Tetrahedron Letters 50 (2009) 4727–4730

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

$Co_2(CO)_8$-induced domino reactions of ethyl diazoacetate, carbon monoxide and ferrocenylimines leading to 2-(1-ferrocenyl-methylidene)-malonic acid derivatives

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ARTICLE INFO

Article history:
Received 5 May 2009
Revised 22 May 2009
Accepted 5 June 2009
Available online 11 June 2009

Keywords:
Domino reactions, β-Lactams
Cobalt-catalysis
Carbonylation

ABSTRACT

Novel 2-(1-ferrocenyl-methylidene)-malonic acid derivatives are obtained upon reacting ethyl diazoacetate, carbon monoxide and ferrocenylimines in the presence of $Co_2(CO)_8$ as catalyst under mild conditions. Presumably, the reaction involves three steps taking place in a domino fashion, (i) carbonylation of ethyl diazoacetate leading to a ketene derivative, (ii) [2+2] cycloaddition of the ketene with the ferrocenylimine present in the reaction mixture resulting in the formation of a β-lactam and (iii) N(1)-C(4) cleavage of the β-lactam ring. In most cases, 2-(1-ferrocenyl-methylidene)-malonic acid derivatives are obtained as a separable mixture of *E*- and *Z*-isomers in ratios depending on the structure of the imine component.

As part of our ongoing research towards the synthesis of ferrocene bioconjugates via transition metal-catalyzed carbonylation reactions,[1] we decided to investigate the possibility of the synthesis of ferrocenyl β-lactams. The special properties of ferrocene, such as high stability, reversible change of the valency state, non-benzoic aromatic structure, low toxicity towards mammals and potential as an iron source, make its derivatives ideal candidates for drug design. In some cases, the introduction of a ferrocenyl moiety has been found to enhance the biological activity of the original compound.[2] It was shown that ferrocene-substituted penicillin had improved stability to β-lactamase attack without a reduction in antibiotic activity.[3] Hence, it is no surprise that several ferrocene-substituted β-lactam derivatives have been synthesized and their antibiotic activity has been tested.[4–9]

Recently, a new domino reaction, comprising the cobalt-catalyzed carbonylation of ethyl diazoacetate in the presence of nucleophilic reagents leading to various malonic acid derivatives was developed.[10–12] The carbonylation step results in the formation of ethoxycarbonylketene which can be scavenged by alcohols or secondary amines (Scheme 1).[10,11] Also, the reaction has been shown to produce *N*-alkyl-*trans*-1-ethoxycarbonyl-4-phenyl-β-lactams using *N*-alkyl-benzaldimines as the nucleophiles.[12]

However, upon reacting ferrocenylimine **1a** with ethyl diazoacetate and carbon monoxide in the presence of $Co_2(CO)_8$ as the catalyst,[13] we found that instead of the expected β-lactam, a mixture of two isomeric 2-(1-ferrocenyl-methylidene)-malonic acid derivatives, **2a** and **3a**, was produced (Scheme 2). As the one-step synthesis of such compounds can also be of interest, we decided to investigate this domino reaction in the presence of various ferrocenylimines **1a–h** (Scheme 2, Table 1).

The reaction conditions were determined based on the results of a detailed investigation of a similar reaction of *N*-*tert*-butylbenzaldimine.[12] The reaction of an equimolar amount of ferrocenylimine and ethyl diazoacetate in the presence of 5 mol % of $Co_2(CO)_8$ under 80 bar CO pressure resulted in the selective formation of 2-(1-ferrocenyl-methylidene)-malonic acid derivatives. An earlier study showed that, under ambient conditions, the reaction of ethyl diazoacetate (EDA) with $Co_2(CO)_8$ gave dinitrogen and ethoxycarbonylcarbene-bridged dicobalt carbonyl complexes $Co_2(CO)_7(CHCO_2Et)$ and $Co_2(CO)_6(CHCO_2Et)_2$ depending on the molar ratio of EDA and $Co_2(CO)_8$.[10] Under an atmosphere of carbon monoxide, the ethoxycarbonylcarbene ligand of these complexes couples with CO to give ethoxycarbonylketene which is replaced by CO. The highly reactive ethoxycarbonylketene either dimerizes or reacts with ferrocenylimines **1a–h** leading to β-lactam derivatives.

The formation of 2-(1-ferrocenyl-methylidene)-malonic acid derivatives can be rationalized by the N(1)-C(4) cleavage of the initially formed β-lactams. It should be mentioned that no lactam products could be isolated or could be detected by GC–MS in the reaction mixtures which show that the ferrocenyl lactam structure is highly unstable under the present reaction conditions.

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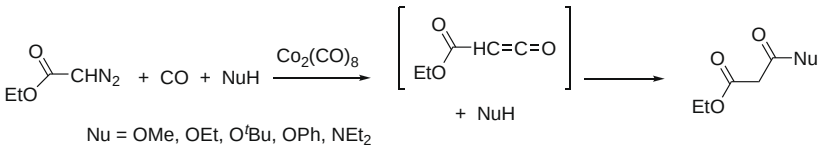
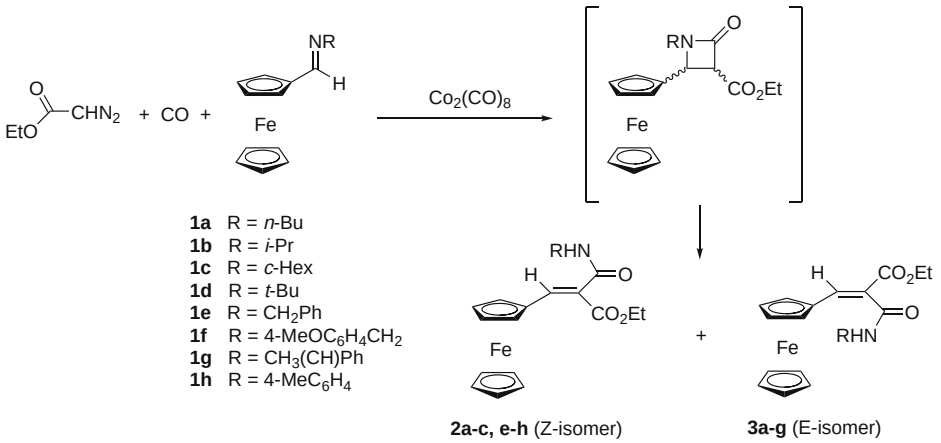
doi:10.1016/j.tetlet.2009.06.035



Scheme 1. Cobalt-catalyzed carbonylation of ethyl diazoacetate in the presence of nucleophilic reagents.



Scheme 2. Domino reaction of ethyl diazoacetate, carbon monoxide and ferrocenylimines **1a–h** in the presence of $Co_2(CO)_8$.

Table 1
Synthesis of 2-(1-ferrocenyl-methylidene)-malonic acid derivatives **2** and **3** via the domino reaction of ethyl diazoacetate, carbon monoxide and ferrocenylimines **1a–h**[a]

Entry	Imine	Ratio of products[b]		Combined yields of products **2** and **3** (%)
		2	**3**	
1	**1a**	18	82	48
2	**1b**	38	62	34
3	**1c**	16	84	50
4	**1d**	0	100	33
5	**1e**	15	85	54
6	**1f**	13	87	39
7	**1g**	11	89	82
8	**1h**	100	0	26

[a] Reaction conditions: 5 mol % $Co_2(CO)_8$, imine/ethyl diazoacetate = 1/1, in CH_2Cl_2, 80 bar CO, room temperature, 24 h.
[b] Determined from the yields of **2** and **3**.

N(1)-C(4) cleavage of β-lactams is not unprecedented, but until now, similar reactions were shown to proceed by palladium-catalyzed hydrogenolysis[14] or in the presence of either an excess of a base (NaH[15] or LDA[7]) or an excess of an acid (*p*-TsOH).[9] To the best of our knowledge, complete N(1)-C(4) cleavage under neutral conditions has not been reported before.

Both the conversion of ferrocenylimines and the selectivities of the reactions depend greatly on the properties of the substituent on the imine nitrogen. With the exception of the reaction of **1d**, the use of *N*-alkyl or *N*-arylalkylimines as reaction partners led to a mixture of two isomeric products[16] in moderate to good yields. In contrast, reactions of **1d** and the *N*-arylimine **1h** resulted in a single *E* or *Z* isomeric product.

The latter results are in accordance with the previous findings of Bonini[9] and Brown[17] concerning the synthesis of *N*-aryl- and *N*-*t*-butylamido malonates, respectively. Bonini and co-workers synthesized various α,β-unsaturated amides by acidic cleavage of 4-ferrocenyl-*N*-aryl-β-lactams and they observed the exclusive formation of the *Z*-isomers.[9] In contrast, only the more stable *E*-ethyl *tert*-butylamido-benzylmalonate was isolated from the Knoevenagel condensation of benzaldehyde with ethyl *t*-butylamidoacetate, although both isomers were detected in the reaction mixture by GC–MS.[17]

The structures of the two isomers **2a** and **3a** were proved unequivocally by NOESY experiments. Cross peaks were observed between the protons of the substituted cyclopentadienyl ring (at 4.51 ppm) and the amide NH proton (at 5.76 ppm) in the spectrum of **3a** as well as between the same ferrocenyl protons and the NCH_2 protons at 3.31 ppm. No such cross peaks were observed in the NOESY spectrum of **2a**.

The structure, as well as the relative energies of 2-(1-ferrocenyl-methylidene)-malonic acid derivatives has been computed within the framework of the density functional formalism.[18] The B3LYP functional was employed[19] in combination with the 6-31G(d,p) basis set.[20] For preliminary calculations the *N*-*n*-butyl derivatives were chosen, that is, **2a** and **3a** (*Z*- and *E*-isomers, respectively). For both isomers, both the s-*trans* (designated as **2a1** and **3a1**) and s-*cis* (**2a2** and **3a2**) conformers were considered and are depicted in Figure 1. The species **3a1** is lowest in energy among the four isomers, whilst the relative energies of the other unsaturated amides are in a small range between 2.3 kcal/mol (**2a1**) and 2.8 kcal/mol (**2a2**). The s-*cis* conformer **3a2** is higher in energy by

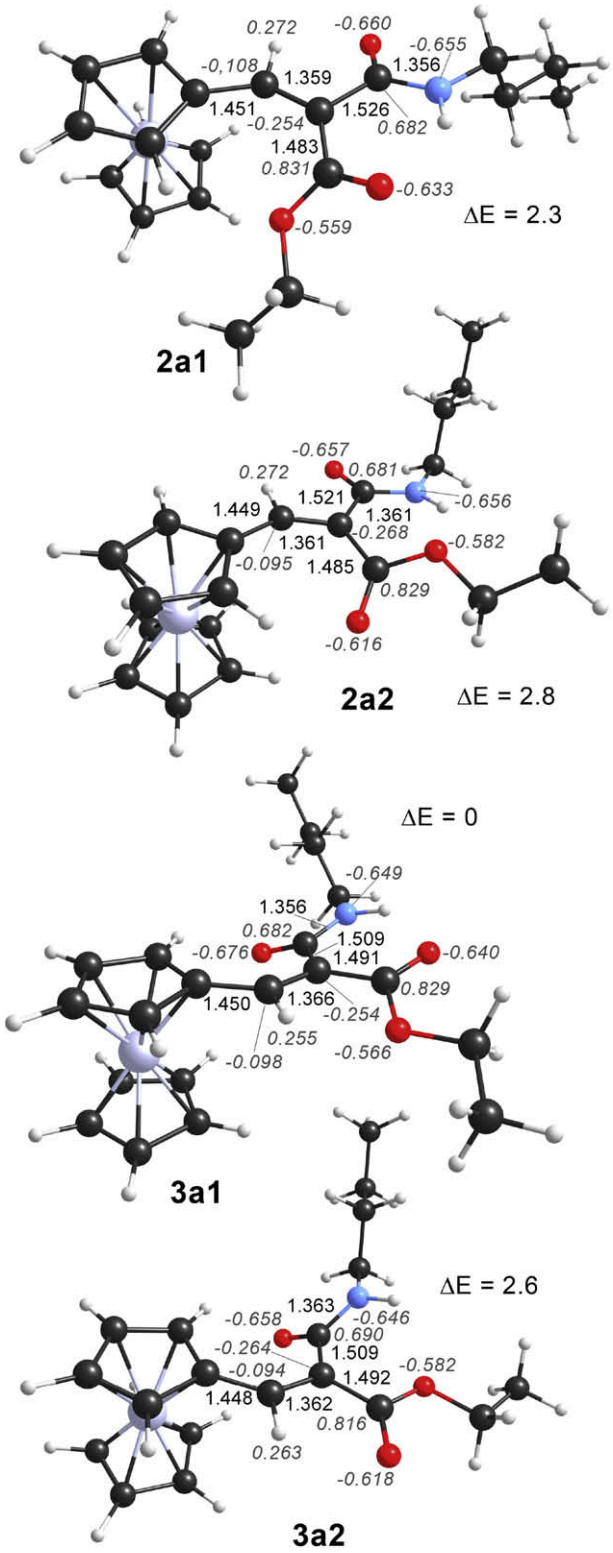


Figure 1. Computed structures of the *N*-*n*-butyl unsaturated amides **2a** and **3a**. Bond lengths are given in Å, ZPVE-corrected relative energies are given in kcal/mol. NPA charges are written in italics.

2.6 kcal/mol than **3a1**, thus for both the *E*- and *Z*-isomers, the *s*-*trans* conformers are predicted to be more stable.

The higher stability of **3a1** can be rationalized by a weak hydrogen bond between the olefinic hydrogen and the sp^3 oxygen of the ester group. Natural population analysis reveals a somewhat less positive hydrogen, and less negative oxygen compared to the other isomers.

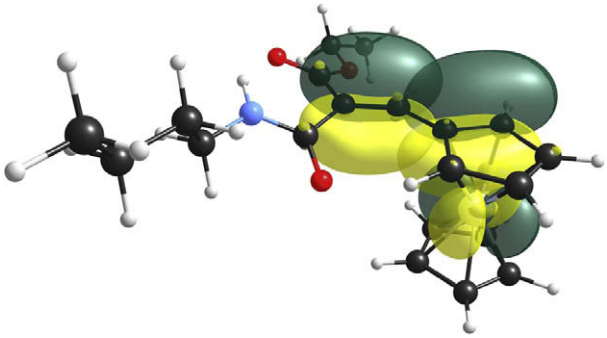


Figure 2. Electron delocalization between carbon–carbon π-bonds and a one-centre natural bond orbital of *d*-character of the iron of isomer **3a1**.

In order to shed some light on the electron delocalization of the ferrocene-substituted unsaturated amides, the natural bond–bond polarizability indices (NBBP)[21] were examined. The NBBP indices are indicative of how perturbation of one bond will affect the others through conjugative or hyperconjugative couplings. The olefinic carbon–carbon bond shows a fairly high NBBP value (0.369) with one of the one-centre natural bond orbitals (NBOs) of iron, as well as with one of the NBOs of π-symmetry of the cyclopentadienyl ring (0.261). The NBO analysis reveals that the d_{xy} orbital of Fe has the highest contribution in the one-centre NBO involved in the conjugated system. The extended electron delocalization in **3a1** is depicted in Figure 2.

In summary, the domino reaction presented herein can serve as an efficient method for the synthesis of 2-(1-ferrocenyl-methylidene)-malonic acid derivatives from ferrocenylimines in a single operation and under relatively mild conditions. Research towards optimization of the reaction conditions and clarification of the influence of the structure of the imine on the selectivity of the reaction is in progress.

Acknowledgements

The authors thank the Hungarian National Science Foundation for financial support (OTKA NK71906). The support of Bolyai Grant of the Hungarian Academy of Sciences for T.K. is also acknowledged.

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13. In a typical reaction 0.3 mmol of ferrocenylimine, 0.3 mmol of ethyl diazoacetate and 0.015 mmol of $Co_2(CO)_8$ were reacted in a stainless steel autoclave in 3 ml of CH_2Cl_2 as solvent under 80 bar CO pressure at room temperature for 24 h. The solvent was removed in vacuo and the residue was purified by column chromatography (silica gel, eluent: *n*-hexane/EtOAc = 3/1).
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16. *Selected spectroscopic data for* **2a**: ^{1}H NMR (δ):7.91 (s, 1H, =CH); 7.39 (t, J = 7.3 Hz, 1H, NH); 4.43 (t, J = 1.8 Hz, 2H, Cp); 4.40 (t, J = 1.8 Hz, 2H, Cp); 4.21 (q, J = 7.2 Hz, 2H, OCH_2); 4.12 (s, 5H, Cp); 3.29 (q, J = 7.3 Hz, 2H, $NHCH_2$); 1.49 (quin, J = 7.3 Hz, 2H, CH_2); 1.32 (sext, J = 7.3 Hz, 2H, CH_2); 1.23 (t, J = 7.2 Hz, 3H, CH_3); 0.88 (t, J = 7.3 Hz, 3H, CH_3). ^{13}C NMR (δ): 170.3; 169.3; 147.0; 120.4; 77.2; 71.5; 71.3; 69.8; 61.2; 39.7; 31.5; 20.2; 13.9; 13.8. MS (*m*/z/rel. int.): 383 (M^+) (100); 318 (68); 274 (22); 121 (14); 56 (7). *Selected spectroscopic data for* **3a**: ^{1}H NMR (δ): 7.48 (s, 1H, =CH); 5.76 (t, J = 7.0 Hz, 1H, NH); 4.51 (t, J = 1.8 Hz, 2H, Cp); 4.38 (t, J = 1.8 Hz, 2H, Cp); 4.18 (q, J = 7.3 Hz, 2H, OCH_2); 4.14 (s, 5H, Cp); 3.31 (q, J = 7.0 Hz, 2H, $NHCH_2$); 1.48 (quin, J = 7.0 Hz, 2H, CH_2); 1.31 (sext, J = 7.0 Hz, 2H, CH_2); 1.25 (t, J = 7.3 Hz, 3H, CH_3); 0.86 (t, J = 7.0 Hz, 3H, CH_3). ^{13}C NMR (δ): 166.6; 165.4; 143.6; 124.1; 75.9; 71.7; 70.7; 69.9; 61.1; 39.4; 31.3; 20.0; 14.2; 13.7. MS (*m*/z/rel. int.): 383 (M^+) (100); 318 (69); 274 (21); 121 (18); 56 (6).
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