Journal of Saudi Chemical Society (2012) **16**, 161–173

King Saud University

**Journal of Saudi Chemical Society**

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ORIGINAL ARTICLE

# Synthesis, characterization and coordination chemistry of substituted β-amino dicarbonyls

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Received 26 November 2010; accepted 24 December 2010
Available online 1 January 2011

**KEYWORDS**

β-Amino dicarbonyls;
Michael reaction;
Crystallography

**Abstract** An efficient and facile method for the synthesis of novel structurally diverse β-amino dicarbonyl compounds is described by exploring the aza-Michael addition reaction in an aqueous medium as a key step. Thereby, 2-(aryl-disubstituted-amino-1-yl-methyl)-malonic acid diethyl esters were achieved in a good to excellent yields. These products were easily isolated with enough purity just by using simple recrystallization. The crystals of the compounds (**17**) and (**24**) have been obtained and studied by X-ray crystallographic analyses.

## 1. Introduction

The HIV-1 Integrase (HI) is a valid target for chemotherapeutic intervention due to its involvement in the viral replication process (Goldgur et al., 1999; Walker et al., 2007; Gopi et al., 2009). The chemical inhibition of HI could be reached via intermolecular coordination between HI/chemical inhibitor/metals ($Mg^{2+}$ and $Mn^{2+}$, co-factors of the HI), leading to the formation of bimetallic complexes (Lebon et al., 2002; Dayam et al., 2007; Dayam and Neamati, 2004; Sechi et al., 2009; Zenga et al., 2008). In fact, the most successful strategy to inhibit the HI is to explore the structural core of β-diketo acid type, as briefly illustrated in Fig. 1 (Sorrell et al., 1991; Bacchi et al., 2008; Sechi et al., 2006; Orvig and Abrams, 1999). In view of this, it is highly desirable to obtain the improved protocols for the synthesis of β-diketo acid (Amslinger, 2010).

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Peer review under responsibility of King Saud University.
doi:10.1016/j.jscs.2010.12.005

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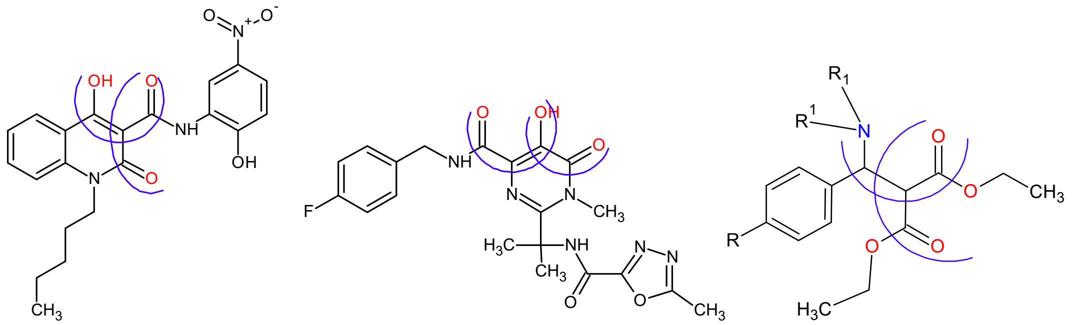

**(I)** **Elviltegavir** **(14)-(35)**

**Figure 1** Some of the HIV inhibitors under clinical trials or those (**I** and **Elviltegavir**) were recently approved by US FDA.

For the preparation of such polydentate ligands, the aza-Michael addition seems to be a key-step (Hayashi et al., 1996). Among the large number of unconventional methodologies, this kind of reaction has widely been employed to generate structurally diverse β-amino dicarbonyl compounds (Zhu et al., 2009; Kumar et al., 2008). Most of these unconventional methodologies have used Lewis acids, which although leading to satisfactory yields but it still requires the alternatives (Basu et al., 2004; Wabnitz and Spencer, 2002). Moreover, the use of an aqueous medium (Ranu and Banerjee, 2007; Ranu and Mandal, 2007; Ranu et al., 2005) has been a successful source in achieving expected results in better yield with greener touch eliminating the use of hazardous solvents. Usually, these types of substrates are less reactive or conversely more resistant to undergo the Michael addition which results in low conversion of the desired adducts. From the synthetic point of view, this is a considerable limitation on the Michael reaction process and poses a significant challenge.

To this end, we decided to investigate the feasibility of applying the aza-Michael reactions to the more challenging substituted alkene derivatives. Our idea is to explore the application of this key-step to the synthesis of a set of polydentate O,O,N-ligands (Scheme 1), in order to highlight the versatility of the procedure as well as to generate some insights regarding the 3D crystalline structure of two compounds (**17**) and (**24**).

## 2. Chemistry

Our synthetic strategy is very clear. In the first step, 2-arylidene-malonic acid ethyl esters (**1**)–(**13**) were prepared by the condensation of substituted arylaldehydes with diethyl-malonate in ethanol under reflux condition, using piperazine and glacial acetic acid as a catalyst. This procedure furnished the intermediates, 2-arylidene-malonic acid ethyl esters (**1**)–(**13**), quickly and in excellent yields (Scheme 1).

To further explore the scope and limitations of the aza-Michael reaction, compound (**1**) was chosen as the model precursor because of its thermo stability and also due to the less reactivity of pyrazole towards traditional aza-Michael addition. It was found that the stirring of compound (**1**) and pyrazole together in water at room temperature for 12 h led to the formation of 71% of (**15**) (Scheme 2). During the investigation of experimental conditions, it was possible to observe that the acid catalyst (AcOH, 0.1 mol%) accelerates the reaction but it is not essential (Meskini et al., 2010a,b,c).

Having well established and developed reaction conditions, it was identified that precursors (**1**)–(**13**) reacted quickly; with various secondary amines under catalyst-free conditions to provide the desired adducts (**14**)–(**35**) in good to excellent yields. These products were characterized using spectroscopic ($^1$H and $^{13}$C NMR, IR and MS) and micro-analytical data.

The compounds (**14**)–(**35**) are insoluble in water. The compound (**16**) has been recrystallized from ethanol to obtain the single suitable crystal and studied by X-ray diffraction study (Meskini et al., 2010a,b,c). Since, NaOH is a strong base therefore it is likely that the compounds are saponified into carboxylate units upon dissolution to form substituted β-amino dicarboxylates of sodium. However, we were unable to obtain the hypothetical bimetallic species by conventional means. The attempts to crystallise the substituted β-amino dicarboxylate derivative of (**16**) resulted in crystallisation of a polymeric complex; the poly[[bis{l3-2-[(3,5-dimethyl-1H-pyrazol-1-yl)(phenyl)methyl]propanedioato}tetrasodium](I) 7.5-hydrate] (**16′**) (Scheme 3). The compound (**16′**) has been used then in our laboratory as a starting material in organometallic chemistry and surprisingly its coordination mode has not been reported previously in literature. Since it is such an important precursor its structure will be briefly described here (Fig. 2).

The coordination of $Cu(NO_3)_2{\cdot}2H_2O$ to β-amino dicarboxylate ligands (**14**)–(**35**) in basic medium led us to obtain bimetallic complexes (Scheme 4 and Fig. 3).

## 3. Results and discussion

In order to get more insight into the theoretically possible points of metallic coordination, we have aimed to replace the phenyl by 4-chloro-phenyl, 4-methyl-phenyl or trifluoro-methyl-phenyl fragments (Scheme 2).

Analyzing the X-ray crystallography data (Figs. 4 and 5), it has revealed that the crystal is subject of a weak torsion around the C1–C2 bond, of dihedral angle [N(1), C(1), C(2), H(2)] equal to 68.04(2)°. The nitrogen atom N(1) is trivalent with N(1)–C(1), N(1)–C(15) and N(1)–C(22) bonds of 1.484(1), 1.473(2) and 1.471(2) Å, respectively; they do not remain trans, indicating a cis 1,2-addition. Confirmation of the *cis*-addition is also indicated by the ORTEP of compound (**24**) in which it is easy to see the dihedral angle [N(1), C(1), C(2), H(2)] in the same range. This observed geometric form was confirmed by studying the crystallographic features for the compounds (**17**) and (**24**).