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Copper(I)-Catalysed Multicomponent Reaction: Straightforward Access to 5-Hydroxy-1*H*-pyrrol-2(5*H*)-ones

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Abstract: A copper-catalysed multicomponent coupling reaction between readily available (*Z*)-3-iodoacrylic acids, terminal alkynes, and primary amines was developed to smoothly access a small library of 5-hydroxy-1*H*-pyrrol-2(5*H*)-ones in good yields. This practical and general process was applied to a short-steps synthesis of the natural product pulchellalactam.

Keywords: copper catalysis; 5-hydroxy-1*H*-pyrrol-2(5*H*)-ones; multicomponent reaction

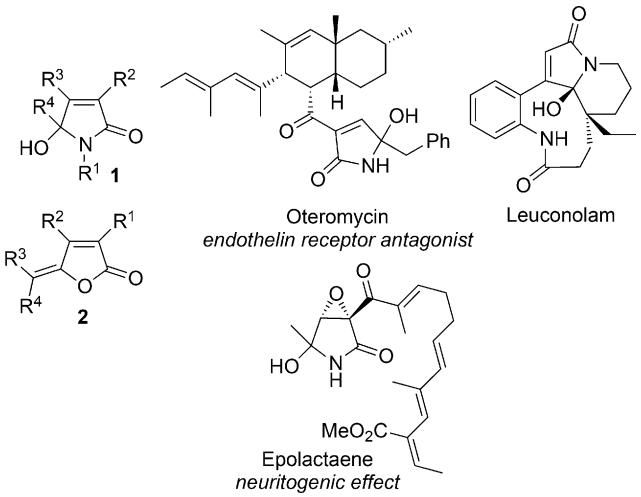


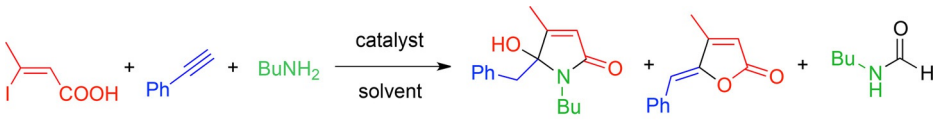
Figure 1. Examples of biologically active compounds having a γ-hydroxylactam moiety.

The 5-hydroxy-1*H*-pyrrol-2(5*H*)-one framework (**1**) is an interesting target since these five-membered heterocyclic compounds are not only present in numerous natural products[1] and designed pharmaceutical molecules[2] displaying significant biological properties but also they are versatile building blocks in organic synthesis (Figure 1).[3] In this context, the development of new strategies for the construction of these scaffolds has triggered considerable attention and several approaches have been reported in the literature.[4] However, many of them suffer from drawbacks like poor selectivity, low chemical yields, substrate limitations and/or commercially unavailable starting materials. In this context, the development of a broad scope method is highly desirable and still constitutes a significant and attractive synthetic challenge. To this purpose, multiple bond-forming transformations (MBFTs) appear to be one of the most efficient tools. Among them, multicomponent reactions (MCRs) are especially attractive synthetic strategies[5] to provide large libraries of diversely substituted organic compounds from readily available starting materials and in a simple and atom economical transformation.

In this context, we wish to propose a new MCR process to prepare 5-hydroxylactams (**1**). We have recently shown that γ-alkylidenebutenolides **2** could efficiently be obtained *via* a palladium-free Sonogashira-type coupling between (*Z*)-β-iodo-α,β-unsaturated acids **3** and terminal alkynes **4** in the presence of a catalytic amount of copper(I).[6]

Furthermore, it has been reported on several occasions that γ-alkylidenebutenolides **2** could be converted into the corresponding γ-hydroxylactams **1** upon treatment with an excess of primary amines **5**.[7] In order to expand the synthetic possibilities of copper-catalysed formation of heterocyclic moieties, we supposed that this one-pot palladium-free procedure could be conducted in the presence of a primary amine and should directly furnish the corresponding 5-hydroxypyrrol-2(5*H*)-ones **1** (Scheme 1). This new multicomponent reaction would allow a straightforward access to these 5-membered heterocyclic derivatives *via* a copper-catalysed MBFT.

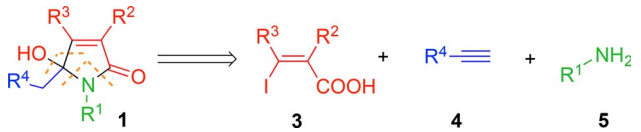
Table 1. Selected examples for the conditions optimization.



3a 4a 5a 1a 2a 6a

Entry	**4a** [equiv.]	**5a** [equiv.]	Solvent	Catalyst Nature	[equiv.]	**1a** [%]	
1	1.3	2	DMF	CuI	0.2	31	**1a:6a** = 1:0.4
2	1.3	2	DMF	$Cu(OAc)_2 \cdot H_2O$	0.2	31	**1a:6a** = 1:0.5
3	1.3	2	DMF	CuOAc	0.2	25	**1a:6a** = 1:0.5
4	1.3	2	DMF	$Cu(OAc)_2$	0.2	24	**1a:6a** = 1:0.5
5	1.3	2	DMF	$Cu(OTf)_2$	0.2	20	**1a:6a** = 1:0.7
6	1.3	2	DMSO	CuI	0.2	42	
7	1.3	2	CH_3CN	CuI	0.2	13	**1a:2a** = 1:0.45
8	1.3	2	*i*-PrOH	CuI	0.2	57	
9	1.3	2	CF_3CH_2OH	CuI	0.2	3	
10	1.3	2	CF_3Tol.	CuI	0.2	3	**1a:2a** = 1:1.2
11	1.3	1.1	*i*-PrOH	CuI	0.2	49	**1a:2a** = 1:0.4
12	1.3	3	*i*-PrOH	CuI	0.2	78	
13	2	2	*i*-PrOH	CuI	0.2	84	
14	2	3	*i*-PrOH	CuI	0.2	89	
15	2	2	*i*-PrOH	CuI	0.05	13	–
16	2	2	*i*-PrOH	CuI	0.1	31	–
17	2	2	*i*-PrOH	CuI	1	79	**1a:2a** = 1:0.05

[a] *Reaction conditions:* **3a** (2.0 mmol, 1 equiv.), K_2CO_3 (2 equiv.), solvent (7 mL).



1 3 4 5

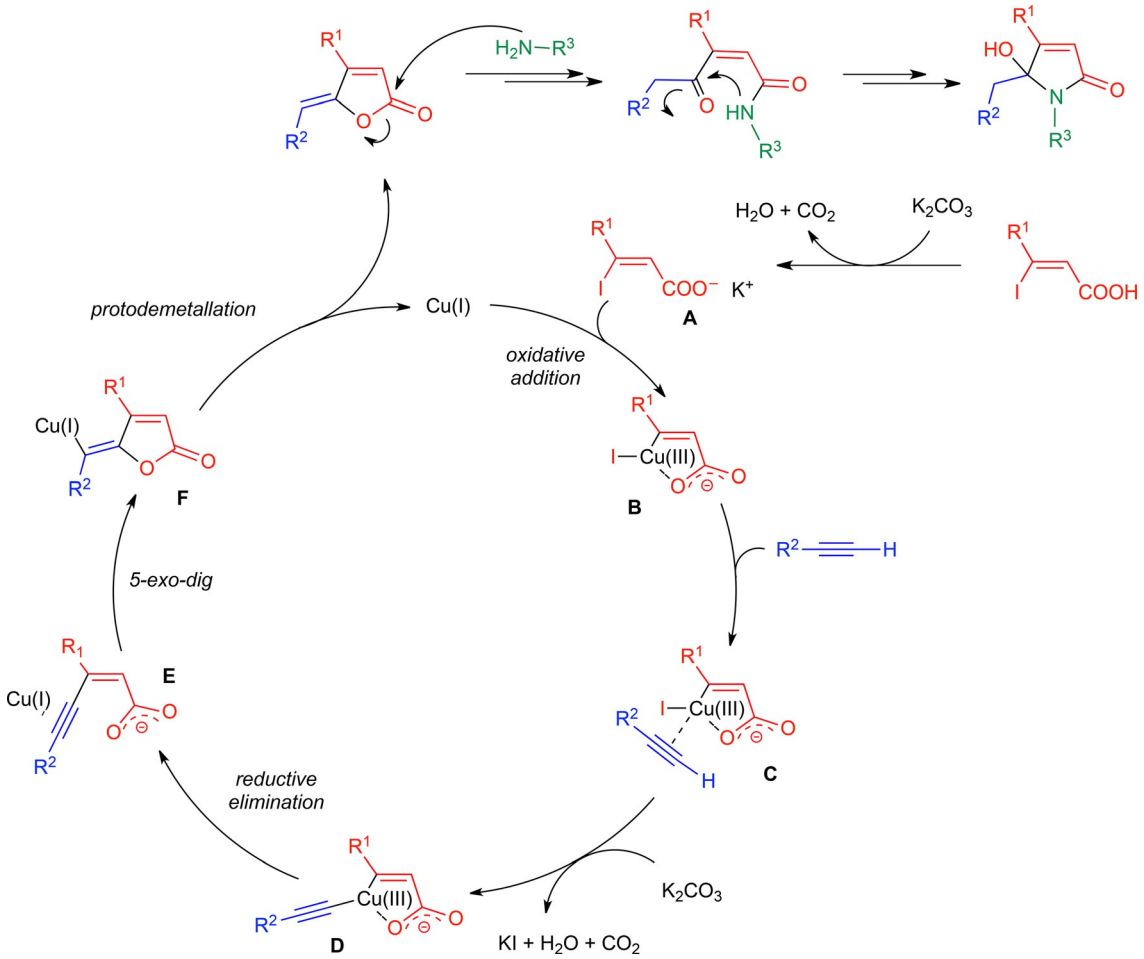
Scheme 1. Retrosynthetic plan for the synthesis of γ-hydroxylactam.

First, (*Z*)-3-iodobutenoic acid **3a**,[8] phenylacetylene **4a** and butylamine **5a** were chosen as benchmark substrates to find the optimised catalytic system (Table 1). The reaction was initially performed by using the catalytic system of our developed copper-catalysed tandem coupling heterocyclisation[6] (1 equiv. of **3a**, 1.3 equiv. of **4a**, 20 mol% of CuI in DMF at 50 °C) in the presence of 2 equiv. of **5a** (entry 1).

After stirring for 12 h, we were delighted to observe the formation of hydroxylactam **1a** in a moderate isolated yield of 31%. It is worthy of note that the analysis of the crude mixture also revealed the presence of butylformamide **6a** in a 0.4/1 mixture with **1a**. However, this first result validated the sequence during which one C–C bond, one C–O bond and two C–N bonds were created in a one-pot fashion.

In order to increase the yield of **1a**, we have screened several copper salts [CuOAc, $Cu(OAc)_2$, $Cu(OTf_2)$, $Cu(OAc)_2 \cdot H_2O$, entries 2–5]. Unfortunately, not only the yields of isolated **1a** were not improved significantly but also we observed an increasing amount of transamidification product **6a** (up to 60%). In order to eliminate the formation of the undesired formamide by-product, we turned our attention to the nature of the solvent (entries 6–11) and best results in terms of yield (57%) were observed with isopropyl alcohol (entry 8). The amounts of alkyne **4a** (1.3 and 2 equiv.) and primary amine **5a** (1.1, 2 and 3 equiv.) were then investigated (entries 11–14). The best compromise between yield and amount of starting material was reached when 2 equiv. of both alkyne and primary amine were used (84%, entry 13). Finally, reducing the catalyst loading (entries 15 and 16) afforded **1a** in lower yield and the use of a stoichiometric amount of copper iodide did not affect the efficiency of the MCR (entry 17). However, less than 5% of γ-alkylidenebutenolide **2a** was still present in the crude mixture. It was also interesting to note that the selectivity of this sequence for which neither 1,4 or 1,6 Michael addition products nor enamine products (resulting from the cross coupling of vinyl iodide and amine) were observed.

For the MCR process, two mechanistic scenarios could be considered. The first one could involve a Sonogashira-type coupling (without palladium) and the second one a Castro–Stephens-type coupling. However, preliminary experiments run in our group have shown that when the reaction of the formation of the lactone **2** is conducted with one equivalent of alkynyl

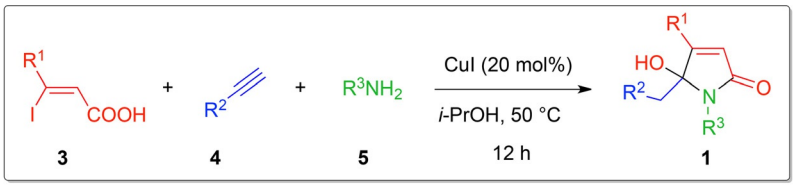


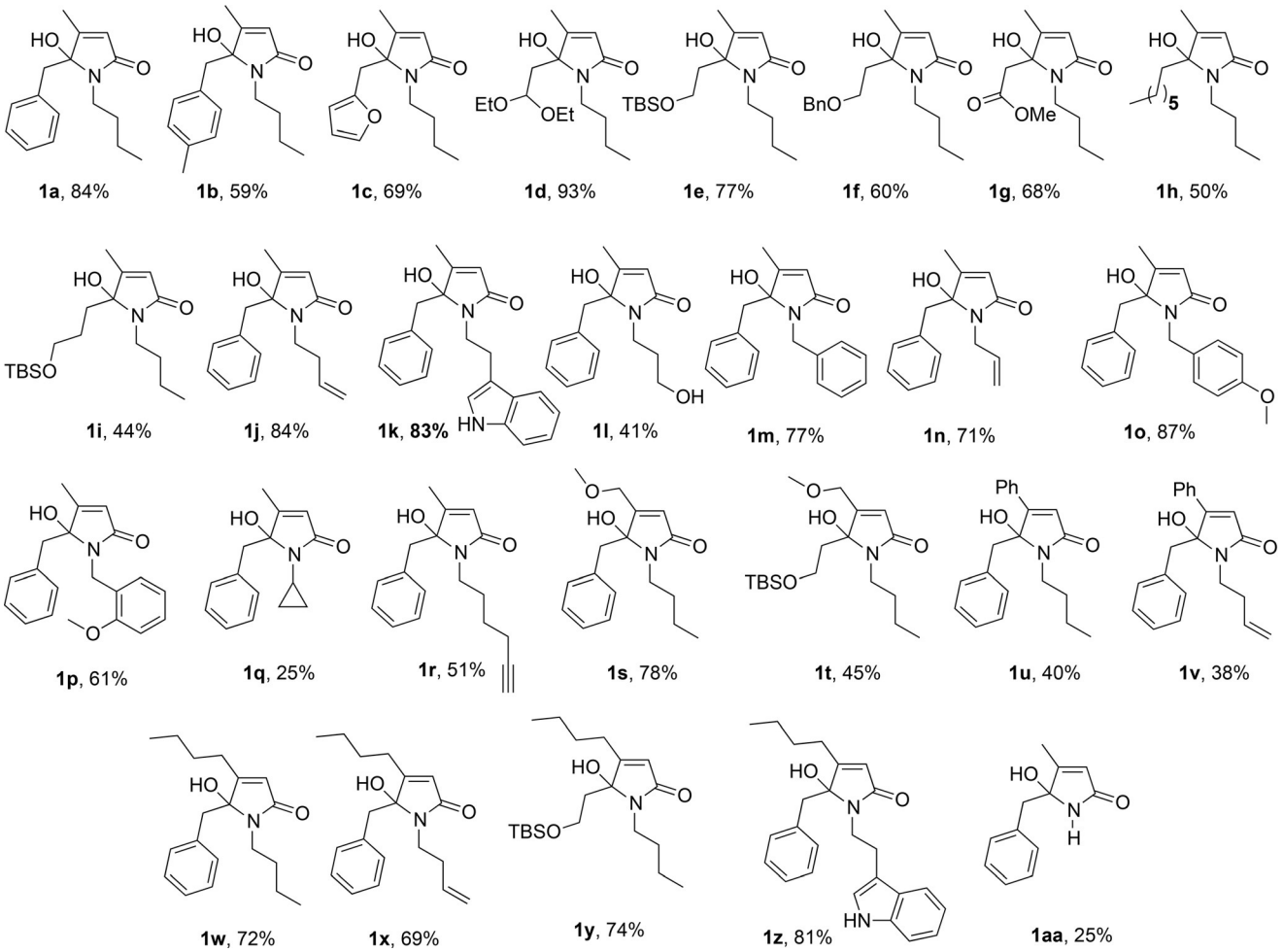
Scheme 2. Plausible mechanism.

copper reagent, no lactone **2a** was formed in the crude mixture. This result led us to disregard the Castro–Stephens-type coupling. Therefore, a plausible mechanism is depicted in Scheme 2. The first step is likely to be an oxidative addition of the copper(I) into the C–I bond of **A** to give copper(III) intermediate **B**. The next steps would involve copper coordination to the triple bond of **4**, followed by an oxidative addition to furnish **D**. Reductive elimination then 5-*exo-dig* cyclisation assisted by copper(I) would lead to vinyl copper intermediate **F** which would give lactone **2** *via* protodemetallation. Finally, addition of the primary amine **5** onto the lactone would furnish the desired hydroxylactams **1**. This last step was confirmed by treating **2a** with **5a** in *i*-PrOH at 50 °C for 12 h with or without K_2CO_3 (2 equiv.) to give **1a** in 77 and 86% yields, respectively.

With the optimised protocol in hand, the scope of this MCR process was then assessed through the variation of (*Z*)-β-iodo-α,β-unsaturated acids **3**, terminal alkynes **4** and the primary amines **5** (Scheme 3). The reaction was found to be general, and diversely substituted and functionalised γ-hydrolactams **1** could be straightforwardly prepared in good yields (up to 93%), demonstrating the versatility of this new MCR process. As a general trend, the methodology is tolerant to a large variety of alkynes with electron-donating and electron-withdrawing groups (for example, alkynes bearing aromatic, heteroaromatic, protected propargyl alcohol, acetal and ester groups, products **1a–g**). When non-activated alkynes possessing a longer alkyl chain were used, such as oct-1-yne or TBS-protected but-4-ynol, the yields of the desired products **1h** and **1i** were lower (50% and 44%, respectively). This decrease of yield was due to a 6-*endo* cyclisation of enynoic acid intermediates affording the corresponding pyran-2-ones (10% and 13%, respectively) which were found to be inert under these conditions.[9]

While nucleophilic amines such as homoallylamine, tryptamine and 3-aminopropanol furnished the desired products (**1j–l**) in fair to good yields, the use of less nucleophilic primary amines required modified conditions. Indeed, 3 equiv. of benzylamine, *para*-methoxybenzylamine or allylamine were necessary to provide the corresponding γ-hydrolactams **1m** (77%),

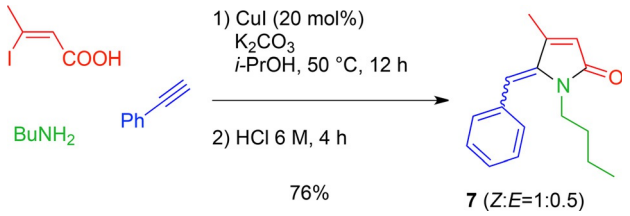




Scheme 3. Scope of the multicomponent reaction.

1n (71%) and **1o** (87%) with satisfactory yields. Pleasingly, compared to benzylamine, only 2 equiv. of *ortho*-methoxybenzylamine (more nucleophilic amine) could be used to obtain **1p** in 61% yield without detecting the presence of the intermediate γ-alkylidenebutenolide. The limitation of the reaction was obtained with deactivated amines such as aromatic amines (for example, aniline). We have also performed the reaction with hex-5-ynylamine. Interestingly, the MCR was totally chemoselective and only the hydroxylactam **1r** was obtained in 51%, demonstrating the better reactivity of terminal aromatic alkynes compared to alkylalkynes. The reaction was also conducted with NH_3 (2 M in *i*-PrOH) and with NH_4OAc. Best results were obtained with NH_3 but it is worthy of note that 10 equiv. of NH_3 and a time reaction of 72 h were necessary to obtain the desired hydroxylactam **1aa** (without the presence of **2a**) in 25% yield. Further investigations by varying the substituent on the β position of **3** were also undertaken. In all these cases, the MCR process afforded γ-hydroxylactams **1s–z** in acceptable to good yields, giving the proposed method a general and straightforward character.

Our next purpose was to investigate the reactivity of 5-hydroxy-1*H*-pyrrol-2(5*H*)-ones **1** as an equivalent of the *N*-acyliminium ion for the direct synthesis of γ-alkylidenebutyrolactams **7** (Scheme 4). The idea was



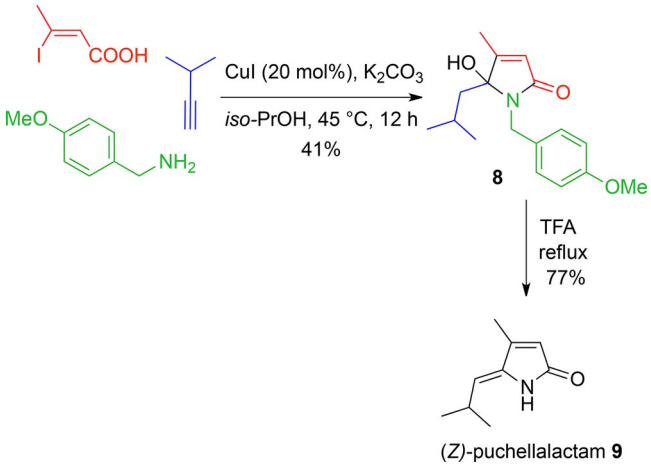
Scheme 4. One-pot sequence.

to develop a cascade in which four individual steps are combined in a synthetic sequence (enyne coupling/heterocyclization/γ-hydroxylactam formation/dehydration).

From a practical point of view, quenching the reaction by an aqueous HCl solution (6 M), in place of a saturated aqueous NH_4Cl solution and stirring the reaction mixture for 4 h more at 50 °C afforded the desired γ-alkylidenebutyrolatam **7** in 76% yield as a (*Z*/*E* = 1/0.5) mixture of diastereomers. One more time, these results demonstrated the power and the versatility of this copper-catalysed formation of heterocyclic moieties.

Finally, to illustrate this powerful MCR process, we have next realized the total synthesis of pulchellalactam, a CD45 protein tyrosine phosphatase inhibitor (Scheme 5).[10] When (*Z*)-3-iodobutenoic acid **3a** (1 equiv.), *para*-methoxybenzylamine (3 equiv.) and volatile 3-methylbutyne (4 equiv.) were exposed to a catalytic amount of copper, the desired hydroxylactam **8** was obtained in 41% yield.[11] The dehydration and the deprotection of amide steps were then performed in one-pot using trifluoroacetic acid (TFA) at reflux.[12] The reaction afforded a 9:1 separable mixture of (*Z*)- and (*E*)-puchellalactam **9**. The (*Z*)-natural product was isolated in 77% yield.

In summary, a practical and general copper-catalysed multicomponent reaction of readily accessible alkynes, primary amines and (*Z*)-3-iodoacrylic acids has been developed to furnish the corresponding 5-hydroxy-1*H*-pyrrol-2(5*H*)-ones in good yields. This sequence is based on a cascade in which three individual steps are combined in a synthetic process (eneyne coupling/heterocyclization/γ-hydroxylactam formation). This methodology can be extended for the direct synthesis of γ-alkylidenebutyrolactams in a one-pot cascade.



Scheme 5. Total synthesis of pulchellalactam.

Experimental Section

General Procedure for the Synthesis of 1

The (*Z*)-3-substituted 3-iodoprop-2-enoic acid derivative **3** (2.0 mmol, 1 equiv.) was dissolved in *i*-PrOH (7 mL) in an oven-dried-Schlenck tube. K_2CO_3 (553 mg, 4.0 mmol, 2 equiv.) was then added to the solution and the suspension was stirred for 10 min under argon. The mixture was then degassed at −78 °C for 2 × 10 min and the reaction vessel backfilled with argon. After warming to room temperature, terminal alkyne **4** (4.0 mmol, 2 equiv.), primary amine **5** (4.0 mmol, 2 equiv.) and finally CuI (76 mg, 0.4 mmol, 0.2 equiv.) were added. The mixture was then rapidly degassed and the vessels backfilled with argon. The sealed Schlenck tube was placed in the preheated oil bath (50 °C) and the mixture was stirred overnight. The reaction mixture was cooled to 0 °C, then quenched by the addition of an aqueous saturated solution of NH_4Cl and stirred for further 15 min. The crude mixture was filtered through a pad of Celite®. The aqueous phase was extracted with ethyl acetate (3 × 40 mL) and the combined organic layers were washed with brine (2 × 40 mL), dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was then purified by flash chromatography on silica gel.

Acknowledgements

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