Journal of Saudi Chemical Society (2016) **20**, S227–S230

King Saud University

**Journal of Saudi Chemical Society**

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ORIGINAL ARTICLE

# Synthesis of novel tetrahydroquinoline derivatives from α,α′-bis(substituted-benzylidene)cycloalkanones

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Received 20 June 2012; accepted 25 September 2012
Available online 7 November 2012

**KEYWORDS**

Tetrahydroquinoline;
Cyano-pyran;
$NH_4OAC$;
α,α′-Bis(substituted benzylidene)cycloalkanones;
Cyano-pyridine

**Abstract** In this paper, we describe a two-step synthesis of a series of substituted tetrahydroquinoline analogies. In the first step α,α′-bis(substituted-benzylidene)cycloalkanones are reacted with malononitrile to afford 2-amino-3-cyano-4*H*-pyrans. The second step involves the conversion of pyrans into 2-amino-5,6,7,8-tetrahydroquinoline-3-carbonitrile derivatives using $NH_4OAC$.


## 1. Introduction

Tetrahydroquinoline moiety is an important structural feature of various natural products and pharmaceutical agents that have exhibited a broad range of biological activities (Perry et al., 1986; Williamson et al., 1995; Johnson et al., 1989). Substituted tetrahydroquinolines are the core structures in many important pharmacological agents and drug molecules such as anti-arrhythmic and cardiovascular agents, anticancer drugs, immunosuppressants and as ligands for 5-HTIA and NMDA receptors (Guo et al., 2002).

The study on the structure–activity relationships of tetrahydroquinolines showed that the main attention should be paid to the following aspects: the stereochemistry, the substitution and the ring fused to the 3,4-position of the tetrahydroquinoline (Hoemann et al., 2002). Many of forts directed the electron-donating group toward the 4-position of tetrahydroquinoline ring but the introduction of a substituent at the 3-position proved to be difficult (Cheng et al., 2002). Hence, there has been considerable interest in the development of new and efficient protocols for the synthesis of tetrahydroquinoline derivatives (Yadav et al., 2004; Powell and Batey, 2003; Spanedda et al., 2003).

Many naturally occurring as well as synthetic compounds containing the pyridine structure exhibit interesting pharmacological properties. As a consequence many efficient procedures have been reported in the literature for the synthesis of functionalized pyridines (Movassaghi and Hill, 2006; Suzuki et al., 2007; Trost and Gutierrez, 2007; Hajbi et al., 2007). Pyridine is one of the most popular N-heteroaromatics incorporated into the structure of many pharmaceuticals. Among these, cyanopyridines with different alkyl and aryl groups were found to have antimicrobial, anti hypertensive, cardiovascular, anti-inflammatory, analgesic, antipyretic properties as well as 1KK-b inhibitor properties (Manna et al., 1992, 1999; Murata

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Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

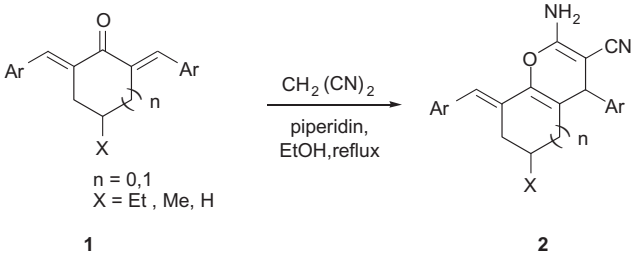
http://dx.doi.org/10.1016/j.jscs.2012.09.018

et al., 1994). The preparation of the 2-amino-3-cyanopyridine derivatives has been reported in the literature from chalcones on treatment with ammonium acetate via Michael-type condensation (Vyas et al., 2009) as well as via a one pot coupling reaction of four components (Shi et al., 2005) acetophenone, benzaldehyde, malononitrile, and ammonium acetate in conventional heating mode or under microwave irradiation and by other methods (Sharma et al., 2000; Farhanullah et al., 2003). So 2-amino-3-cyanopyridines are versatile intermediates for the synthesis of nitrogen heterocycles. As a part of our ongoing research on heterocyclic compounds of biological significance (Bigdeli et al., 2008a,b, 2011), we have carried out a two-step reaction setup for the synthesis of some novel tetrahydroquinoline analogues.

## 2. Result and discussion

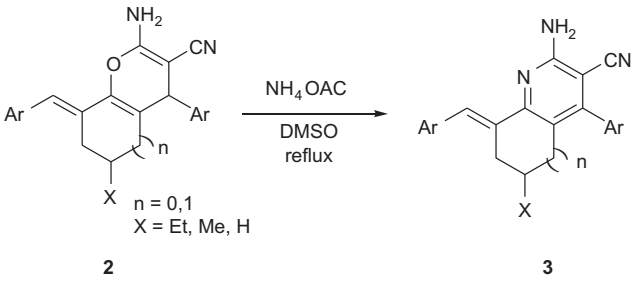
α,α′-Bis(substituted-benzylidene) cycloalkanone derivatives (**1**) were prepared from Cross-Aldol condensation of cyclic ketones with various aromatic aldehydes **2** bearing electron withdrawing groups (such as nitro, halide), and electron donating groups (such as methyl, methoxy), according to the reported procedures (Habibi et al., 2011). Use of different aryl groups does not affect the yields. The yields for naphthyl derivative are, however, lower relative to the phenyl analogues. Then 4*H*-pyran derivatives **2** were synthesized via a bicomponent reaction of α,α′-bis(substituted-benzylidene) cycloalkanones **1** and malononitrile in the presence of piperidine under reflux conditions (Scheme 1, Table 1).

A series of heterocycles **2a**–**e** were prepared and converted into the corresponding novel pyrano[2,3-*b*]pyridines **3a**–**e** in reaction with $NH_4OAC$ (Scheme 2). The reactions seem to show similar results (65–80%, Table 2) irrespective of the ring size of the cycloalkanones under investigation. However, some of 2-amino-3-cyano-4*H*-pyrans substituent which contains chloro and nitro groups in their aldehyde structure reacts with ammonium acetate in very low yield.




1 2

**Scheme 1** Synthesis of 4*H*-pyran derivatives.




2 3

**Scheme 2** synthesis of tetrahydroquinoline analogues from 4*H*-pyran derivatives.

The structures of compounds **3a**–**e** were deduced from their spectroscopic data and also their elemental analysis. The $^1$H NMR spectrum of the products showed that a distinguished peak at region $\delta$ = 3.90–4.20 ppm for the –CH protons in 2-amino-3-cyano-4*H*-pyrans was disappeared. The IR spectrum of **3b** shows three bands at 3359, 3214 ($NH_2$) and 2212 (CN) $cm^{-1}$. $^1$H NMR spectrum of **3a** exhibited two singlet for the vinyl ($\delta$ = 8.05 ppm) and $NH_2$ ($\delta$ = 6.03 ppm) protons, a complex signal ($\delta$ = 7.28–7.53 ppm) for the phenyl protons, along with three multiple signals ($\delta$ = 1.67, 2.41 and 2.81) due to the three methylene protons. The proton-decoupled $^{13}$C NMR spectrum of **3b** exhibited distinct resonances in agreement with the tetrahydroquinoline structure. Partial assignments of these resonances are given in the experimental section. The spectral data of **3a**–**e** were similar to **3b** except for differences in the proton resonances of the substituents.

## 3. Experimental

### *3.1. General procedure for the synthesis of 2-amino-3-cyano-4H-pyrans (2a–e)*

α,α′-Bis(substituted-benzylidene)cycloalkanones (1.0 equiv), malononitrile (1.2 equiv) and catalytic amount of piperidine (0.1 equiv) were refluxed in ethanol (10 ml) for 2–5 h. After cooling the solvent was removed and the residue was recrystallized from ethanol. The results are tabulated in Table 1.

### *3.2. (8E)-2-Amino-6-ethyl-5,6,7,8-tetrahydro-4-(naphthalen-2-yl)-8-((naphthalen-6-yl) methylene)-4H-chromene-3-carbonitrile (2e)*

Yield 80%. Mp = 204–207 °C. IR (KBr, $cm^{-1}$): 3457, 3329, 2195 $cm^{-1}$. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ = 0.71 (3H, t, $J$ = 7.3 Hz, $CH_3$), 1.21 (2H, m, $CH_2$), 1.63 (2H, m, $CH_2$), 1.98–2.05 (3H, m, CH, $CH_2$), 4.15 (1H, m, CH), 4.57 (2H, s,

**Table 1** Preparation of 2-amino-3-cyano-4*H*-pyrans from α,α′-bis(substituted benzylidene)cycloalkanones.

| Entry | *n* | Ar | Product | Time (h) | Yield (%) | M.P (°C) |
|---|---|---|---|---|---|---|
| 1 | 0, X = H | $C_6H_5$– | **2a** | 3 | 75 | 232–231 (235–236)[a] |
| 2 | 1, X = H | $C_6H_5$– | **2b** | 2 | 80 | 248–250 (250–251)[a] |
| 3 | 1, X = H | 4-Me$C_6H_4$– | **2c** | 3 | 76 | 189–190 (191–193)[a] |
| 4 | 1, X = H | 4-MO$C_6H_4$– | **2d** | 3 | 76 | 199–196 |
| 5 | 1, X = Et | β- Naphttyl | **2e** | 4 | 80 | 244–245 |

[a] M.P reference: Mobinikhaledi et al. (2015).