

AlCl₃·6H₂O/KI/H₂O/CH₃CN: A New Alternate System for Dehydration of Oximes and Amides in Hydrated Media

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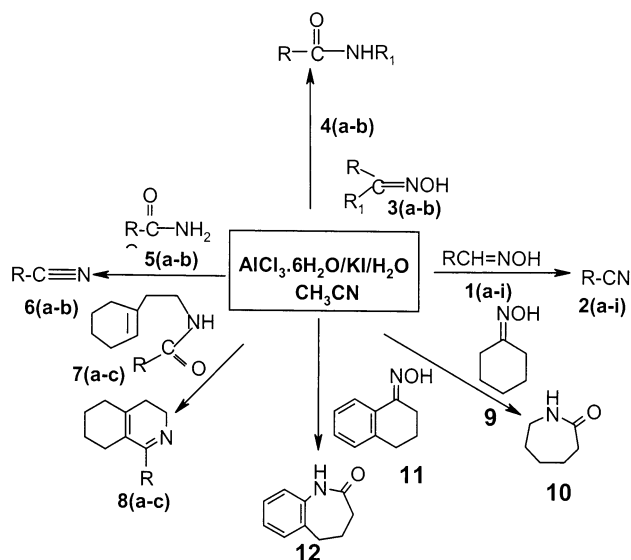
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Abstract: Dehydration of oximes and amides to nitriles was carried out using the AlCl₃·6H₂O/KI/H₂O/CH₃CN system. It produced isoquinoline derivatives **8a–c** (Bischler Naperi-alski reaction) when reacted with amides **7a–c** in hydrated media. Also, the keto oximes produced anilides (Beckmann rearrangement) with the system under the same reaction conditions.

Dehydration of oximes and amides to nitriles is an important transformation in organic syntheses. In the last 40 years, a number of efficient methods have been developed for the dehydration of oximes and amides to nitriles,^{1a,b} and the search for better reagents is still continues.^{1c} Also, it is reported that these conversions may be performed either by using bacterial enzymes with aldoximes^{1d} or by employing oximes ethers under basic conditions.^{1e} But the methods developed so far have their own limitations, for example, the use of extremely anhydrous reaction conditions,¹ very corrosive and moisture sensitive reagents,^{1–3} use of toxic and hazardous chemicals,^{4,5} cumbersome workup procedures and problems associated with waste disposal,^{6,7} and lack of versatility in the transformations conducted in hydrated media.^{1d,e}

The chemistry and potentialities of AlCl₃·6H₂O as a reagent in organic synthesis has been less explored,⁸ particularly in the presence of KI in *hydrated media*.⁹ In continuation of our research in aluminum chemistry,^{1a,8–10}

SCHEME 1



we now wish to report the AlCl₃·6H₂O/KI/CH₃CN system as a new, efficient, and versatile alternate system for the dehydration of oximes and amides to nitriles and intramolecular cyclodehydration of amides to isoquinoline derivatives and keto oximes to anilides in *hydrated media*.

Aldoxime (Scheme 1, compound **1a**) was reacted with the AlCl₃·6H₂O/KI/CH₃CN system [1 equiv of AlCl₃·6H₂O/KI, 1 equiv of **1a**] in a mixture of acetonitrile and water (5:1) at reflux temperature for 6 h, and after workup with 5% ammonium hydroxide solution, it produced *p*-methoxybenzotrile (Scheme 1, compound **2a**) in 95% yield without formation of triazine¹¹ in the reaction mixture. It was observed that the acid-susceptible^{1a} groups like methyl ether (Scheme 1, compound **1a**) and furan (Scheme 1, compound **2h**) were unaffected under the reaction conditions and both *E* and *Z* isomers of the oximes could be converted to nitriles (in most cases the oximes used were the mixture of *E* and *Z* isomers). Similarly, the amides (Scheme 1, compounds **5a,b**) under the same reaction condition could be converted to its corresponding nitriles (Scheme 1, compounds **6a,b**) in good yields in the hydrated media. Also, when the system was treated with the amides (Scheme 1, compounds **7a–c**), intramolecular cyclodehydration (Bischler Naperi-alski reaction) occurred¹³ and resulted industrially important isoquinoline derivatives (Scheme 1, compounds **8a–c**), the key intermediates for dextromethorphan [anti-tussive drug] and its analogues.¹⁴ Also, It was observed that when the

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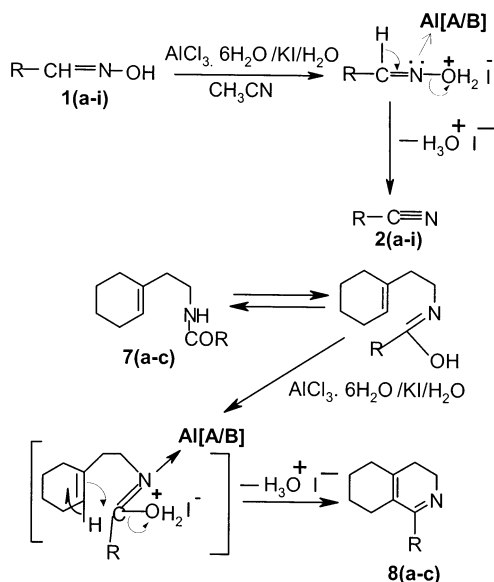
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SCHEME 2



system was treated with keto oximes, Beckmann rearrangement¹² occurred and produced anilides in good yields (Scheme 1, compounds **4a,b**). Besides, when reacted with cyclohexanone oximes (Scheme 1, compounds **9** and **11**), it produced ring-enlargement products (Scheme 1, compounds **10** and **12**). Acetonitrile was the best solvent among $CHCl_3$, CH_2Cl_2 , and CCl_4 in terms of yield and time. The reaction did not proceed at all in the absence of KI.

Regarding the mechanism of the reactions, it may be proposed that $AlCl_3 \cdot 6H_2O$ is, in reality,^{9,15} $[Al(H_2O)_6]Cl_3$, and reacts with KI to form $[Al(H_2O)_6]I_3$, which can exist as $[Al(H_2O)_5(OH)]^{2+} H^+ 3I^-$ (**A**) or $[Al(H_2O)_4(OH)_2]^{+} 2H^+ 3I^-$ (**B**) etc. in solution. The liberated proton forms HI acid, which in the presence of aluminum dehydrated oximes and amides to nitriles as shown below (Scheme 2).

In conclusion, a new, efficient and versatile system for dehydration of amides and oximes in *hydrated media* is developed. The significant features of the system are as follows: (a) dehydration can be performed in *hydrated media*; (b) acid-susceptible groups are tolerated under the reaction conditions; (c) less toxic and hazardous chemicals can be used; (d) moderate to high yields are obtained without side products; and (e) applications are versatile.

Experimental Section

General Experimental Procedure: Representative Procedure for Dehydration of *p*-Methoxybenzaloxime. $AlCl_3 \cdot 6H_2O$ (0.240 g, 1 mmol) and KI (0.498 g, 3 mmol) were stirred

TABLE 1. Synthesis of Nitriles, Anilides, and Isoquinolines

| entry | products R | products R ₁ | yield ^{a,b,d} (%) | time (h) ^c |
|-----------|--|-------------------------|----------------------------|-----------------------|
| 2a | 4-CH ₃ O-C ₆ H ₄ ⁻ | | 96 ^a | 6 ^c |
| 2b | C ₆ H ₅ ⁻ | | 95 ^a | 9 ^c |
| 2c | 4-CH ₃ -C ₆ H ₄ ⁻ | | 80 ^a | 8 ^c |
| 2d | Ph-CH=CH ⁻ | | 75 ^a | 7 ^c |
| 2e | <i>n</i> -C ₇ H ₁₅ ⁻ | | 70 ^a | 8.5 ^c |
| 2f | 4-Cl-C ₆ H ₄ ⁻ | | 75 ^a | 6 ^c |
| 2g | 3-pyridine | | 69 ^a | 8 ^c |
| 2h | 2-C ₄ H ₃ O ⁻ | | 60 ^a | 7.5 ^c |
| 2i | 2-C ₄ H ₃ S ⁻ | | 67 ^a | 8.5 ^c |
| 4a | Ph ⁻ | CH ₃ | 80 ^a | 12 ^c |
| 4b | Ph ⁻ | Ph | 82 ^a | 13 ^c |
| 6a | Ph ⁻ | | 94 ^a | 7 ^c |
| 6b | Ph-CH-CH ₃ ⁻ | | 92 ^a | 10 ^c |
| 8a | PhCH ₂ ⁻ | | 87 ^b | 10 ^c |
| 8b | 4-Cl-C ₆ H ₄ -CH ₂ ⁻ | | 81 ^b | 9 ^c |
| 8c | 4-Me-O-C ₆ H ₄ -CH ₂ ⁻ | | 86 ^b | 12 ^c |
| 10 | | | 75 ^a | 17 ^c |
| 12 | | | 72 ^a | 15 ^c |

^a The compounds were identified by IR, ¹H NMR, and mass analyses and compared with authentic samples. ^b The spectral data were compared with our reported results.^{10d} ^c The temperature was 80 °C for all experiments. ^d Isolated yield.

in acetonitrile and water (25 mL, 5:1) at room temperature for 0.5 h, and *p*-methoxybenzaloxime (**1a**) (0.151 g, 1 mmol) was added. The reaction mixture was refluxed at 80 °C for 6 h, and the progress of the reaction was monitored by TLC. The solvent was distilled under reduced pressure, and the residue was diluted with water (25 mL) and extracted with dichloromethane. The organic layer was washed with 5% ammonium hydroxide solution (25 mL) and then with water (50 mL). The organic layer was dried over anhydrous sodium sulfate, and evaporation of the solvent and recrystallization from petroleum ether (40–60 °C) gave *p*-methoxybenzoxime (**2a**) in 95% yield, mp 58 °C (lit.¹ mp 57–59 °C).

This procedure was followed for the dehydration of all compounds listed in Table 1. The compounds were identified by comparison of spectral data (IR, ¹H NMR, mass analyses) with those reported.^{1,10d}

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