JOC The Journal of Organic Chemistry

Note

Copper(II) triflate as a reusable catalyst for the synthesis of trans-4,5-diamino-cyclopent-2-enones in water

Rafael F. A. Gomes, Nuno R. Esteves, Jaime A. S. Coelho, and Carlos A. M. Afonso

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.7b02931 • Publication Date (Web): 05 Feb 2018

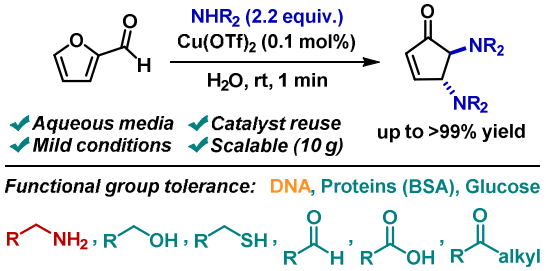
ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

Copper(II) triflate as a reusable catalyst for the synthesis of *trans*-4,5-diamino-cyclopent-2-enones in water

Rafael F. A. Gomes, Nuno R. Esteves, Jaime A. S. Coelho,* Carlos A. M. Afonso*

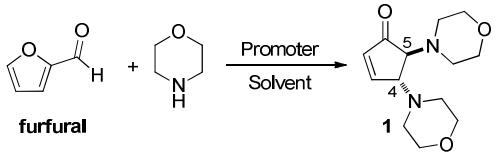
Research Institute for Medicines (iMed.ULisboa), Faculty of Pharmacy, Universidade de Lisboa, Av. Prof. Gama Pinto, 1649-003, Lisboa, Portugal



ABSTRACT: *Trans*-4,5-diamino-cyclopent-2-enones (CP) are usually prepared by Lewis acid-catalyzed condensation of furfural and a secondary amine in an organic solvent. The reaction proceeds through the formation of a Stenhouse salt (SS) intermediate followed by an electrocyclization reaction to afford the desired CP. Herein, we described the use of $Cu(OTf)_2$ as a very efficient catalyst for the synthesis of CP in water at room temperature. Furthermore, the mild reaction conditions, catalyst reusability and outstanding functional group tolerance suggests that this CP platform can be further used in chemical biology.

The ever increasing population growth, and the concomitant industrial development have led to an increase demand for chemicals and energy, which is leading to a depletion of the oil reservoirs.[1] In this context, new sustainable sources for fuels and bulk chemicals are of the highest interest, and biomass is the most attractive alternative.[2] Furfural is easily obtained from xylose and is included in the U.S. Department of Energy top 10+4 list of biobased materials.[3] The selective transformation of furfural to *trans*-4,5-diamino-cyclopent-2-enones promoted by dysprosium in dry acetonitrile was reported by Batey and co-workers in 2007.[4] The product is formed through a Nazarov type electrocyclization of a Stenhouse salt intermediate.[5] In addition, the same group also reported the total synthesis of natural product Agelastatin A from *trans*-4,5-bis(diallylamino)-cyclopent-2-enone.[6] Driven by the pioneering work of Batey in this field, several alternative reaction conditions for the selective synthesis of *trans*-4,5-diamino-cyclopent-2-enones were developed (Scheme 1), such as the use of ionic liquid 1-methylimidazolium tetrafluoroborate,[7] tosylamine as a metal free procedure,[8] aluminium(III) chloride,[9] Dy^{III}/Ni^{III} heteronuclear clusters,[10,11] and erbium(III) chloride in ethyl lactate as a more sustainable alternative[12]. In addition, our team reported the use of erbium(III) chloride immobilized on silica as a reusable catalyst for the same transformation.[13] During the conclusion of the current work, Nardi and co-workers reported the preparation of *trans*-4,5-diamino-cyclopent-2-enones in water under microwave irradiation (60 °C, 5 min).[14]

Scheme 1. Selected methodologies for the synthesis of *trans*-4,5-dimorpholino-cyclopent-2-enone (**1**).



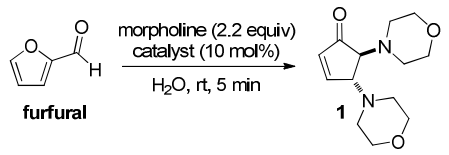
Previous work	**Promoter, solvent**	**yield of 1 (time)**
(Batey, **2007**)	$Dy(OTf)_3$, acetonitrile	quant. (16 h)
(Venkateswarlu, **2009**)	[HMim][BF_4]	98% (5 min)
(Procopio, **2013**)	$ErCl_3{\bullet}6H_2O$, ethyl lactate	99% (30 min)
(Wang, **2013**)	$TsNH_2$ (80ºC), acetonitrile	86% (5 h)
(Afonso, **2013**)	$AlCl_3$, acetonitrile	68% (5 h)
(Kostakis, **2015**, **2016**)	Dy^{III}/Ni^{II} cluster, acetonitrile	quant. (16 h)
(Afonso, **2017**)	$ErCl_3{\bullet}6H_2O$ on silica, *n*-butanol	66% (30 min)
(Nardi, **2017**)	MW (60ºC), **water**	quant. (5 min)
This work	$Cu(OTf)_2$, **water**	quant. (1 min)

Recently, we have been interested in the preparation of *trans*-4,5-diamino-cyclopent-2-enones in aqueous media both for the appealing environmentally friendly characteristics, and for the potential application of the cyclopentenone platform to chemical biology. Conjugation of small molecules with biomolecules is a very challenging field that has attracted the interest of

several research groups.[15,16] In this context, it is important to develop new strategies for chemo and site selective introduction of non-natural functionalities in biomolecules because it allows the difficult process of introducing non-natural amino acids on the protein skeleton to be avoided.[17–19] Such reactions have to meet the following requirements: 1) be compatible with aqueous media, 2) have fast kinetics and complete conversion, 3) be orthogonal. We envisioned that the selective formation of cyclopentenones bearing secondary amines, not often found in biological media, could be an easy and cheap procedure to insert both an external secondary amine and an enone that can be further functionalized.

The reaction of furfural with morpholine in water resulted in the formation of traces amount of the desired product **1** after 5 minutes (Table 1, entry 1). Based on that, we started this study by testing several Lewis acids catalysts under the same reaction conditions. To our delight, 10 mol% of $Dy(OTf)_3$ afforded **1** in 53% yield (Table 1, entry 2). Other Lewis acids, such as $Sc(OTf)_3$, $GdCl_3.6H_2O$, $ErCl_3$, $ZnCl_2$ or $AlCl_3$, were not able to catalyse the reaction (up to 42% yield, Table 1, entry 3). Remarkably, $Cu(OTf)_2$ afforded **1** in outstanding isolated yield (quantitative, Table 1, entry 4). It is noteworthy that full conversion was observed in most cases. Remarkably, the use of 10 mol% of $Cu(OTf)_2$ results in full conversion of the starting materials in less than 1 min. Next, we investigated the influence of the copper ligand by evaluating several different copper salts under the same reaction conditions. The tested salts afforded up to 50% yield of **1** in opposite to an outstanding yield obtained with the trifluoromethanesulfonate salt (Table 1, entry 5). Furthermore, the Brønsted acids *p*-toluenosulfonic acid and triflic acid afforded low yield of **1** (25% and 32% yield, respectively, Table 1, entry 6). Further reduction of $Cu(OTf)_2$ loading to 1 mol% did not affect the performance and **1** was obtained in excellent yield after 10 minutes reaction time (quantitative, Table 1, entry 7). In addition, the combined scale up to 10 g of furfural and reduction of catalyst load to 0.1 mol% afforded the product in 93% yield after 8h as a 6.7:1 mixture of **1** and the thermodynamically more stable regioisomer 2,4-dimorpholino-cyclopent-2-enone (Table 1, entry 8).[4] Full conversion to the 2,4 regioisomer was observed after 24h. Finally, similar efficiency of the catalyst was observed in an organic solvent (acetonitrile, quantitative yield of **1**, Table 1, entry 9).

Table 1. Optimization of the reaction conditions for the synthesis of *trans*-4,5-dimorpholino-cyclopent-2-enone[a]

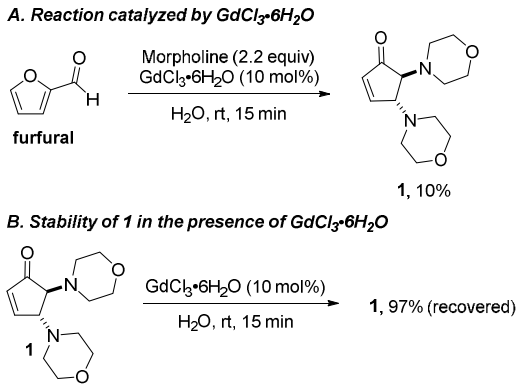


Entry	Catalyst	Yield (%)[b]
1	none	traces
2	$Dy(OTf)_3$ (10 mol %)	53
3	Lewis acid[c] (10 mol %)	up to 42
4	$Cu(OTf)_2$ (10 mol %)	quant.[d] (quant.)[e]
5	CuX[c] (10 mol %)	up to 46
6	Brønsted acid (10 mol %)	up to 32
7	$Cu(OTf)_2$ (1 mol %)	quant. (10 min)
8[f]	$Cu(OTf)_2$ (0.1 mol %)	93[g] (8 h)
9[h]	$Cu(OTf)_2$ (10 mol %)	quant.

[a] Reaction conditions: furfural (0.2 mmol), morpholine (2.2 equiv), catalyst (10 mol %), H2O (0.2 mL), rt, 5 min. [b] Isolated yield. [c] See SI for complete list. [d] The reaction time is 1 minute. [e] The reaction concentration is 0.1 M (2 mL of H2O). [f] Reaction performed using 10 gram of furfural. The reaction was stirred for 1h in an ice bath, after which was allowed to warm until room temperature. [g] The product was isolated as a 6.7:1 mixture of **1** and the corresponding 2,4-isomer. [h] The reaction solvent is acetonitrile (2 mL).

To further understand the low yield of **1** in the reaction catalysed by other Lewis acids, we first note that full conversion was obtained in all cases. For example, the reaction of furfural with morpholine in water catalysed by GdCl3 afforded the desired product in 10% yield (Scheme 2A). A negligible decomposition (Scheme 2B) of the product in the presence of GdCl3 in water point towards an unselective catalysis, in which GdCl3, as well as the other Lewis acids tested, promote the undesired side reactions of furfural or intermediates.

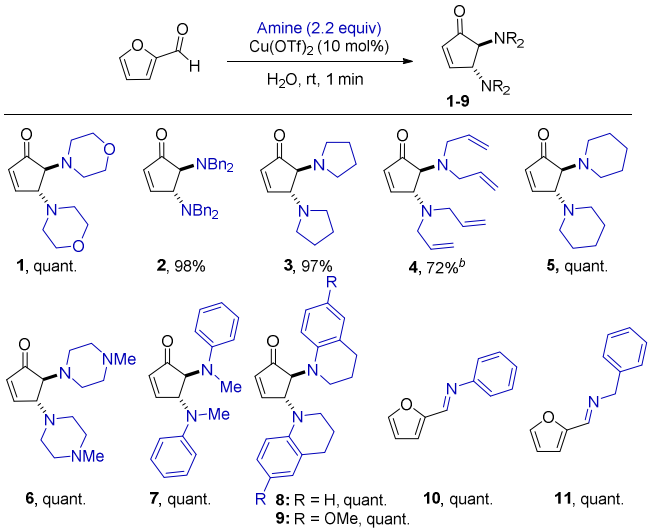
Scheme 2. Stability study of cyclopentenone **1** in the presence of LA in aqueous medium.



With the optimized conditions in hands, the amine scope was evaluated (Scheme 3). Several secondary amines, including cyclic amines and anilines were well tolerated and afforded the corresponding product in excellent yield (up to >99% yield) in a very short reaction time (1 minute). Diallylamine also reacted with furfural to give the

corresponding product **4** in 72% yield (80% conversion) after 4 h reaction. When pyrrolidine or *N*-methyl-piperazine were employed, if the mixture was allowed to react for longer periods of time isomerization to the more stable 2,4-diamino-cyclopent-2-enones was observed. The more challenging primary amines[4] such as aniline and benzylamine did not offered the desired product and the intermediate imine was isolated in these cases.

Scheme 3. Reaction scope for the formation of *trans*-4,5-diamino-cyclopent-2-enones under the optimized conditions



[a] Reaction conditions: furfural (1.0 mmol), amine (2.2 equiv), $Cu(OTf)_2$ (10 mol %), H_2O (1 mL), rt, 1 min. The average yield of 3 experiments are shown [b] Reaction time is 4 h.

In general, the synthesis of cyclopentenones was a very efficient reaction under the conditions reported herein and water was the only by-product generated. Based on that, we envisioned that the ability to easily extract the product from the aqueous reaction medium using an organic solvent (diethyl ether) would allow reuse of catalyst. Remarkably, $Cu(OTf)_2$ was reused 4 times without considerable loss of catalytic activity. Furthermore, the yield of **1** remained greater than 50% after 4 times. The results obtained during 7 cycles are summarized in Figure 1.

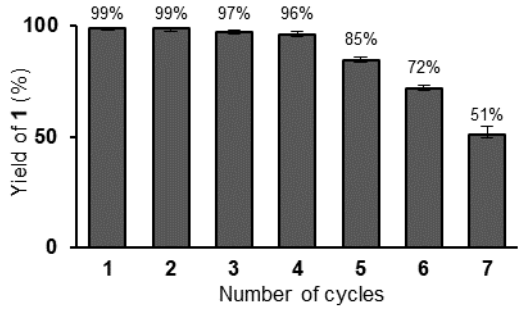
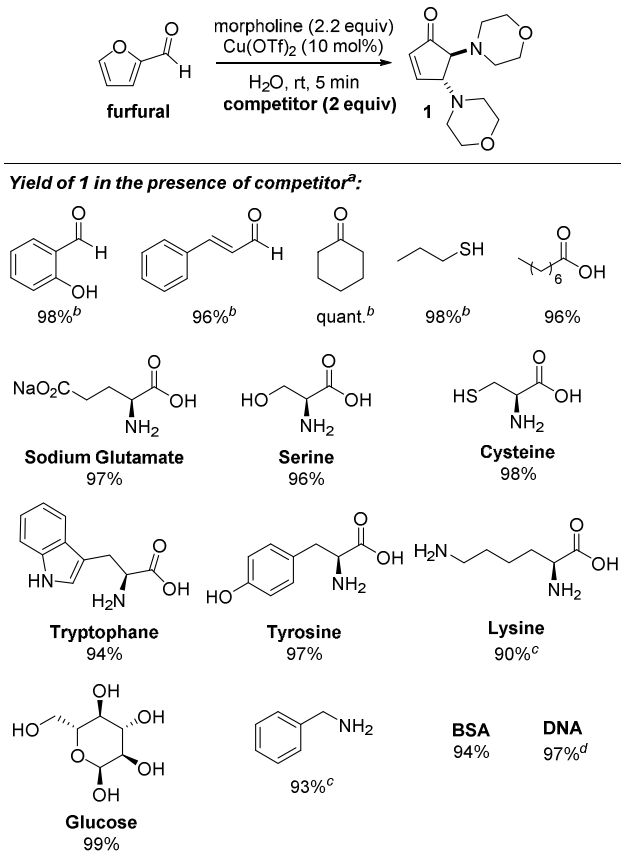


Figure 1. Catalyst reuse on the synthesis of **1** in aqueous media. Reaction conditions: furfural (1.0 mmol), morpholine (2.2 equiv), $Cu(OTf)_2$ (10 mol %), H_2O (1 mL), rt, 1 min. Isolated yield by diethyl ether extraction. All the experiments were performed in triplicate.

We next sought to study the functional group tolerance of the reaction by performing the $Cu(OTf)_2$-catalyzed reaction of furfural with morpholine in the presence of selected molecules bearing different functional groups (Scheme 4). Both aldehydes and ketones can potentially inhibit the reaction by reaction of the amine substrate with these electrophiles. Surprisingly, the yield of **1** was not significantly affected in the presence of salicylaldehyde, cinnamaldehyde or cyclohexenone. Thiols, commonly found as detoxification platforms due to their nucleophilic and antioxidant character, were also tested. In this case the concern was the known ability of thiols to undergo 1,4-addition, however, **1** was isolated in 98% yield under our reaction conditions. Carboxylic acids, commonly found in the C-terminal region of proteins and in several biomolecules were also tested because of their potential ability to protonate amines. Gladly, the reaction proceeded smoothly in the presence of 2 equivalents of octanoic acid and **1** was isolated in 96%. Primary amines, frequently found in proteins (e.g. as lysine regions), and one of the most used sites for bioconjugation, were of great concern because of the potential competition with the secondary amine substrate. Furthermore, the reaction with primary amines give the corresponding imine in nearly quantitative yield as observed in the amine substrate scope study. In fact, the $Cu(OTf)_2$-catalyzed reaction of furfural with morpholine in the presence of 2 equivalents of benzylamine offered the imine when performed in acetonitrile (result not shown). However, the use 4.4 equivalents of morpholine and water as the solvent allowed the isolation of the desired product **1** in very good yield (93% yield, Scheme 4). Similarly, the reaction in the presence of lysine required an excess of morpholine in order to achieve very good yield of **1**. Several other amino acids such as tryptophan, serine, cysteine, sodium glutamate and tyrosine were tested with no significant inhibition of the reaction. In addition, the presence of glucose in the reaction medium was also well tolerated with no decrease in yield or apparent reaction rate. Finally, the reaction efficiency was also studied in the presence of selected macromolecules. The presence of bovine serum albumin (BSA), chosen as a model protein, did not affected the reaction yield, affording 94% of **1** in the presence of 200% w/w of BSA (relative to furfural). However, we observed a decrease to 82% yield of **1** (100% yield based on recovered furfural, result not shown) in the presence of 200% w/w of DNA from salmon. Remarkably, extension of the reaction time to 15 minutes afforded the product in 97% yield. Based on that we propose that the apparent decrease of the reaction rate is due to the trapping of the catalyst by the DNA rather than undesired reactions of the morpholine. No other products were identified during the competition assays.

Scheme 4. Cu(OTf)2-catalyzed reaction of furfural with morpholine in the presence of an external additive.



[a] The values correspond to the isolated yield of **1**. [b] Yield determined by ^{1}H NMR yield after extraction. [c] Reaction performed with 4.4 equivalents of morpholine. [d] Reaction time is 15 minutes.

In conclusion, we described a fast methodology for the synthesis of *trans*-4,5-diamino-cyclopent-2-enones (CP) in water at room temperature using $Cu(OTf)_2$ as catalyst. This protocol is distinguished by its operational simplicity, mild reaction conditions, great efficiency, high tolerance to the presence of external molecules with several functional-groups, and amenability to gram-scale synthesis. We anticipate that these characteristics will allow for further applications in bioorthogonal transformations.

EXPERIMENTAL SECTION

General Remarks

All solvents were distilled prior use. Furfural was distilled and stored at 4°C. Unless otherwise stated, all reagents were used as received from commercial suppliers. Reaction progress was monitored by thin layer chromatography (TLC) performed on aluminium plates coated with silica gel F254 with 0.2 mm thickness. ^{1}H and ^{13}C NMR spectra were acquired on Bruker MX300 spectrometer.

General procedure for the synthesis of *trans*-4,5-dimorpholino-cyclopent-2-enone 1 in water

To a solution of a selected catalyst (10 mol%) in water (0.2 mL) was added morpholine (40 µL, 0.45 mmol, 2.2 equiv) and furfural (20 mg, 0.2 mmol). The reaction was allowed to stir vigorously at room temperature for 5 minutes. Then the reaction mixture was diluted with water (0.8 mL) and extracted with diethyl ether (3 × 1 mL). The organic phase was dried with $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude mixture was analysed by ^{1}H-NMR.

Stability of *trans*-4,5-dimorpholino-cyclopent-2-enone 1

To a solution of $GdCl_3 \cdot 6H_2O$ (7 mg, 0.019 mmol, 10 mol%) in water (0.1 mL) was added an aqueous solution of *trans*-4,5-dimorpholino-cyclopent-2-enone (50 mg, 0.2 mmol in 0.1 mL water). The mixture was allowed to stir vigorously at room temperature for 15 minutes. The solution was diluted with water (0.8 mL) and extracted with diethyl ether (3 × 1 mL). The solvent was evaporated under reduced pressure and the crude mixture was analysed by ^{1}H-NMR.

General procedure for the catalyst reuse in the preparation of *trans*-4,5-dimorpholino-cyclopent-2-enone 1

To a solution of Cu(OTf)2 (40 mg, 10 mol%) in water (1 mL) was added morpholine (225 µL, 2.29 mmol, 2.2 equiv) and furfural (100 mg, 1.04 mmol). The reaction was allowed to stir vigorously at room temperature for 1 minutes. Diethyl ether was added to the reaction mixture (2 mL) and after 1 min of vigorous stirring the phases were separated. The process was repeated one more time and the collected organic phases were dried with $MgSO_4$ and evaporated under reduced pressure to yield the pure *trans*-4,5-dimorpholino-cyclopent-2-enone. The remaining aqueous layer was loaded with more morpholine (200 µL, 2.29 mmol, 2.2 equiv.) and furfural (100 mg, 1.04 mmol) and the process repeated for 7 cycles.

General procedure for the preparation of *trans*-4,5-dimorpholino-cyclopent-2-enone in the presence of small molecules competitors

To a solution of Cu(OTf)2 (8 mg, 10 mol%) in water (0.2 mL) was added the corresponding competitor (2 equiv), morpholine (40 µL, 0.45 mmol, 2.2 equiv) and furfural (20 mg, 0.2 mmol). The reaction was allowed to stir vigorously at room temperature for 5 minutes. Then the reaction mixture was diluted with water (0.8 mL) and extracted with diethyl ether (3 × 1 mL). The organic phase was dried with $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude mixture was analysed by ^{1}H-NMR.

Procedure for the preparation of *trans*-4,5-dimorpholino-cyclopent-2-enone in the presence of BSA

To a solution of Cu(OTf)2 (8 mg, 10 mol%) in water (0.2 mL) was added BSA (40 mg), morpholine (40 µL, 0.45 mmol, 2.2 equiv) and furfural (20 mg, 0.2 mmol). The reaction was allowed to stir vigorously at room temperature for 5 minutes. Then the reaction mixture was diluted with cold acetone (2 mL) and left at -20°C for 1 h. The sample was centrifuged and the supernatant was evaporated under reduced pressure. Water (1 mL) was added to the crude mixture and the reaction was extracted with diethyl ether (3 × 2 mL). The

collected organic phases were dried with $MgSO_4$ and the solvent was evaporated under reduced pressure to afford the final product in 94% yield.

Procedure for the preparation of *trans*-4,5-dimorpholino-cyclopent-2-enone in the presence of DNA

To a solution of Cu(OTf)2 (8 mg, 10 mol%) in water (0.2 mL) was added DNA (40 mg), morpholine (40 µL, 0.45 mmol, 2.2 equiv) and furfural (20 mg, 0.2 mmol). The reaction mixture was allowed to stir vigorously at room temperature for 5 minutes. Then the reaction mixture was diluted with cold ethanol (2 mL) and left at -20°C for 1 h. The sample was centrifugated to remove the precipitated DNA and the supernatant was evaporated under reduced pressure. Water (1 mL) was added to the crude mixture and the reaction was extracted with diethyl ether (3 × 2 mL). The combined organic phases were dried with $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude mixture was analysed by ^{1}H-NMR.

Procedure for the preparation of *trans*-4,5-dimorpholino-cyclopent-2-enone in a 10-gram scale

To a round bottom flask loaded with a Cu(OTf)2 (4 mg, 0.1 mol%) and water (100 mL) were added morpholine (20 mL, 229 mmol, 2.2 equiv) and furfural (10 g, 104 mmol) in an ice bath. The reaction was allowed to stir vigorously for 1 h. Then the ice bath was removed and the reaction was allowed to stir at room temperature. Aliquots of 0.1 mL were taken at 3 h and 8 h, extracted with CDCl3 and analysed by 1H-NMR. After 8 h, 50 mL of the homogenous reaction mixture was collected from the flask, diluted with water (200 mL) and extracted with MTBE (3 × 200 mL). The combined organic phases were dried with $MgSO_4$ and the solvent was evaporated under reduced pressure to give a crude product (12.2 g, 93%) as a 6.7:1 mixture of isomers **1** and 2,4-dimorpholino-cyclopent-2-enone. The remaining 50 mL of the reaction mixture were stirred for an additional 16 h after which similar work-up protocol was performed to yield the regioisomer 2,4-dimorpholino-cyclopent-2-enone in 87% yield (11.4 g).

General procedure for the preparation of *trans*-4,5-diamino-cyclopent-2-enones

To a solution of Cu(OTf)2 (40 mg, 10 mol%) in water (1 mL) was added amine (2.29 mmol, 2.2 equiv.) and furfural (100 mg, 1.04 mmol). The reaction was allowed to stir vigorously at room temperature for 1 minutes. Then the reaction mixture was diluted with water (9 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic phases were dried with $MgSO_4$ and the solvent was evaporated under reduced pressure to yield the pure cyclopent-2-enones as shown by ^{1}H-NMR analysis.

trans-4,5-bismorpholino-cyclopent-2-enone **(1)** The product was isolated in quantitative yield (262 mg) as a yellow solid. The spectral data is in agreement with the literature.[4]

trans-4,5-bis(dibenzylamine)-cyclopent-2-enone **(2)** The product was isolated in 98% yield (482 mg) as a yellow solid. The spectral data is in agreement with the literature. [4]

trans-4,5-bispyrrolidine-cyclopent-2-enone **(3)** The product was isolated in 97% yield (222 mg) as a yellow oil. The spectral data is in agreement with the literature.[7]

trans-4,5-bis(diallylamine)-cyclopent-2-enone **(4)** The product was isolated in 72% yield (204 mg) as a brown oil. The spectral data is in agreement with the literature. [4]

trans-4,5-bispiperidino-cyclopent-2-enone **(5)** The product was isolated in quantitative yield (258 mg) as a yellow oil. The spectral data is in agreement with the literature. [7]

trans-4,5-bis(N-methylpiperazine)-cyclopent-2-enone **(6)** The product was isolated in quantitative yield (290 mg) as an orange oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 6.2, 2.2 Hz, 1H) 6.22 (dd, *J* = 6.2, 1.8 Hz, 1H) 3.89 (q, *J* = 2.1 Hz, 1H) 3.35 (d, *J* = 3.0 Hz, 1H) 2.76-2.79 (m, 2H) 2.61-2.69 (m, 6H) 2.47 (broad s, 8H) 2.29 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 46.1, 49.2, 49.4, 55.4, 65.7, 67.9, 135.3, 161.4, 206.0. MS (ESI-MS) *m/z* calcd for $C_{15}H_{26}N_4O$ $[M + H]^+$ 279.2179, found 279.2177.

trans-4,5-bis(N-methylaniline)-cyclopent-2-enone **(7)** The product was isolated in quantitative yield (304 mg) as a red oil. The spectral data is in agreement with the literature. [4]

trans-4,5-bis(dihydroquinoline)-cyclopent-2-enone **(8)** The product was isolated in quantitative yield (358mg) as a yellow solid. The spectral data is in agreement with the literature. [4]

trans-4,5-bis(6-methoxy-dihydroquinoline)cyclopent-2-enone **(9)** The product was isolated in quantitative yield (421mg) as a orange oil ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 6.3, 2.0 Hz, 1H) 6.57-6.60 (m, 2H) 6.42-6.48 (m, 4H) 6.00 (d, *J* =8.8 Hz, 1H) 5.25 (m, 1H) 4.24 (d, *J* = 3.6 Hz, 1H) 3.7 (s, 6H) 3.08-3.26 (m, 4H) 2.65-2.77 (m, 4H) 1.87-1.97 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.6, 22.8, 27.3, 28.3, 42.4, 45.6, 55.7, 60.6, 68.8, 112.0, 112.2, 112.4, 113.2, 115.5, 115.7, 125.2, 125.3, 134.3, 138.0, 138.8, 151.6, 151.8, 162.3, 202.8. MS (ESI-MS) *m/z* calcd for $C_{25}H_{29}N_2O_3$ $[M + H]^+$ 405.2173, found 405.2189.

1-(furan-2-yl)-N-phenylmethanimine **(10)** The product was isolated in quantitative yield (178 mg) and 93% purity as a brown oil. The spectral data is in agreement with the literature. [20]

N-benzyl-1-(furan-2-yl)methanimine **(11)** The product was isolated in quantitative yield (192 mg) as a brown oil. The spectral data is in agreement with the literature. [21]

ASSOCIATED CONTENT

Supporting Information.
^{1}H and ^{13}C NMR spectra for compounds **1-10**.
The supporting information is available free of charge via the Internet at http://pubs.acs.org."

AUTHOR INFORMATION

Corresponding Author

* E-mail: jaimeacoelho@ff.ulisboa.pt
* E-mail: carlosafonso@ff.ulisboa.pt

ACKNOWLEDGMENT

We thank the Fundação para a Ciência e Tecnologia (SFRH/BPD/100433/2014, PD/BD/128316/2017, PTDC/QEQ-QOR/3644/2014 and UID/DTP/04138/2013), COMPETE Programme (SAICTPAC/0019/2015) and European Research Area Net-work; ERANet LAC (ref. ELAC2014/BEE-0341) for financial support.

REFERENCES

(1) Gaurav, N.; Sivasankari, S.; Kiran, G.; Ninawe, A.; Selvin, J. *Renew. Sustain. Energy Rev.* **2017**, *73*, 205–214.
(2) Saxena, R. C.; Adhikari, D. K.; Goyal, H. B. *Renew. Sustain. Energy Rev.* **2009**, *13* (1), 167–178.
(3) Bozell, J. J.; Petersen, G. R. *Green Chem.* **2010**, *12* (4), 539.
(4) Li, S.-W.; Batey, R. A. *Chem. Commun.* **2007**, *8*, 3759–3761.
(5) Stenhouse, J. *Liebigs Ann* **1850**, *74*, 278.
(6) Duspara, P. A.; Batey, R. A. *Angew. Chem. Int. Ed.* **2013**, *52* (41), 10862–10866.
(7) Ramesh, D.; Reddy, T. S.; Narasimhulu, M.; Rajaram, S.; Suryakiran, N.; Mahesh, K. C.; Venkateswarlu, Y. *Chem. Lett.* **2009**, *38* (6), 586–587.
(8) Liu, J. Q.; Yu, J. J.; Zhu, M. Y.; Li, J.; Zheng, X. Z.; Wang, L. M. *Synthesis* **2013**, *45* (15), 2165–2170.
(9) Nunes, J. P. M.; Afonso, C. A. M.; Caddick, S. *RSC Adv.* **2013**, *3*, 14975–14978.
(10) Griffiths, K.; Gallop, C. W. D.; Abdul-Sada, A.; Vargas, A.; Navarro, O.; Kostakis, G. E. *Chem. Eur. J.* **2015**, *21* (17), 6358–6361.
(11) Griffiths, K.; Kumar, P.; Mattock, J. D.; Abdul-Sada, A.; Pitak, M. B.; Coles, S. J.; Navarro, O.; Vargas, A.; Kostakis, G. E. *Inorg. Chem.* **2016**, *55* (14), 6988–6994.
(12) Procopio, A.; Costanzo, P.; Curini, M.; Nardi, M.; Oliverio, M.; Sindona, G. *ACS Sustain. Chem. Eng.* **2013**, *1* (5), 541–544.
(13) Estevão, M. S.; Afonso, C. A. M. *Tetrahedron Lett.* **2017**, *58* (4), 302–304.
(14) Nardi, M.; Costanzo, P.; De Nino, A.; Di Gioia, M. L.; Olivito, F.; Sindona, G.; Procopio, A. *Green Chem.* **2017**, 19, 5403-5411.
(15) Cal, P. M. S. D.; Bernardes, G. J. L.; Gois, P. M. P. *Angew. Chem. Int. Ed.* **2014**, *53* (40), 10585–10587.
(16) Sletten, E. M.; Bertozzi, C. R. *Angew. Chem. Int. Ed.* **2009**, *48* (38), 6974–6998.
(17) Ernst, R. J.; Krogager, T. P.; Maywood, E. S.; Zanchi, R.; Beránek, V.; Elliott, T. S.; Barry, N. P.; Hastings, M. H.; Chin, J. W. *Nat. Chem. Biol.* **2016**, *12* (10), 776–778.
(18) Kato, A.; Kuratani, M.; Yanagisawa, T.; Ohtake, K.; Hayashi, A.; Amano, Y.; Kimura, K.; Yokoyama, S.; Sakamoto, K.; Shiraishi, Y. *Bioconjug. Chem.* **2017**, *28* (8), 2099–2108.
(19) de Graaf, A. J.; Kooijman, M.; Hennink, W. E.; Mastrobattista, E. *Bioconjug. Chem.* **2009**, *20* (7), 1281–1295.
(20) Blanco-Ania, D.; Hermkens, P. H. H.; Sliedregt, L. A. J. M.; Scheeren, H. W.; Rutjes, F. P. J. T. *Tetrahedron* **2009**, *65* (27), 5393–5401.
(21) Pezzetta, C.; Veiros, L. F.; Oble, J.; Poli, G. *Chem. Eur. J.* **2017**, *23* (35), 8385–8389.