# 8-Bromocaffeine (8-BC): A New Versatile Reagent for Conversion of Aldoximes into Nitriles

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**Abstract:** A rapid and highly convenient synthesis of nitriles from the corresponding aldoximes using 8-bromocaffeine (8-BC) is described. In this protocol, aldoximes react with 8-BC in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and *N*,*N*-dimethylformamide (DMF) to furnish the corresponding nitriles under both microwave-assisted and/or conventional heating (reflux) conditions in short times and in good to excellent yields. This methodology is highly efficient for structurally diverse aldoximes including aliphatic, aromatic, and heteroaromatic oximes.

**Key words:** nitriles, oximes, synthetic methods, dehydration

The nitrile moiety is a key constituent in numerous natural products, and it also serves as an important synthetic intermediate for pharmaceuticals, agricultural chemicals, dyes, and material sciences.[1,2] There are numerous general methods for the introduction of nitrile groups from various organic functional groups.[3,4] Among these, the conversion of oximes[1–4] and/or O-substituted aldoximes[5,6] into nitriles has been shown to be a suitable and attractive strategy for the preparation of both aliphatic and aromatic nitriles because the very toxic cyanide ion is not used. To date, many different reagents and conditions have been established for the dehydration of aldoximes to give nitriles. For example, $Pd(OAc)_2/PPh_3$,[7] *N*-(*p*-toluenesulfonyl) imidazole (TsIm),[8] $[RuCl_2(p\text{-cymene})]_2$/molecular sieves,[9] 2-chloro-1-methyl pyridinium iodide,[10] triethyl amine/$SO_2$,[11] $PPh_3/CCl_4$,[12] acetic anhydride,[13] Vilsmeier reagent,[14] Burgess reagent,[15] cyanuric chloride,[16] di-2-pyridylsulfite,[17] $AlI_3$,[18] $TiCl_3(OTf)$,[19] $AlCl_3{\cdot}6H_2O/KI$,[20] chlorosulfonic acid,[21] *S*,*S*-dimethyl dithiocarbonate,[22] and sulfonyl chlorides[23] have been employed as dehydrating agents for this transformation. Although many of these methods possess synthetic value, their practical application may encounter some drawbacks such as the use of expensive or less readily available reagents, harsh reaction conditions, low yields, long reaction time, tedious work-up, complex reaction procedures, or limited substrate scope. Consequently, the search for a mild, rapid, and universally applicable method for the conversion of aldoximes into nitriles still continues.

Caffeine is a well-known natural product belonging to the xanthine alkaloid family, and interest in its social consumption in drinks and foods, as well as its significance in pharmaceutical and cosmetic applications are ongoing.[24a] 8-Bromocaffeine (8-BC, CAS-No: 10381-82-5) is a commercially available and stable compound that can easily participate in nucleophilic aromatic substitution reactions. Additionally, 8-BC is an important precursor for many drug syntheses.[24b] However, to the best of our knowledge, there have been no reports on the application of 8-BC as a reagent in organic chemistry. In attempts at the synthesis of the aldehyde *O*-1,3,7-trimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-8-yl oxime (i.e., adducts of aldoximes and 8-BC) in basic media for certain pharmaceutical studies (Figure 1), the formation of nitriles and 1,3,7-trimethyl uric acid in remarkable yields were observed, instead of the desired adducts. Therefore, we found that 8-BC could be considered as an appropriate dehydrating agent for the conversion of aldoximes into nitriles.

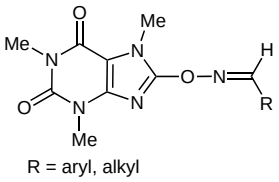
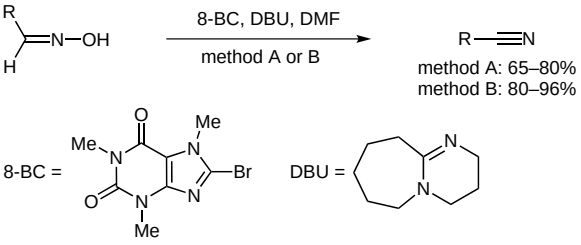



**Figure 1** General structure of aldehyde *O*-1,3,7-trimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-8-yl oxime

In a continuation of our ongoing research on nitrile chemistry,[8,25] we now report 8-BC as a new, highly efficient and stable dehydrating reagent for the conversion of aldoximes into nitriles using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in DMF under conventional heating and/or microwave-assisted conditions (Scheme 1).




**Scheme 1** Conversion of aldoximes into nitriles using 8-BC under conventional heating (A) and/or microwave-assisted (B) conditions

After several attempts, it was found that the combination of 8-BC and DBU in DMF heated to reflux (Scheme 1, conditions A) can be used for the synthesis of both aro-

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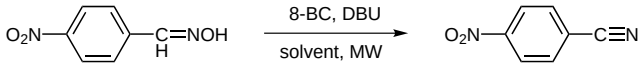
matic and aliphatic nitriles through dehydration of aldoximes after 1–3 hours in reasonable yields (65–80%). To promote the reaction and to attain more satisfactory results, we conducted the reaction under microwave irradiation (Scheme 1, conditions B).

To optimize the reaction conditions, we initially chose the reaction of 4-nitrobenzaldehyde oxime with 8-BC (1.2 equiv) under microwave irradiation to afford 4-nitrobenzonitrile as a model reaction. We screened a variety of solvents and examined their effect on reaction times and yield (Table 1). The reaction proceeded in the absence of solvent, but low yields of the nitrile were attained. DMF (entry 4) was found to be the most appropriate solvent and was therefore used for all subsequent reactions. Use of hexamethylphosphoramide (HMPA), *N*-methyl-2-pyrrolidinone (NMP) or dimethyl sulfoxide (DMSO; Table 1, entries 2, 3, and 8) led to moderate yields of 4-nitrobenzonitrile; whereas, other solvents were inefficient for the conversion of 4-nitrobenzaldehyde oxime into 4-nitrobenzonitrile.

**Table 1** Effect of Solvent on the Conversion of 4-Nitrobenzaldehyde Oxime into 4-Nitrobenzonitrile



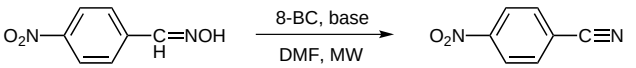

| Entry | Solvent | Time (s) | Yield (%)[a] |
|---|---|---|---|
| 1 | none | 300 | 25 |
| 2 | HMPA | 120 | 70 |
| 3 | NMP | 80 | 83 |
| 4 | DMF | 30 | 96 |
| 5 | MeCN | 120 | 38 |
| 6 | toluene | 300 | n.r.[b] |
| 7 | THF | 210 | trace |
| 8 | DMSO | 70 | 74 |

[a] Isolated yield.
[b] No reaction.

The effect of various organic and inorganic bases on the model reaction was then investigated (Table 2). In the absence of base, no reaction was achieved, even when the reaction time was prolonged. Among the examined bases, DBU (entry 7) was the most appropriate base for the reaction. Moderate yields of 4-nitrobenzonitrile were obtained by using $Cs_2CO_3$, $K_2CO_3$ or $Al_2O_3$ (entries 2, 3 and 6) whereas other bases were inefficient.

We also evaluated the effect of microwave power on the progress of the model reaction (Table 3). The best result was obtained when microwave irradiation was applied at 300 W; low yields of 4-nitrobenzonitrile were obtained at 100 and 200 W. Further increases in irradiation power (>300 W) caused no distinguishable improvement in the progress of the reaction.

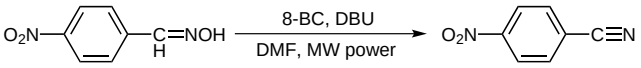
**Table 2** Effect of Base on the Conversion of 4-Nitrobenzaldehyde Oxime into 4-Nitrobenzonitrile




| Entry | Base | Time (s) | Yield (%)[b] |
|---|---|---|---|
| 1 | none | 300 | n.r.[c] |
| 2 | $Cs_2CO_3$ | 90 | 87 |
| 3 | $K_2CO_3$ | 120 | 70 |
| 4 | MgO | 120 | 30 |
| 5 | $Et_3N$ | 180 | 26 |
| 6 | $Al_2O_3$[a] | 70 | 85 |
| 7 | DBU | 30 | 96 |
| 8 | DABCO | 180 | 37 |
| 9 | DMAP | 180 | 45 |

[a] Basic alumina.
[b] Isolated yield.
[c] No reaction.

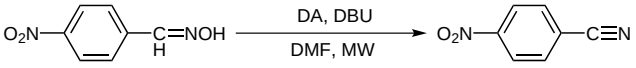
**Table 3** Effect of Microwave Irradiation Power on the Conversion of 4-Nitrobenzaldehyde Oxime into 4-Nitrobenzonitrile




| Entry | Irradiation power (W) | Time (s) | Yield (%)[a] |
|---|---|---|---|
| 1 | 100 | 240 | 25 |
| 2 | 200 | 90 | 58 |
| 3 | 300 | 30 | 96 |
| 4 | 400 | 30 | 90 |
| 5 | 500 | 60 | 75 |
| 6 | 600 | 60 | 60 |

[a] Isolated yield.

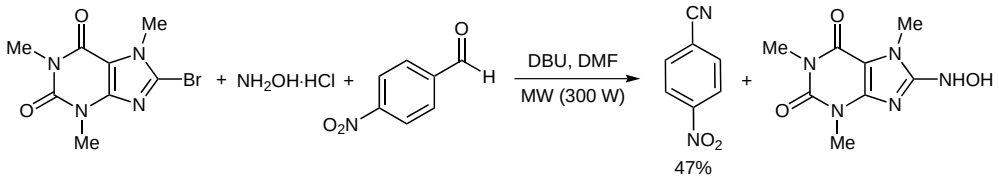
**Table 4** A Comparative Study of Dehydrating Agents in the Model Reaction




DA = dehydrating agent

| Entry | Dehydrating reagent | Time (s) | Yield (%)[a] |
|---|---|---|---|
| 1 | cyanuric chloride | 70 | 90 |
| 2 | 8-BC | 30 | 96 |
| 3 | $Ac_2O$ | 90 | 94 |
| 4 | 2-chloro-1-methylpyridinium iodide | 110 | 91 |

[a] Isolated yield.




**Scheme 2** The 3CRs of aldehyde, $NH_2OH{\cdot}HCl$ and 8-BC under microwave irradiation

The optimized amount of 8-BC was found to be 1.2 equivalent per equivalent of oxime. To establish the dehydrating potency of 8-BC, we performed the same experiment with other dehydrating agents under the same conditions applied to the model reaction. The comparative data are shown in Table 4. A higher yield of nitrile was obtained in a shorter reaction time using 8-BC (entry 2). Although other dehydrating reagents afforded satisfactory results, the reactions required longer to reach completion.

Because multicomponent reactions (MCRs) avoid time-consuming and costly purification processes,[26] we were interested in the direct conversion of aldehydes into nitriles through 3CRs of aldehyde, $NH_2OH{\cdot}HCl$, and 8-BC under microwave irradiation (Scheme 2). In this context, the microwave-assisted reaction of 4-nitrobenzaldehyde with $NH_2OH{\cdot}HCl$ and 8-BC was achieved in the presence of DBU in DMF, however, the reaction led to the formation of 4-nitrobenzonitrile in low yields (47%). The low yield attained in this MCR approach was attributed to scavenging of $NH_2OH$ by 8-BC and to the formation of considerable amounts of 8-hydroxyamino-1,3,7-trimethyl-3,7-dihydropurine-2,6-dione.

**Table 5** Investigation of the Reaction Scope under Conventional Heating (Conditions A) and Microwave Irradiation (Conditions B)

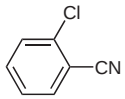
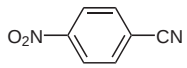
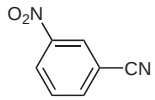
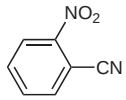
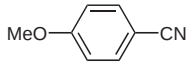
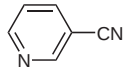
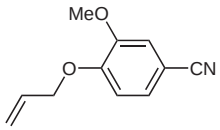
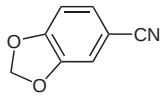
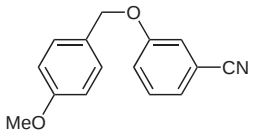
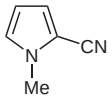
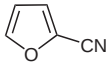
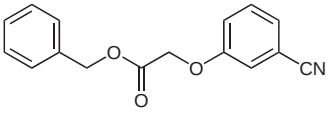
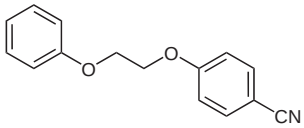
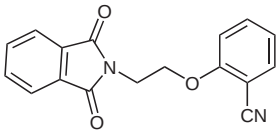
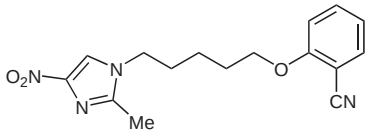
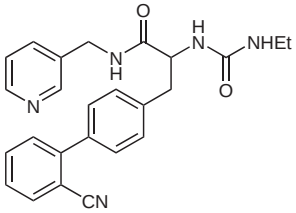
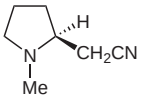
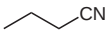
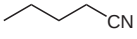
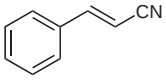
| Entry | R-CN[a] | IR ($cm^{-1}$)[b] | Conditions A | | Conditions B | |
|---|---|---|---|---|---|---|
| | | | Yield (%)[c] | Time (h) | Yield (%)[c] | Time (s) |
| 1[8] |  | 2223 | 80 | 1 | 95 | 30 |
| 2[8] |  | 2220 | 72 | 1.5 | 90 | 110 |
| 3[8] |  | 2230 | 80 | 1 | 96 | 30 |
| 4[8] |  | 2228 | 75 | 1.25 | 93 | 70 |
| 5[8] |  | 2237 | 68 | 1.75 | 86 | 130 |
| 6[8] |  | 2224 | 79 | 1 | 96 | 40 |
| 7[8] |  | 2233 | 77 | 1.25 | 92 | 60 |
| 8[27] |  | 2239 | 73 | 2 | 87 | 120 |
| 9[28] |  | 2225 | 75 | 2 | 90 | 100 |

**Table 5** Investigation of the Reaction Scope under Conventional Heating (Conditions A) and Microwave Irradiation (Conditions B) (continued)

| Entry | R-CN[a] | IR ($cm^{-1}$)[b] | Conditions A | | Conditions B | |
|---|---|---|---|---|---|---|
| | | | Yield (%)[c] | Time (h) | Yield (%)[c] | Time (s) |
| 10[29] |  | 2230 | 75 | 1.75 | 92 | 90 |
| 11[8] |  | 2202 | 72 | 1.5 | 88 | 70 |
| 12[30] |  | 2228 | 73 | 1.5 | 90 | 60 |
| 13[8] |  | 2221 | 70 | 2.15 | 87 | 110 |
| 14[8] |  | 2223 | 73 | 1.75 | 89 | 50 |
| 15[8] |  | 2215 | 65 | 2.75 | 81 | 170 |
| 16[8] |  | 2222 | 67 | 2.75 | 83 | 160 |
| 17[29] |  | 2223 | 65 | 3 | 80 | 180 |
| 18[31] |  | 2220 | 69 | 1.5 | 84 | 70 |
| 19[8] |  | 2227 | 76 | 1 | 90 | 40 |
| 20[8] |  | 2232 | 74 | 1 | 88 | 40 |
| 21[35] |  | 2214 | 78 | 1.25 | 90 | 70 |

[a] All products were characterized by $^{1}H$ and $^{13}C$ NMR, IR, CHN and MS analysis.[38]
[b] IR signal of nitrile.
[c] Isolated yield.

To explore the scope of this method, the optimized reaction conditions were applied to a range of aldoximes (Table 5). It is clear that this method is highly efficient and useful for aromatic (Table 5, entries 1–6, 8–10, 13, and 14), heteroaromatic (entries 7, 11, and 12), aliphatic (entries 19 and 20), and conjugated (entry 21) aldoximes as

well as other aldoximes containing *N*-heterocycles (entries 15–18). This protocol is favorably chemoselective for compounds with multiple functional groups. Additionally, excellent results were obtained for aryl aldoximes with different substituents at the *meta* and/or *para* positions; lower yields of nitriles were obtained for *ortho*-substituted aromatic aldoximes. By using this procedure, both *E*- and *Z*-isomers of oximes could be converted into the corresponding nitriles; in most cases, the oxime used in these experiments were mixtures of *Z*- and *E*-isomers. Furthermore, by using this method, the configuration of asymmetric carbons remains intact {Table 5, entry 18; $[\alpha]_D^{24}$ –69.5° (*c* = 1.0, MeOH)}. The data presented in Table 5 clearly show that the microwave-assisted reaction is superior to the conventional heating procedure because higher yields and shorter reaction time were obtained when the former technique was employed (method B).

To rationalize the dehydrating ability of 8-BC and to understand the mechanism of the reaction, quantum mechanical calculations on Gaussian 03W[32] and NBO 5.0 programs,[33] employing the DFT method at the B3 LYP/6-31G** level, have been applied to the reactants and reaction intermediates. Some of the calculated results are summarized in Table 6.

Benzaldehyde oxime was selected as the sample aldoxime (R = Ph in Scheme 1) for theoretical investigations. As shown in Figure 2, there are two possible conformations for the *E*-isomer (which is more stable than the *Z*-isomer) of this molecule. Between these, *E*-isomer (2) is 4.55 kcal/mol more stable than the *E*-isomer (1).

In accordance with the theoretical calculations, the linkage of the Br atom to the caffeine causes an enhancement in positive charge on C(8), which, in turn, make this atom susceptible to attack by an aldoxime molecule such as (*E*)-benzaldehyde oxime in a $S_NAr$ type reaction. The generated intermediate 8-caffeinyl *O*-oxime ether can also exist as *E*- and/or *Z*-isomers. The calculations show that the former is quite planar and 2.80 kcal/mol more stable than the nonplanar *Z*-isomer. Furthermore, two different *E*-isomers can also be assigned for this intermediate by 180° rotation about the N–O single bond (see Figure 2). According to the conformational analysis, *E*-isomer (2) is about 6.0 kcal/mol more stable than *E*-isomer (1). Upon linkage of the 8-caffeinyl moiety to O(24) of aldoxime, and due to the electron-withdrawing character of 8-caffeinyl, the charge density of O(24) atom is transferred to N(7) and, especially, to N(9) (because of the conjugated resonance form), in such a way that the charge densities of these nitrogen atoms in both (1) and (2) isomers are enhanced. The calculations also show that, upon formation of the mentioned linkage, the positive charge on C(8) is enhanced. Therefore, O(24) adjacent to the 8-caffeinyl fragment becomes a good leaving group and, in the presence of DBU, the aldoxime is dehydrated to its corresponding nitrile.

These results are confirmed by analyzing the orbitals' donor–acceptor interactions. The second order perturbation theory analysis of Fock matrix in NBO basis show that there is an interaction of the type $n_{O(24)} \rightarrow \pi^*_{N(25)-C(26)}$ [where n is the second lone pair of O(24)] with the energy of 17.88 kcal/mol in isomer (2) of the studied (*E*)-benzaldehyde oxime. Similar analysis for the intermediate 8-caffeinyl *O*-benzaldehyde oxime ether shows that the mentioned interaction is reduced (12.68 kcal/mol), which means that the tendency of the lone pair of the oxygen to transfer toward the oxime part of the molecule is decreased. Instead, another strong interaction of the kind $n_{O(24)} \rightarrow \pi^*_{C(8)-N(9)}$ with an energy of 37.11 kcal/mol is calculated for the 8-caffeinyl *O*-benzaldehyde oxime ether intermediate, which shows that the oxygen charge has a high tendency to transfer toward the 8-caffeinyl part of this molecule. These changes in the mentioned interactions also cause the O(24)–N(25) bond in the studied intermediate (bond length 1.421 Å) to be weaker than that in (*E*)-benzaldehyde oxime (bond length 1.401 Å).

**Table 6** Conformations, Absolute Energies and Partial Atomic Charges Calculated at the B3 LYP/6-31G** Level of DFT Theory

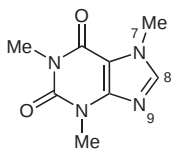
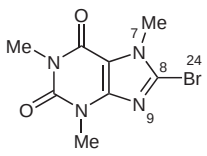
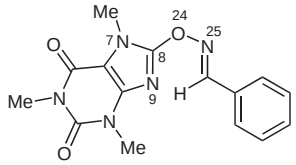
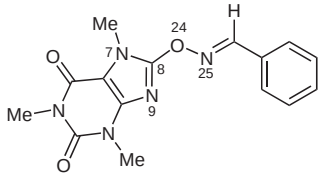
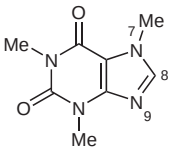
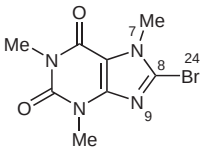
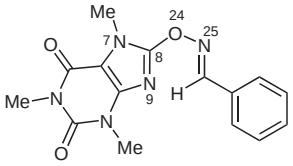
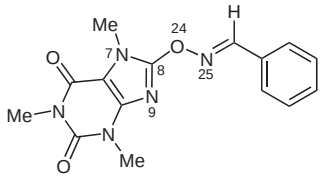
| Parameter |  Caffeine |  8-BC |  *E*-isomer (1) |  *E*-isomer (2) |
|---|---|---|---|---|
| *E* (hartrees) | –680.39019 | –3251.48924 | –1080.06453 | –1080.07411 |
| Δ*E* (kcal/mol) | | | 6.01 | 0.00 |
| **Mulliken charge** | | | | |
| N(7) | –0.513 | –0.533 | –0.593 | –0.595 |
| C(8) | 0.285 | 0.446 | 0.814 | 0.807 |
| N(9) | –0.521 | –0.521 | –0.617 | –0.558 |
| Br(24) | | –0.054 | | |

**Table 6** Conformations, Absolute Energies and Partial Atomic Charges Calculated at the B3 LYP/6-31G** Level of DFT Theory (continued)

| Parameter |  Caffeine |  8-BC |  *E*-isomer (1) |  *E*-isomer (2) |
|---|---|---|---|---|
| O(24) | | | –0.461 | –0.457 |
| N(25) | | | –0.176 | –0.154 |
| **NBO charge** | | | | |
| N(7) | –0.362 | –0.374 | –0.383 | –0.390 |
| C(8) | 0.226 | 0.306 | 0.736 | 0.748 |
| N(9) | –0.523 | –0.520 | –0.606 | –0.557 |
| Br(24) | | 0.124 | | |
| O(24) | | | –0.378 | –0.395 |
| N(25) | | | –0.118 | –0.116 |

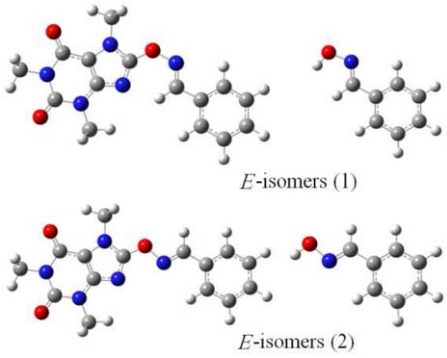
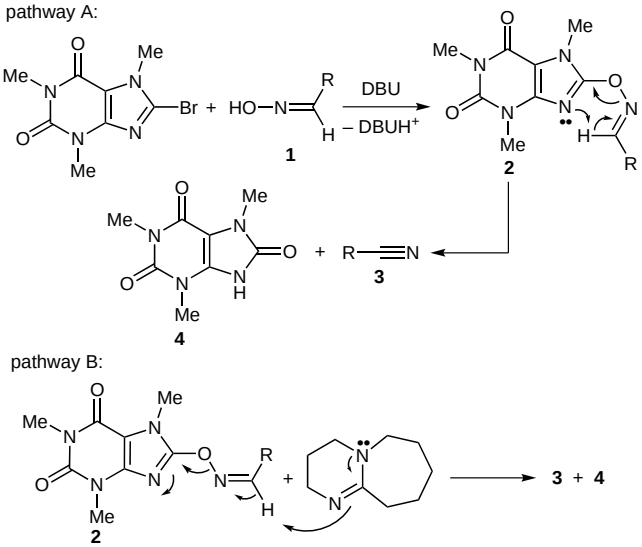



**Figure 2** The optimized geometries for the different *E*-isomers of benzaldehyde oxime (right) and the intermediate 8-caffeinyl *O*-oxime ether (left) at the B3 LYP/6-31G** level of theory

These results confirm that O(24) adjacent to the 8-caffeinyl fragment becomes a good leaving group in the reaction intermediate, to produce nitriles from their corresponding aldoximes, in the presence of DBU.

A plausible mechanism for 8-BC/DBU mediated conversion of aldoximes into nitriles is proposed (Scheme 3). In this mechanism, we suggest that a preliminary $S_NAr$ type reaction of 8-BC with oxime (**1**) in the presence of DBU occurs to afford compound **2** as the key intermediate. In pathway (**A**), the conversion proceeds in a concerted-type 1,4-elemination of compound **2**, which undergoes thermal elimination to afford nitrile **3**, followed by the liberation of 1,3,7-trimethyluric acid (1,3,7-trimethyl-7,9-dihydro-3*H*-purine-2,6,8-trione; **4**), whereas in pathway (**B**), in the presence of base, the conversion proceeds through 1,2-elemination of **2**. 1,3,7-Trimethyluric acid **4** (CAS-No: 5415-44-1; Mp >300 °C) is a nontoxic, naturally occurring compound that is normally produced from the metabolism (oxidation) of caffeine in living organs.[34] The generation of **4** through the course of reaction was easily followed by TLC analysis.




**Scheme 3** A plausible mechanism for conversion of aldoximes into nitriles using 8-BC. Path A: 1,4-elimination; Path B: 1,2-elimination.

In summary, a convenient and facile method has been established for the conversion of aliphatic and aromatic aldoximes into nitriles using 8-bromocaffeine[36] in the presence of DBU and DMF under microwave or conventional heating conditions. The simple experimental procedure, mild reaction conditions, short reaction time, relatively high yields of products, generality, and versatility are advantages of the current method.[37]



## Acknowledgment

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(36) 8-BC [CAS Number: 10381-82-5] is commercially available; however, using freshly prepared 8-BC affords more favorable results. Fresh 8-BC can be easily prepared by using the following procedure: To a round-bottom flask (500 mL) containing freshly distilled $CH_2Cl_2$ (300 mL) was added caffeine (19.4 g, 0.1 mol) and NBS (35.2 g, 0.2 mol). When the solids had dissolved in solvent, water (100 mL) was added and the container was closed and stirred for 5 d. The solution was transferred into a separator funnel and solution of cold NaOH (100 mL, 2 M) was added the mixture was shaken to decolorize the mixture. The organic layer was separated, washed with water (2 × 200 mL), dried over $Na_2SO_4$ (30 g), filtered, and evaporated to provide pure 8-BC (26 g, ca. 100%).
(37) General procedure for microwave-assisted conversion of aldoximes into nitriles by using 8-BC: Into a laboratory microwave oven equipped with a condenser, was inserted a round-bottom flask (50 mL) containing a solution of aldoxime (5 mmol), DBU (5 mmol), and 8-BC (6 mmol) in DMF (6 mL). The mixture was then irradiated at 300 W for the indicated time (Table 5). When TLC monitoring indicated no further improvement in the reaction, the crude products were suspended in $CH_2Cl_2$ (30 mL) and washed with $H_2O$ (2 × 100 mL). The organic layer was dried over $Na_2SO_4$ (10 g) and concentrated to afford the crude product, which was purified by column chromatography on silica gel (*n*-hexane–EtOAc). All products were characterized by $^1H$ NMR, $^{13}C$ NMR, IR, CHN and MS analysis.
(38) Selected spectral data:
**4-(Allyloxy)-3-methoxy benzonitrile (Table 5, Entry 8):** White solid; $R_f$ = 0.47 (EtOAc–*n*-hexane, 1:5); mp 59–60 °C; $^1H$ NMR (250 MHz, $CDCl_3$): δ = 3.93 (s, 3 H, $CH_3$), 4.60 (dd, *J* = 1.3, 5.1 Hz, 2 H, $OCH_2$), 5.48 (dd, *J* = 1.5,

11.2 Hz, 2 H, =$CH_2$), 6.11–6.14 (m, 1 H, =CH), 7.01 (d, *J* = 8.1 Hz, 1 H, ArH), 7.13 (s, 1 H, ArH), 7.25 (d, *J* = 8.1 Hz, 1 H, ArH); $^{13}$C NMR (250 MHz, $CDCl_3$): δ = 54.17, 68.43, 104.51, 114.03, 115.94, 119.70, 119.93, 128.21, 134.58, 157.04, 161.37; MS: *m*/*z* (%) = 189.08 (30); Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.74; H, 5.94; N, 7.52.

**3-(4-Methoxybenzyloxy) benzonitrile (Table 5, Entry 10):** White solid; $R_f$ = 0.31 (EtOAc–*n*-hexane, 1:9); mp 94–95 °C; $^1$H NMR (250 MHz, $CDCl_3$): δ = 3.86 (s, 3 H, $OCH_3$), 5.30 (s, 2 H, $OCH_2$), 7.11 (d, *J* = 8.2 Hz, 2 H, ArH), 7.25–7.30 (m, 3 H, ArH), 7.39–7.46 (m, 3 H, ArH); $^{13}$C NMR (250 MHz, $CDCl_3$): δ = 51.16, 69.45, 112.86, 115.37, 118.70, 121.57, 123.97, 127.05, 128.14, 130.91, 132.28, 158.76, 162.29; MS: *m*/*z* (%) = 239.09 (36); Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.42; H, 5.60; N, 5.80.

**2-[2-(1,3-Dioxoisoindolin-2-yl)ethoxy]benzonitrile (Table 5, Entry 15):** White solid; $R_f$ = 0.48 (EtOAc–*n*-hexane, 1:1); mp 148–149 °C; $^1$H NMR (250 MHz, $CDCl_3$): δ = 4.03 (t, *J* = 5.9 Hz, 2 H, $NCH_2$), 4.22 (t, *J* = 5.9 Hz, 2 H, $OCH_2$), 6.88–6.91 (m, 2 H, aryl), 7.36–7.42 (m, 2 H, aryl), 7.58–7.63 (m, 2 H, aryl), 7.68–7.73 (m, 2 H, aryl); $^{13}$C NMR (250 MHz, $CDCl_3$): δ = 36.52, 65.19, 102.29, 112.29, 115.88, 121.31, 123.34, 131.86, 133.59, 133.76, 134.11, 159.66, 167.89; MS: *m*/*z* (%) = 292.08 (52); Anal. Calcd for $C_{17}H_{12}N_2O_3$: C, 69.86; H, 4.14; N, 9.58. Found: C, 69.82; H, 4.17; N, 9.63.

**2-[5-(2-Methyl-4-nitro-1*H*-imidazol-1-yl)pentyloxy]-benzonitrile (Table 5, Entry 16):** Bright yellow oil; $R_f$ = 0.45 (EtOAc); $^1$H NMR (250 MHz, $CDCl_3$): δ = 0.73–0.75 (m, 2 H, $CH_2$), 1.05 (m, 4 H, 2 × $CH_2$), 1.59 (s, 3 H, $CH_3$), 3.20 (m, 4 H, $NCH_2$, $OCH_2$), 6.16–6.19 (m, 2 H, ArH), 6.67–6.68 (m, 2 H, ArH), 7.13 (s, 1 H, C(5)-H, imidazole); $^{13}$C NMR (250 MHz, $CDCl_3$): δ = 12.42, 22.37, 27.68, 29.28, 46.51, 68.12, 100.81, 111.99, 116.02, 120.23, 132.97, 134.15, 144.42, 145.57, 159.94, 161.84; MS: *m*/*z* (%) = 314.10 (48); Anal. Calcd for $C_{16}H_{18}N_4O_3$: C, 61.13; H, 5.77; N, 17.82. Found: C, 61.15; H, 5.81; N, 17.79.



 