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Plausible Reaction Path for Haval-Argade Contrathermodynamic Rearrangement in Synthesis of Farinomalein

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This work reports, the plausible reaction path in context of the farinomalein (**1**) and isofarinomalein (**2**) synthesized *via* Stobbe condensation and Haval-Argade Contrathermodynamic Rearrangement.

Keywords: Cyanuric chloride, Maleimide, Stobbe condensation, Regioselectivity, Enthalpy.

INTRODUCTION

The compound farinomalein (**1**) is first reported by Putri *et al.* [1]. This compound is isolated from an entomopathogenic fungus *P. farinosus* HF599. The structure of maleimide-bearing farinomalein (**1**) is determined by spectroscopic analysis and chemical conversion [1]. Farinomalein (**1**) has been evaluated for its potent antifungal activity with (MIC value 5 µg/disk) against the plant pathogenic *P. sojae* P6497, wherein the positive control, amphotericin B used in the assay remarkably shows (MIC value 10 µg/disk) [1-3]. There are three derivatives of the farinomalein (**1**) are reported thereafter along with isoindoline [4]. Synthesis of farinomalein (**1**) started from γ-hydroxy-butenolide [5] and ethyl-3-methyl-2-oxobutyrate [6,7] are reported in date. In present study, the synthesis of farinomalein is attempted started from dimethyl succinate [8,9] yield *pseudonym*: isofarinomalein (**2**), which then further subjected to HA contrathermodynamic rearrangement [10] yield farinomalein (**1**) and isofarinomalein (**2**). These observations are studied with the thermodynamic parameter of the compounds involved in the **Scheme-I**. The significance of the present studies also due to the fact that transformation of dialkylidene-succinimide to alkylmaleimide is practical difficult to achieve by many reagents and reaction conditions [10].

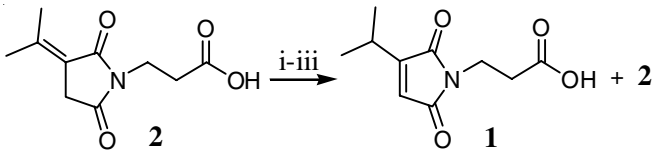
EXPERIMENTAL

The chemical and solvents reagents used for synthesis were analytical grade with minimum purity 99.5 %. The structures of the compounds were confirmed chromatographic and spectroscopic method the details of which are as follows. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker® AC-200 and Varian Mercury Spectrometer 400 MHz unless stated otherwise using $CDCl_3$. Mass spectra were recorded on Agilent® G6540B MS Q-TOF at 70 eV with Electron Spray Ionization technique. The optimized geometries and the enthalpy data of intermediate obtained from semi-empirical calculation using CS MOPAC® pro version 8.0, wherein structure were viewed in Chem3D® Molecular Modeling and Analysis.

The isofarinomalein (**2**) was subjected to HA contra-thermodynamic rearrangement [10] and yielded 33 % the mixture of farinomalein (**1**) and isofarinomalein (**2**) (**Scheme-I**). None of the intermediates were isolated. Isofarinomalein (**2**) regioselectively hydrolyzed by LiOH quantitatively gave 3-(2-carboxyethylcarbamoyl)-4-methylpent-3-enoic acid (**3**). The reaction with cyanuric chloride and triethyl amine at lower temperature led to β-alkyl isomaleimide (**4**) which on further refluxed with acetic acid resulted in farinomalein (**1**) and isofarinomalein (**2**).

RESULTS AND DISCUSSION

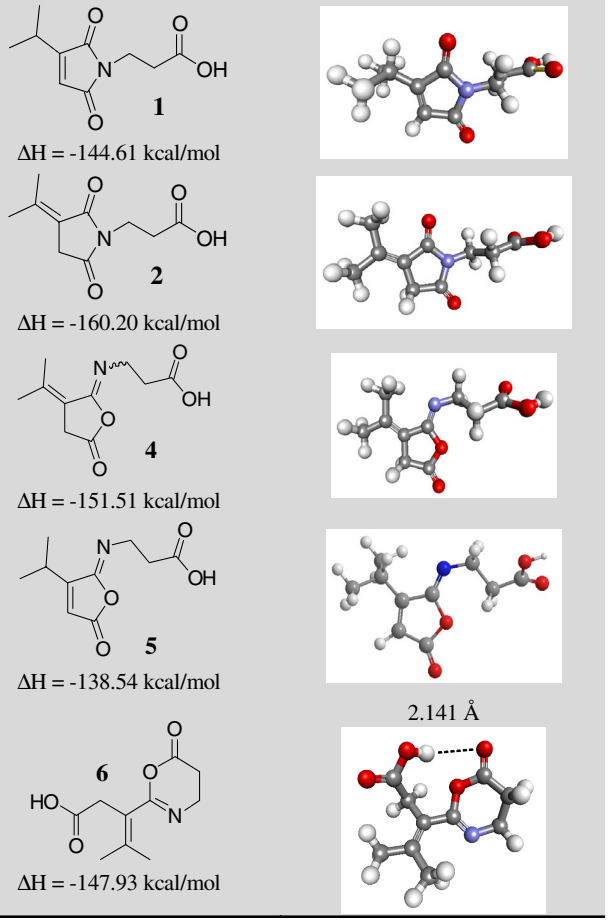
Farinomalein (**1**) and isofarinomalein (**2**) were found in ratio 15:85 (calculated from ^{1}H NMR spectral integration and the area under the peaks in mass spectrogram). The highly regioselective aqueous lithium hydroxide hydrolysis of compound 2 exclusively delivered β-alkylidenesuccinanillic acid (**3**) in almost quantitative yield [10]. The diacid **3** obtained was subjected to kinetic dehydration in order to achieve β-dialkyl-isosuccinimide (**4**). Cyanuric chloride is a fine dehydrating reagent for such kinetic dehydration reactions [11,12]. Although the cyanuric chloride was used in excess the diacid at this



Scheme-I: Reagents, conditions and yields: (i) Aq. LiOH, THF, 0 °C to RT, 5 h (ii) Cyanuric chloride, Et_3N, DCM, 0 °C to room temperature, 8 h (iii) Acetic acid, reflux, 5 h (three steps) 33 %

stage there were two choices to form desired intermediate **4** and other **6** with different proportion. The ring size in ring closure reaction followed by Baldwin rules [13-15]. In this reaction with cyanuric chloride thermodynamically less favoured compound **6** was preferentially formed. The six member cyclic compound with intra-molecular hydrogen bonding distancing by 2.141 Å bears more thermodynamic stability than that of compound **4**. The compound **4** was then subjected to triethylamine wherein exocyclic double bond was dragged into the ring by abstraction of active methylene hydrogen in β-dialkylisosuccinimide (**4**). Thus carbon-carbon double bond migration took place due to extension of π-cloud to butyrioimidolide carbonyl group. The abstraction of the α-methylene proton from the intermediate **4** to form β-alkyl isomaleimide **5** took place in presence of triethyl amine. The kinetically controlled β-alkyl isomaleimide **5** was converted to the desired, thermodynamically more stable alkylmaleimide, farinomalein (**1**) in almost quantitative yield. The transformation **6** to **7** was forbidden due to lack of driving force for migration of carbon-carbon double bond. In compound **6**, six membered ring open and reclosed to formed isofarinomalein (**2**) in acetic acid reflux conditions. After obtaining spectroscopic data we confirmed the structures and the ratio of the compounds in the reaction sequence and to shed some light on the reaction path the additional thermodynamic data Table-1 was obtained from semi-empirical calculation using CS MOPAC® pro version 8.0.

TABLE-1
THE OPTIMIZED GEOMETRIES AND THE ENTHALPY DATA OF INTERMEDIATES OBTAINED FROM SEMI-EMPIRICAL CALCULATION USING CS MOPAC® PRO VERSION 8.0



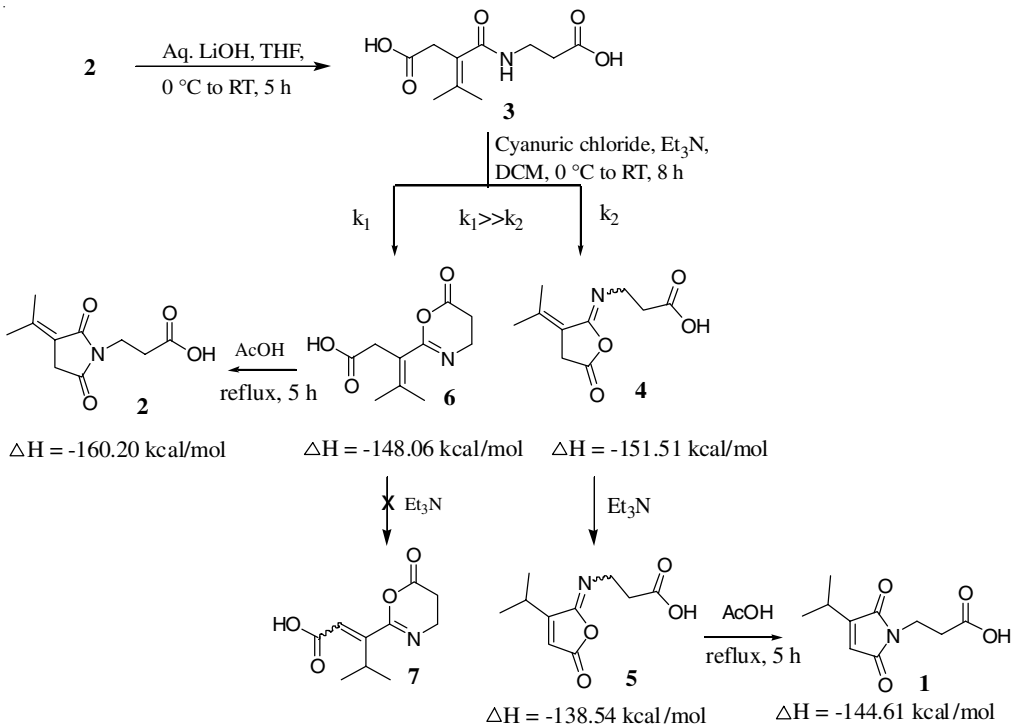


Fig. 1. Plausible reaction path for the formation of farinomalein (**1**) and isofarinomalein (**2**)

The detailed reaction coordinate of formation of farinomalein (**1**) and isofarinomalein (**2**) has been showed in Fig. 1. The number of intermediates encountered in the HA contrathermodynamic rearrangement were also learned, although the enthalpy values of those intermediate were numerically less negative but the overall trend was similar to present study. The scalar values the enthalpy of compounds **2-7** are relatively high this may be due to the presence of acid functional group and intramolecular hydrogen bonding present in it.

The obtained data utilized for the theoretical interpretation *viz.* The compound **3** is converted to intermediate **6** with rate k_1 and compound **4** is converted to intermediate **5** with rate k_2. The intermediate **4** and **6** have enthalpies -151.51 and -148.06 kcal/mol, respectively. The reaction with cyanuric chloride and triethylamine led to kinetically controlled and thermodynamically less product. The practically isolated yields and enthalpies rationally led to plausible fact that $k_1 >> k_2$. Fig. 2 explicitly indicates change in enthalpies with reaction coordinate. The intermediate **6** has intra-molecular hydrogen bonding, which could be agitated by rotation of C-C bond of dihydro-1,3-oxazinone ring with rest of the moiety. The absence of intra-molecular hydrogen bond elevated the ΔH towards less negative and that too favour $k_1 >> k_2$. On the other hand, the intermediate **6** is not having any butyrioimidolide carbonyl group which would shift the allylic hydrogen and overruled the possibility of formation of likely intermediate **7**. The acetic acid reflux coverts the intermediate **4** and **6** to farinomalein (**1**) and isofarinomalein (**2**). The theoretically calculated enthalpy of isofarinomalein and farinomalein are -160.20 and -144.61 kcal/mol, respectively. In conclusion, the intermediates **4** and **6** played crucial role in determining the fate of the HA contrathermodynamic rearrangement in the reaction.

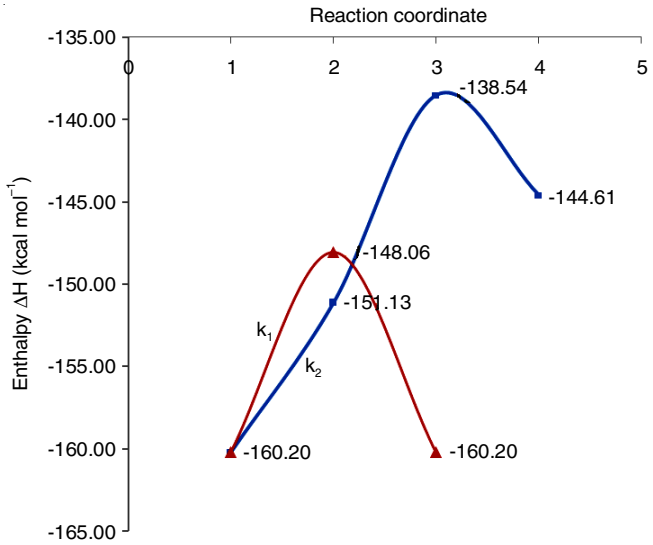


Fig. 2. Graph of enthalpy *vs.* reaction coordinate

Conclusion

The present study gives a rational explanation on the reaction path and the mechanism followed in formation of farinomalein (**1**) and isofarinomalein (**2**). It also demonstrates that kinetic conditions and thermodynamic stability plays an important role in the reaction coordinate.

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