcyanomethylenequinone oximes and other quinone methide oxime derivatives. The analysis of the literature data showed that one of the best approaches for the construction of their backbone is the condensation of benzyl cyanides with 4-unsubstituted nitroarenes or nitroheteroarenes [1], which is a simple way of synthesis of various derivatives of such oximes.

The synthesis of phenylcyanomethylenequinone oxime was first described by Davis et al. [2] in 1960. The authors stated that when benzyl cyanide **1a** and nitrobenzene **2a** are added to a warm alcoholic solution of potassium hydroxide, the reaction mixture becomes dark red and a like-coloured solid soon precipitates. The solid dissolves in water, and upon acidification with acetic acid solution, a new yellow–orange solid precipitates with a yield of 77%; the latter solid is 4-(phenylcyanomethylene)-cyclohexa-2,5-dien-1-one oxime **3a** (Scheme 1).
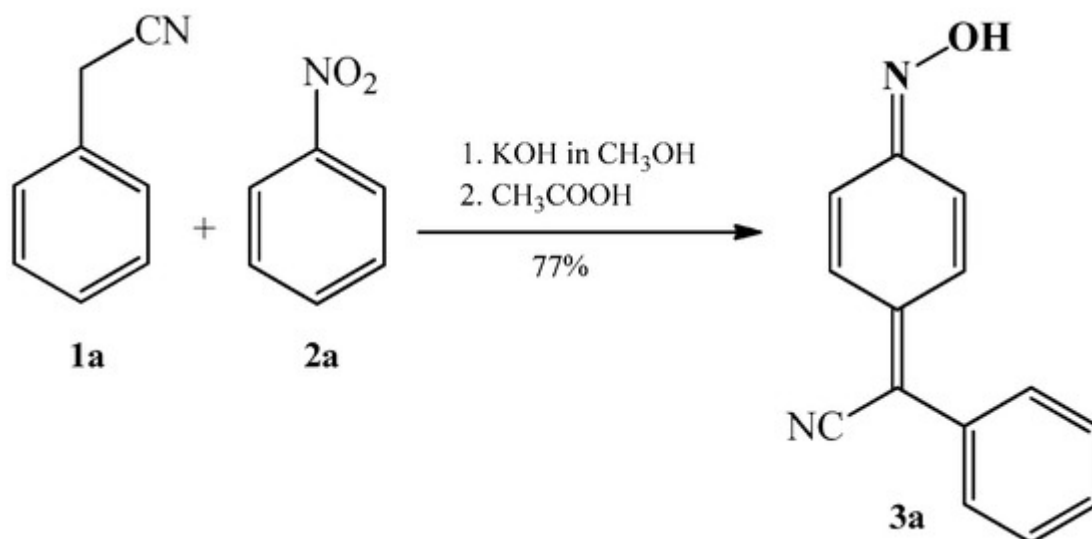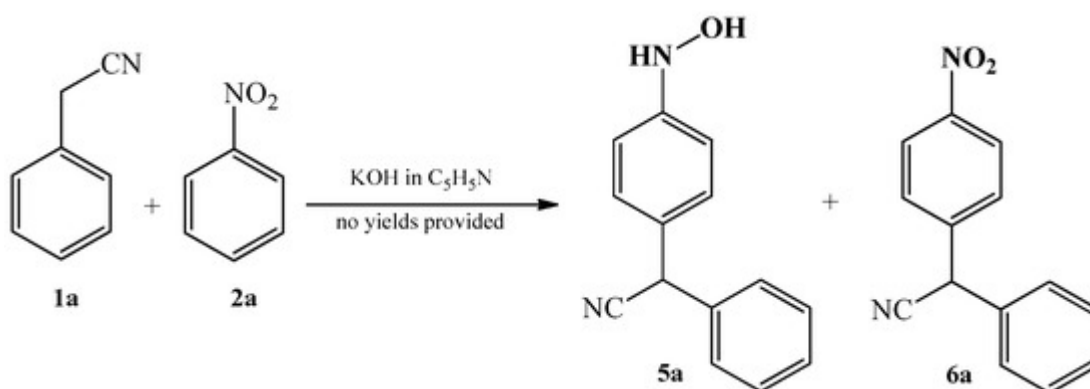
Scheme 1. Condensation reaction of benzyl cyanide **1a** with nitrobenzene **2a** that produces 4-(phenylcyanomethylene)-cyclohexa-2,5-dien-1-one oxime **3a**.

Simultaneously, in that work, the authors also reported that no evidence for the other possible reaction products, except for product **3a**, were obtained. Attempts to isolate possible structures **4a**, **5a**, **6a** were unsuccessful (**Figure 2**).
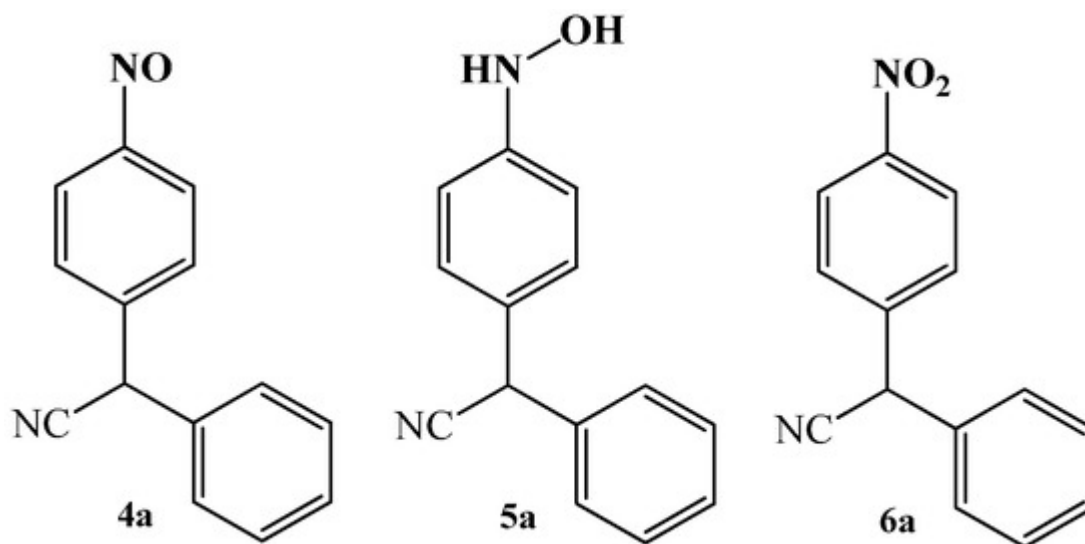
Figure 2. Structures of other potential reaction products of condensation reaction between benzyl cyanide **1a** and nitrobenzene **2a**.

On the other hand, they have noted that in the reaction between benzyl cyanide **1a** and nitrobenzene **2a,** it is possible to obtain other products when the methanol solvent was replaced with pyridine: the mixture of products **5a** and **6a** (Scheme 2) was obtained then.
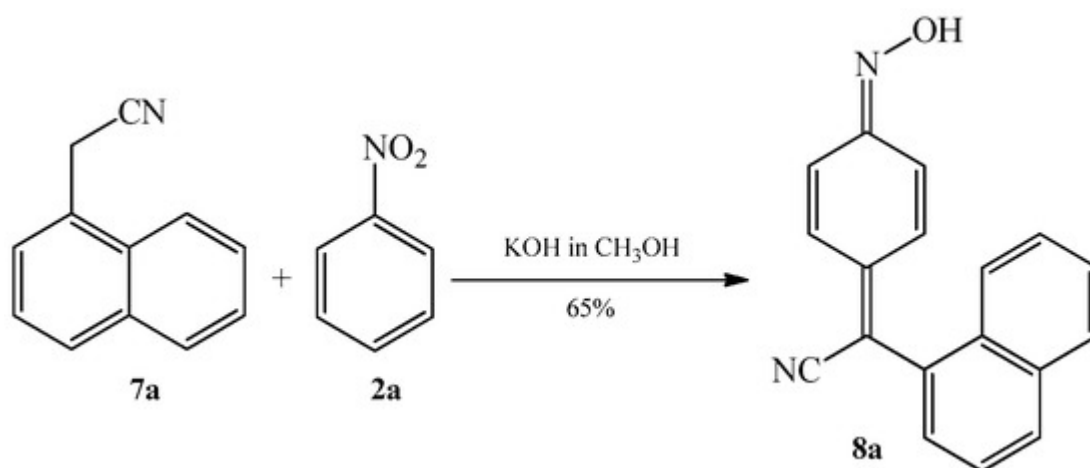

Scheme 2. Condensation reaction of benzyl cyanide **1a** with nitrobenzene **2a** to produce analogues **5a** and **6a** of oxime **3a**.

In the same paper the authors have also shown, for the first time, that nitrobenzene **2a** can react with 4-substituted benzyl cyanides, such as 4-chlorobenzyl cyanide **1b** and 4-methoxybenzyl cyanide **1c**, as well as with α-

naphthylacetonitrile **7a**. Reactions took place in a methanolic solution of potassium hydroxide, forming corresponding quinone oximes **3ba**, **3ca** (Scheme 3), and **8a** (Scheme 4).
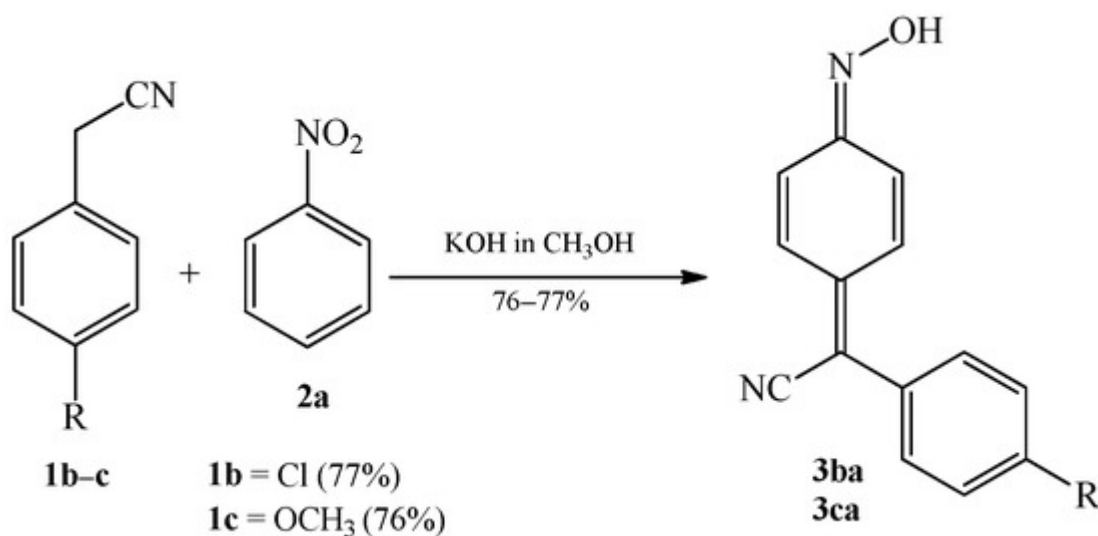

Scheme 3. Condensation reaction of 4-substituted benzyl cyanides **1b**–**c** with nitrobenzene **2a** to produce quinone oximes **3ba** and **3ca**.

Scheme 4. Condensation reaction of α-naphthylacetonitrile **7a** with nitrobenzene **2a** to produce quinone oximes **8a**.

The mechanism of condensation reaction between benzyl cyanide **1a** and nitrobenzene **2a** was described on Scheme 5. In the first step, nitrobenzene **2a** undergoes nucleophilic attack of the benzyl cyanide anion **1'a** at the 4-position, with subsequent addition of a proton to the oxygen of the nitro group to form intermediate **9a**, which can also exist as a potassium salt. Further elimination of a water molecule leads to the formation of the nitroso derivative **4a**. In turn, compound **4a** rapidly transforms into an anion, possessing two alternative forms **10a** and **10'a**. Finally, acidification of the potassium salt **10'a** leads to the formation of phenylcyanomethylenequinone oxime **3a**.
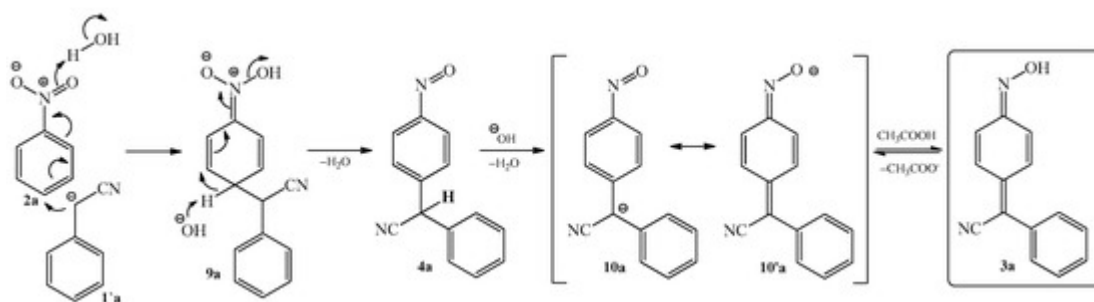
Scheme 5. Mechanism of condensation reaction of nitrobenzene **1a** with benzyl cyanide **2a** to produce 4-(phenylcyanomethylene)-cyclohexa-2,5-dien-1-one oxime **3a**.

In 1962, Lichtenberger and Weiss [3] reproduced the condensation reaction between nitrobenzene **1a** and benzyl cyanide **2a**, proposed by Davis et al. [2]. The authors reported that they had obtained 4-(phenylcyanomethylene)-cyclohexa-2,5-dien-1-one oxime **3a** as the only reaction product, thus confirming previous studies.

In 1961, Davis et al., continuing the study of the course of the condensation of various 4-substituted benzyl cyanides **1a–c** with 4-unsubstituted nitroarenes **11a–n** (Scheme 6), published the work [4] in which detailed preparations, by the previously shown condensation method, were described. As a result, 34 new arylcyanomethylenequinone oxime analogues **12aa–cn** were synthesized (**Table 1**). The reactions were realized in warm alcoholic solution of potassium hydroxide.
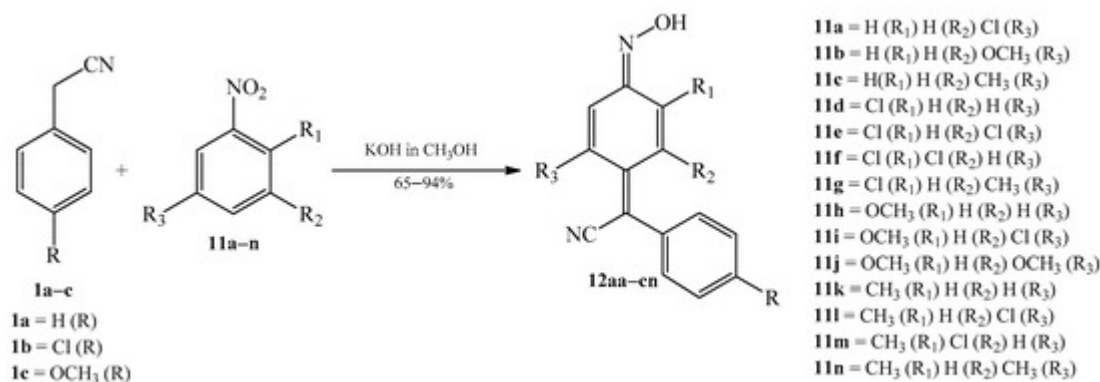

Scheme 6. Condensation reaction of 4-substituted benzyl cyanides **1a–c** with 4-unsubstituted analogues of nitrobenzene **11a–n** to produce quinone oximes **12aa–cn**.

Table 1. Analogues of arylcyanomethylenequinone oximes **12aa–cn**.

Product (Yield [%])	R	R_1	R_2	R_3	Product (Yield [%])	R	R_1	R_2	R_3
12aa	(53)	-H	-H	-H	-Cl	**12be**	(94)	-Cl	-Cl	-H	-Cl
12ab	(25)	-H	-H	-H	-OCH$_3$	**12bf**	(92)	-Cl	-Cl	-Cl	-H
12ac	(76)	-H	-H	-H	-CH$_3$	**12bg**	(77)	-Cl	-Cl	-H	-CH$_3$

| Product (Yield [%])		R	R_1	R_2	R_3	Product (Yield [%])		R	R_1	R_2	R_3
12ad	(92)	-H	-Cl	-H	-H	12bh	(80)	-Cl	-OCH₃	-H	-H
12ae	(93)	-H	-Cl	-H	-Cl	12bi	(81)	-Cl	-OCH₃	-H	-Cl
12af	(53)	-H	-Cl	-Cl	-H	12bj	(80)	-Cl	-OCH₃	-H	-OCH₃
12ag	(77)	-H	-Cl	-H	-CH₃	12bk	(60)	-Cl	-CH₃	-H	-H
12ah	(87)	-H	-OCH₃	-H	-H	12bm	(80)	-Cl	-CH₃	-Cl	-H
12ai	(82)	-H	-OCH₃	-H	-Cl	12bn	(43)	-Cl	-CH₃	-H	-CH₃
12aj	(88)	-H	-OCH₃	-H	-OCH₃	12ce	(91)	-OCH₃	-Cl	-H	-Cl
12ak	(72)	-H	-CH₃	-H	-H	12cg	(80)	-OCH₃	-Cl	-H	-CH₃
12al	(92)	-H	-CH₃	-H	-Cl	12cf	(65)	-OCH₃	-Cl	-Cl	-H
12am	(82)	-H	-CH₃	-Cl	-H	12ci	(84)	-OCH₃	-OCH₃	-H	-Cl
12an	(53)	-H	-CH₃	-H	-CH₃	12cj	(65)	-OCH₃	-OCH₃	-H	-OCH₃
12ba	(100)	-Cl	-H	-H	-Cl	12cl	(88)	-OCH₃	-CH₃	-H	-Cl
12bb	(89)[5]	-Cl	-H	-H	-OCH₃	12cm	(80)	-OCH₃	-CH₃	-Cl	-H
12bd	(100)	-Cl	-Cl	-H	-H	12cn	(69)	-OCH₃	-CH₃	-H	-CH₃

...zene **2b**. ...ot created but an analogue of isoxazole **13** is formed as the only product (Scheme 7). The reaction was carried out in warm alcoholic solution of potassium hydroxide.
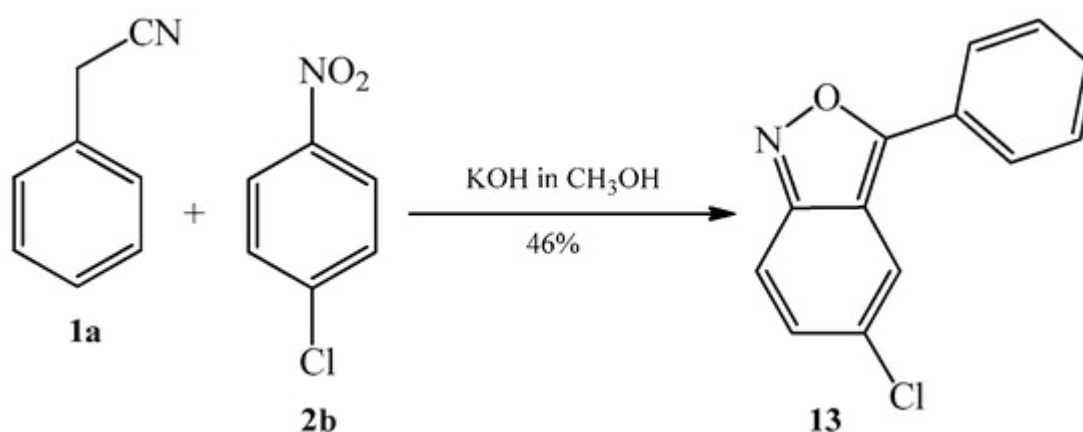
Scheme 7. Condensation reaction of benzyl cyanide **1a** with 4-chloronitrobenzene **2b** to produce 3-phenyl-5-chloroanthranil **13**.

In the same patent, Davis reported that in the reaction between benzyl cyanide **1a** and 4-chloronitrobenzene **2b,** when the solvent is changed from methanol to pyridine, the 4-chloro substituent is not retained in the product. In turn, 4-(phenylcyanomethylene)-cyclohexa-2,5-dien-1-one oxime **3a** is formed (Scheme 8). This variation of the

reaction, in contrast to the previous examples, allows to use 4-substituted nitroarenes in the synthesis of arylcyanomethylenequinone oximes.
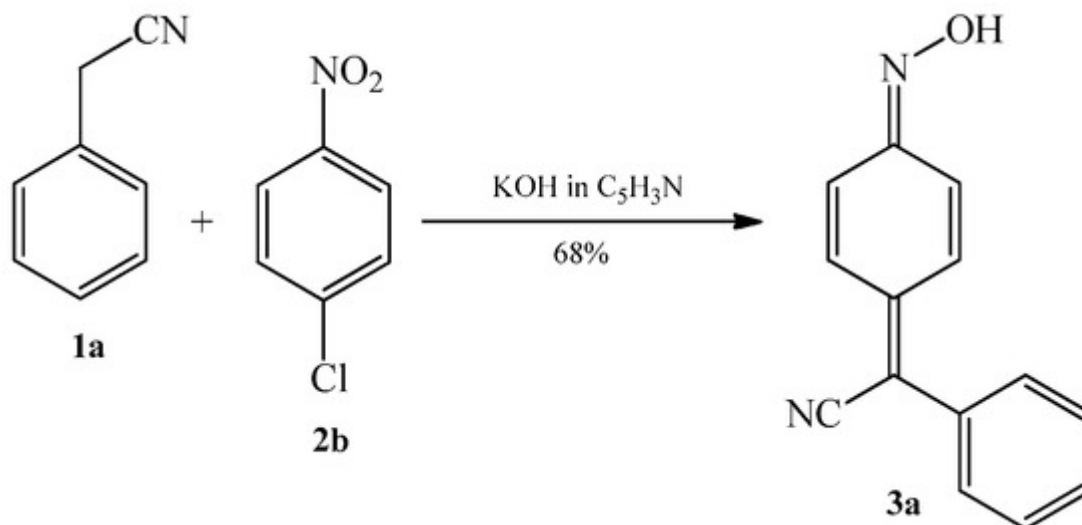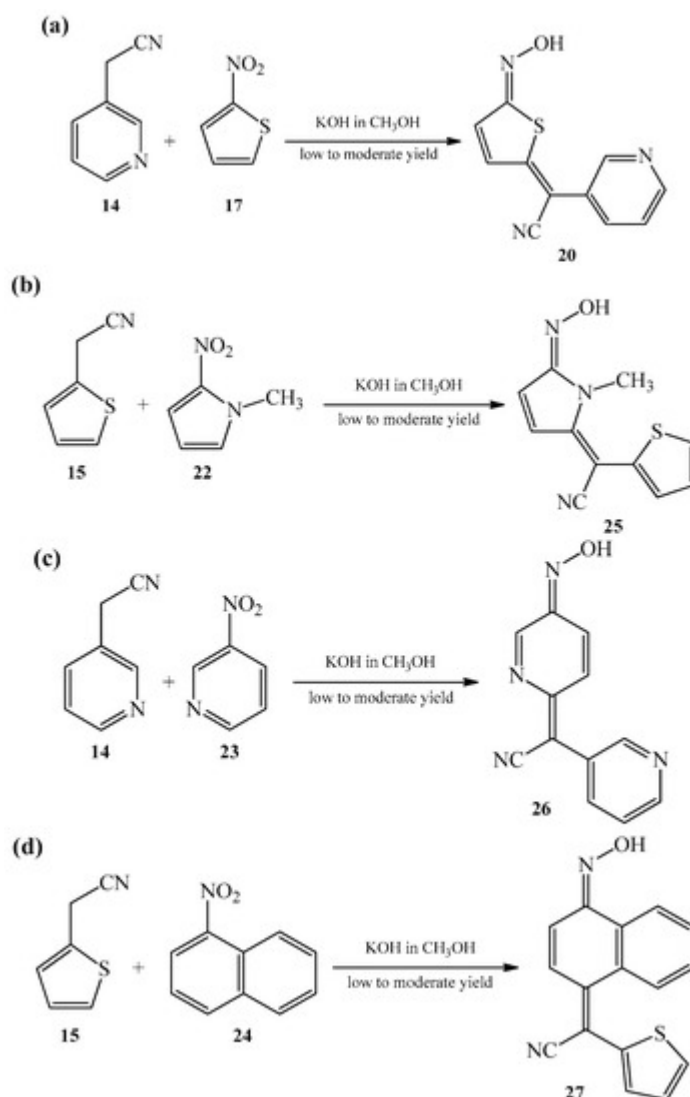

Scheme 8. Condensation reaction of benzyl cyanide **1a** with 4-chloronitrobenzene **2b** to produce 4-(phenylcyanomethylene)-cyclohexa-2,5-dien-1-one oxime **3a**.

In 1965, Marey et al. [6] proposed the use of heteroaromatic analogues of benzyl cyanide **2a** such as 3-pyridylacetonitrile **14** and 2-thienylacetonitrile **15** and (hetero)aromatic nitro compounds like 2-substituted nitrobenzene **16a–c** and 2-nitrothiophene **17** in the condensation reaction. Reactions took place in warm methanolic solution of potassium hydroxide, forming corresponding heterocyclic analogues of arylcyanomethylenequinone oximes **18–21** (Scheme 9). The authors mentioned that yields of all reactions were >10%.
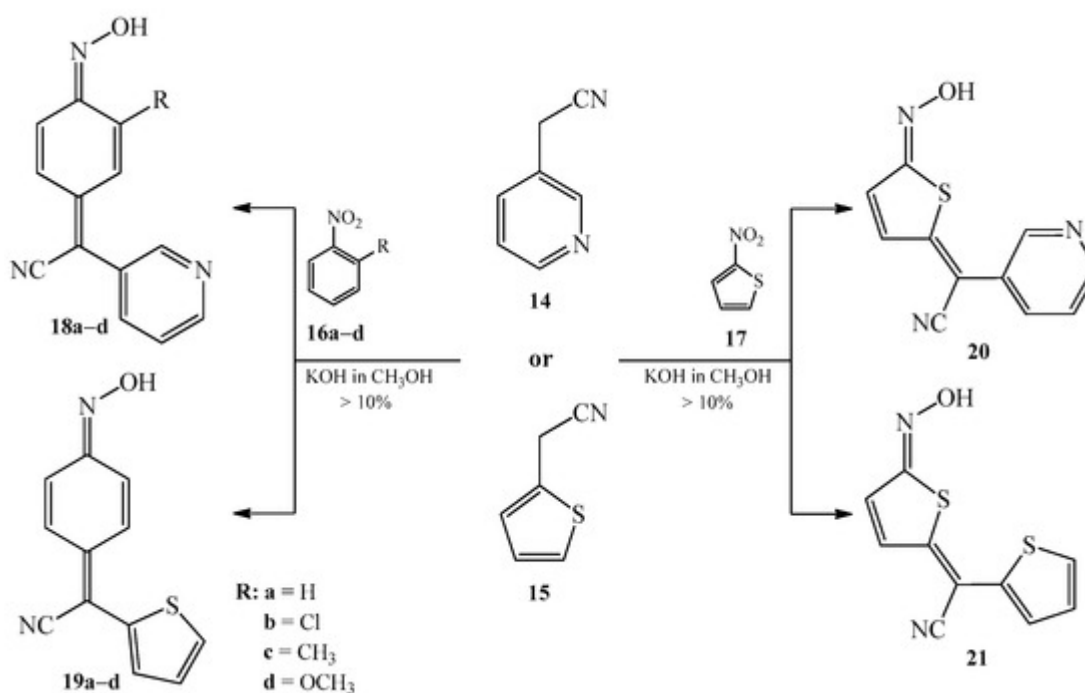
Scheme 9. Condensation reaction of 3-pyridylacetonitrile **14** or 2-thienylacetonitrile **15** with 2-substituted nitrobenzene analogues **16a–c** and 2-nitrothiophene **17** to produce oximes **18–21**.

Continuing the study of synthesis of such heterocyclic oximes, in 1968, Fournari and Marey [7] reported on the study of reactions between heteroarylacetonitriles **14** and **15** with (hetero)aromatic nitro compounds **17** and **22–24**. Reactions took place in a way analogous to the previous one, namely, deploying methanolic solution of potassium hydroxide, forming corresponding oximes **20** and **25–27** (Scheme 10a–d), thereby increasing the range of known oxime derivatives. The compounds were formed in low to moderate yields.

Scheme 10. Condensation reaction between nitriles **14** and **15** and (hetero)aromatic nitro compounds **17, 22–24** forming heterocyclic analogues **20**, **25** (**a,b**), heteroatom containing **26** (**c**), and bi(carbo)cyclic **27** (**d**) heteroarylcyanomethylenequinone oximes.

In the same year, Mitchell in two patents [8][9] described synthesis of derivatives of bis (phenylacetonitrile) oxime **29** and **31a–b** in a reaction of condensation of benzyl cyanide **1a** with 2,2′-dinitrobibenzyl **28** (Scheme 11a) as well as 1,4-bis (cyanomethyl) benzene **30a** with nitrobenzene **2a** (Scheme 11b) and 1,4-bis (cyanomethyl) diphenyl ether

30b, also, with nitrobenzene **2a** (Scheme 11b). All reactions were realized in warm alcoholic solution of potassium hydroxide.
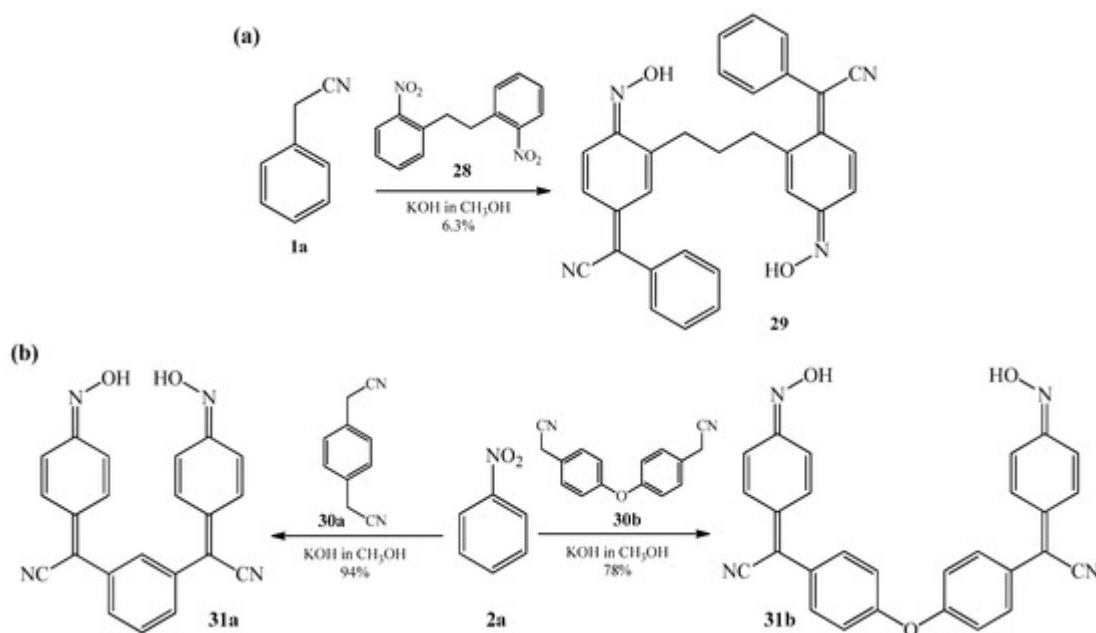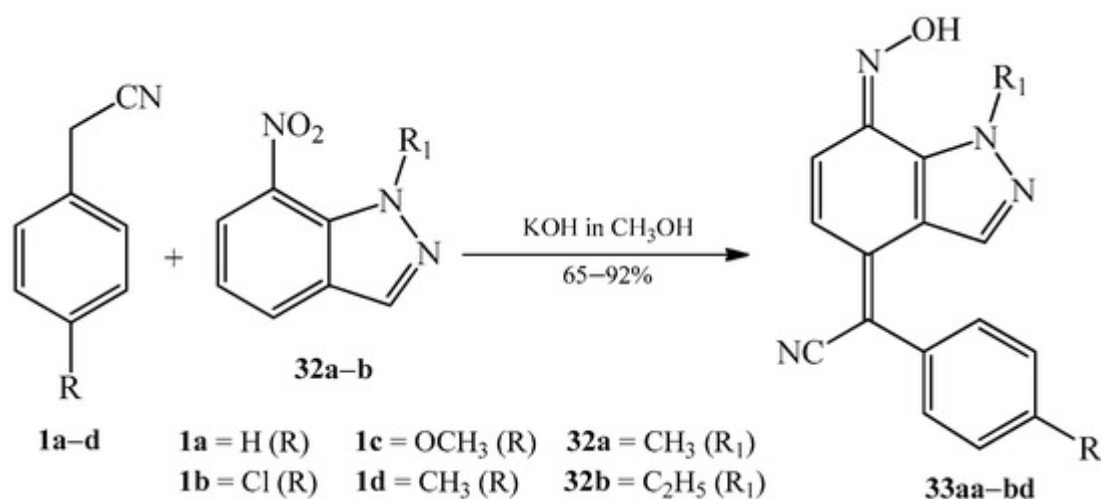

Scheme 11. (**a**) Condensation reaction of benzyl cyanide **1a** with 2,2′-dinitrobibenzyl **28**; (**b**) Condensation reaction of nitrobenzene **2a** with 1,4-bis(cyanomethyl)benzene **30a** and 1,4-bis (cyanomethyl) diphenyl ether **30b**.

In the 1970s, Takahashi et al. began studying the possibility of deploying catalysts and their effect on the course of the condensation reactions. Their research led to forming 4-(phenylcyanomethylene)-cyclohexa-2,5-dien-1-one oxime **3a** in a reaction of benzyl cyanide **1a** with nitrobenzene **2a** mediated by base catalyst [10]. In 1984, Arseniyadis et al. [11] described the mechanisms of addition and substitution reactions of nitrile-stabilized carbanions, including the mechanism of the formation of 4-quinone methide oximes. Later, Freyne and Raeymaekers in 1991 [12], Freyne et al. in 1996 [13], Makosza and Wróbel in 1996 [14], Wróbel in 2000 [15], Yamato et al. in 2000 [16], Suwiński et al. in 2003 [17], Orlov et al. in 2007 [18], Konovalova et al. in 2008 [19], Orlov et al. in 2009 [20], Buehler et al. in 2010 [21], Orlov et al. in 2010 [22], and Hong et al. in 2016 [1] mentioned the synthesis of 4-(phenylcyanomethylene)-cyclohexa-2,5-dien-1-one oxime **3a** by the already presented condensation of benzyl cyanide **1a** with 4-unsubstituted nitrobenzenes **11a**–**n** with attempts to optimize the conditions of these reactions via the use of catalysts, and changes of solvents, reaction times and temperature regimes, among other modifications.

In 2015, Kouakou et al. [23] used the already known approach of regioselective nucleophilic substitution of various 4-substituted benzyl cyanides **1a**–**d** with N-alkyl-7-nitroindazoles **32a**–**b** (Scheme 12). Reactions took place in methanolic solution of potassium hydroxide, forming corresponding 2-(7-hydroxyimino-1-alkyl-1,7-dihydroindazol-4-ylidene)-2-arylacetonitriles **33aa**–**db** (**Table 2**).

Scheme 12. Condensation reaction of various 4-substituted benzyl cyanides **1a**–**d** with N-alkyl-7-nitroindazoles **32a**–**b** to produce quinone oximes **33aa**–**db**.

Table 2. Analogues of 2-(7-hydroxyimino-1-alkyl-1,7-dihydroindazol-4-ylidene)-2-arylacetonitriles **33aa**–**db**.

| Product (Yield (%))		R	R_1	Product (Yield (%))		R	R_1
33aa	(67)	-H	$-CH_3$	**33ca**	(65)	$-OCH_3$	$-CH_3$
33ab	(69)	-H	$-C_2H_5$	**33cb**	(70)	$-OCH_3$	$-C_2H_5$
33ba	(86)	-Cl	$-CH_3$	**33da**	(90)	$-CH_3$	$-CH_3$
33bb	(76)	-Cl	$-C_2H_5$	**33db**	(92)	$-CH_3$	$-C_2H_5$

Alternative approaches to the synthesis of quinone methide oxime derivatives are severely underrepresented in the literature.

2. The Conversion of Quinone Methide Derivatives Using Hydroxylamine

As an alternative approach to the synthesis of quinone methide derivatives of oximes, the reaction of the corresponding quinone methide derivatives with the addition of hydroxylamine should be considered. This method has been known for a long time and has become more common in recent years for the conversion of a keto group into an oxime [24][25][26][27]. As an alternative transformation, which was not used for the synthesis of phenylcarboxymethylomethylenecyclohexa-2,5-dien-1-one oxime core, was presented by Wróbel in 2000 [15]. In that approach, the reaction between the nitroarene and phenylacetic ester furnished the nitroso compound which was in equilibrium with the oxime form.

In 2017, Piazza et al. [28] patented the synthesis of quinone methide oximes **36a**–**d**. The processes were two-stepped. The first stage consisted of conversion of the corresponding hydroxyl derivatives **34a**–**d** to quinone

methides **35a**–**d**. The reactions were realized using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). Dichloromethane (DCM) was used as a solvent. The reactions took place at 0 °C. As the last step, the quinone methides **35a**–**d** were converted to quinone methide oximes **36a**–**d** by the Gilman reagent ((CH_3)$_2$CuLi) and hydroxylamine (NH_2OH), under reflux, with methanol as a solvent (Scheme 13).
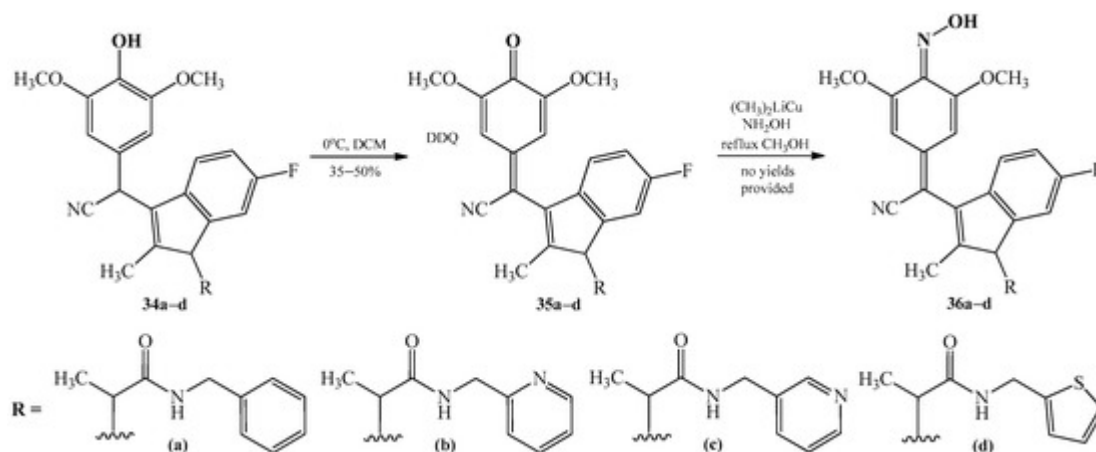
Scheme 13. Two-stepped transformation reaction of hydroxylamine **34a**–**d** to produce quinone methide oximes **36a**–**d.** The structures of substituents R represent drawings (**a**–**d**).

Methods applying quinone methides in obtaining arylcyanomethylenequinone oximes are virtually absent. This is due to the multitude of synthesis steps required in those type of processes leading to arylcyanomethylenequinone [29][30] (Scheme 14). In the presence of one-step condensation reaction of benzyl cyanide derivatives with 4-unsubstituted nitroarenes or their analogues, which is easier to adapt, the absence of processes deploying quinone methides is understandable.
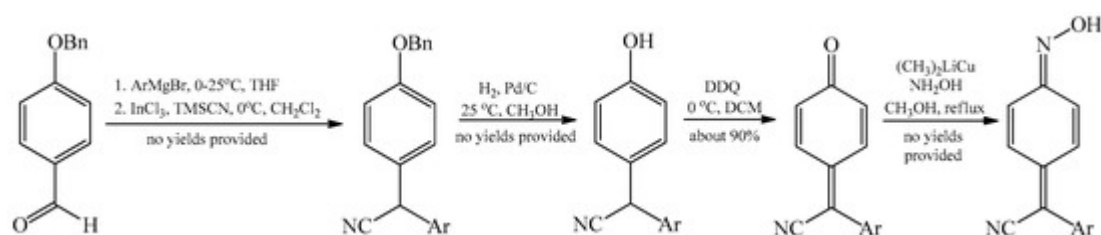
Scheme 14. A concept of multistep transformation of 4-alkoxybenzaldehydes to produce arylcyanomethylene quinone oximes.

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