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One-pot synthesis of tetrazole-1,2,5,6-tetrahydronicotinonitriles and cholinesterase inhibition: Probing the plausible reaction mechanism *via* computational studies

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ABSTRACT

In the present study, one-pot synthesis of 1*H*-tetrazole linked 1,2,5,6-tetrahydronicotinonitriles under solvent-free conditions have been carried out in the presence of tetra-*n*-butyl ammonium fluoride trihydrated (TBAF) as catalyst and solvent. Computational studies have been conducted to elaborate two plausible mechanistic pathways of this one-pot reaction. Moreover, the synthesized compounds were screened for cholinesterases (acetylcholinesterase and butyrylcholinesterase) inhibition which are consider to be major malefactors of Alzheimer's disease (AD) to find lead compounds for further research in AD therapy.

1. Introduction

Solvent-free chemistry holds a unique place in organic synthesis to reduce environmental hazards. The reaction avoids the use of toxic and volatile conventional organic solvents. For solvent-free reactions ionic liquids provide excellent media for organic syntheses. Ionic liquids serve as catalysts in many organic reactions [1]. Tetra-*n*-butylammonium fluoride (TBAF) is a type of an ionic liquid that has been diversely used in organic syntheses. A range of different solvent-free reactions have also been performed in the presence of TBAF as catalyst. Fluoride (F^-) counter anion present in TBAF serves as mild base to promote different chemical reactions [2–4]. In our solvent-free chemistry, a one-pot reaction between acetophenone, malononitrile and trimethylsilyl azide ($TMSN_3$) was explored in the presence of neat TBAF to afford tetrazole linked 1,2,5,6-tetrahydronicotinonitriles **2(a–h)**. The reaction involved (1) fluoride (F^-) mediated Knoevenagel condensation (2) followed by multisteps ring closure to afford corresponding 1,2,5,6-tetrahydronicotinonitriles **(5)**. Consequently (3) the click reaction furnished tetrazole linked 1,2,5,6-tetrahydronicotinonitriles (**2**) (Scheme 1) [5]. Plausible mechanism of such interesting one-pot reaction up to intermediate **(5)** has been suggested by two different logical pathways **(I)** and **(II)** (Scheme 2) [5,6]. The intermediate 1,2,5,6-tetrahydronicotinonitrile **(5)** also served as excellent precursor for the synthesis of [1,6]-naphthyridine ring system [5] found in many biological important molecules [7,8].

Computational study using density field theory (DFT) calculations was carried out to elaborate the most feasible pathway of this one-pot reaction. The scope of reaction was explored with different phenyl substituted acetophenones. A series of tetrazole linked 1,2,5,6-tetrahydronicotinonitriles **2(a–h)** was synthesized under solvent-free conditions in moderate to excellent yield. The structures of compounds **2(a–h)** were confirmed using different spectroscopic techniques.

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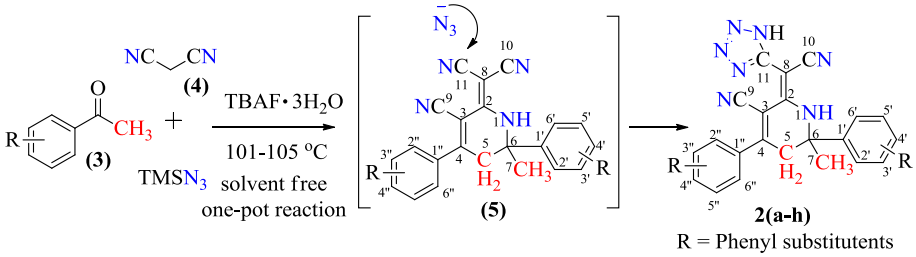
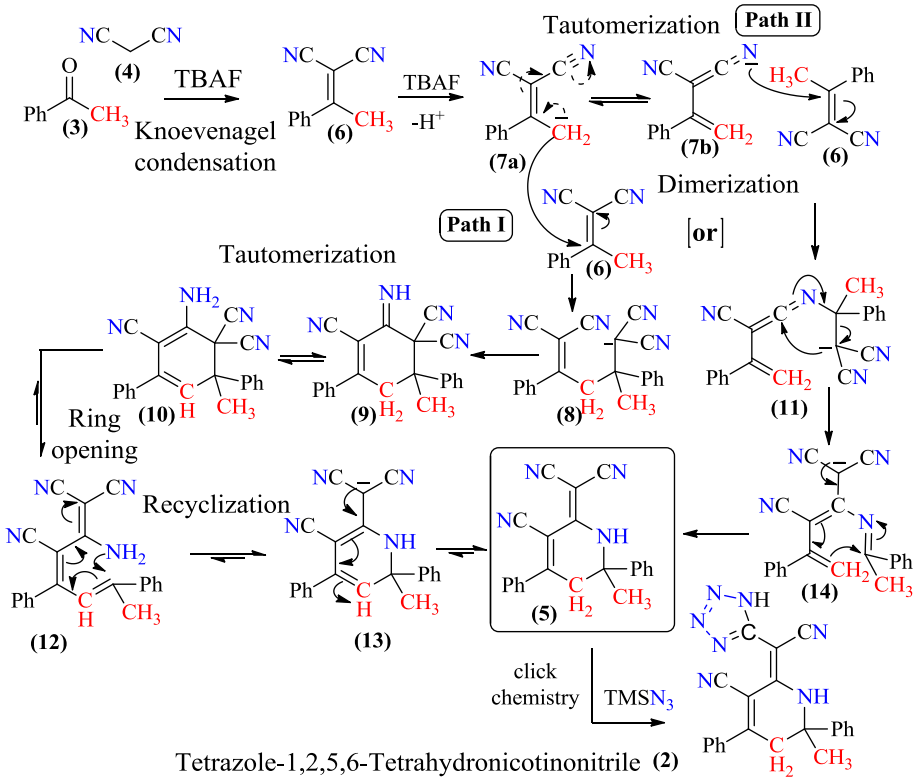


R	Yields (%)	R	Yields (%)
2a, H	(84.8)	**2e**, 3′/3″-Cl	(49.8)
2b, 4′/4″-Me	(53.8)	**2f**, 3′/3″-OMe	(56.8)
2c, 3′/3″-Me	(86.7)	**2g**, 2′/2″-OMe	(65.8)
2d, 4′/4″-F	(47.8)	**2h**, 4′/4″-OH	(70.8)

Scheme 1. One-pot synthesis of tetrazole-1,2,5,6-tetrahydronicotinonitrile **2(a–h)**.



Scheme 2. Plausible pathways **(I)** Michael addition of **(7a)** to **(6)**, or **(II)** dimerization reaction between **(7b)** and **(6)** to yield 1,2,5,6-tetrahydronicotinonitrile **(5)**.

Medicinal chemistry has witnessed an expansion in the use of biologically active nicotine based molecules. Recently, Carreiras et al. [9] synthesized nicotine containing pyridonepezils **(1)** and evaluated their inhibition activity against acetylcholinesterase (AChE) and butyrylcholinesterase (BChE). Based on close structural similarities of our synthetic tetrazole-1,2,5,6-tetrahydronicotinoni trile **(2)** with pyridonepezils **(1)** (Fig. 1), we assessed them for their cholinesterases (AChE and BChE) inhibitory activities. According to so-called cholinergic hypothesis, [10,11] cholinesterases are considered to be major responsible enzymes for the pathogenesis of Alzheimer's disease (AD) complications. AD is a progressive neurodegenerative disorder that leads to gradual memory loss, decline in language skills and other effects on cognitive functions. A report from Alzheimer's disease international describes it as the most common type of dementia which now affects around 36 million people worldwide with 6% of the population being over the age

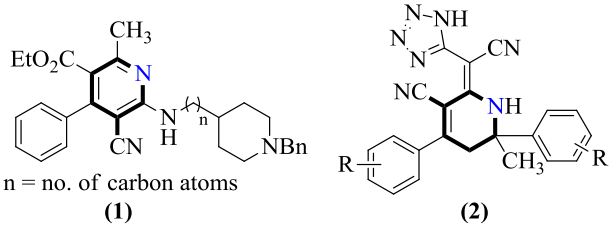


Fig. 1. Structures of pyridonepezil **(1)** and tetrazole linked 1,2,5,6-tetrahydronicotinonitrile **(2)**.

of 65 [12–14]. The major factors contributing to Alzheimer's disease include (1) deposition of β-amyloid [15], (2) oxidative stress [16], (3) aggregation of tau protein [17], and (4) low level of acetylcholine due to severe loss of cholinergic cells in the brain [10].