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Full Paper

Isatin Synthesis

A Palladium-Catalyzed Double Carbonylation Approach to Isatins from 2-Iodoanilines

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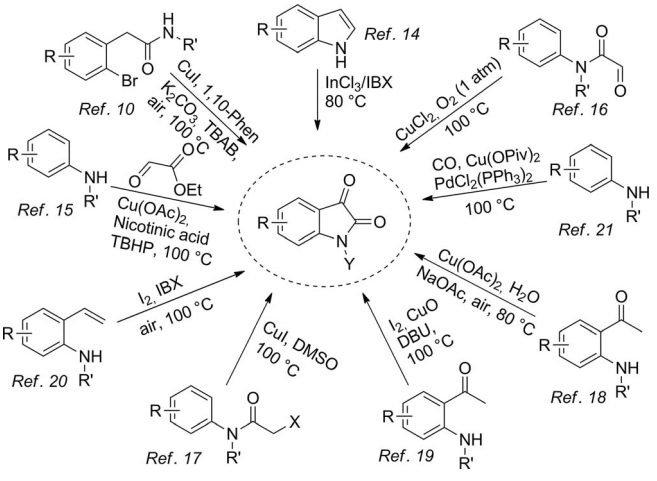
Abstract: A high-yielding procedure for the synthesis of isatins has been developed. Sequential Pd-catalyzed double carbonylation of 2-iodoanilines with near stoichiometric amounts of CO followed by acid-promoted cyclization readily affords an array of isatins. The conversion of 2-iodoanilines to isatins in good to excellent yields was found to proceed with good functional group tolerance. This protocol proved adaptable to ^{13}C-isotope labeling of isatins, which was extended to the synthesis of the ^{13}C-isotope labeled antiviral drug metisazone and the experimental anti-schizophrenia drug ML137.

Introduction

Isatins (1*H*-indole-2,3-diones) are important structures found in a wide range of natural products,[1] pharmaceuticals,[2–4] and dyes.[5] Moreover, isatins are adaptable building blocks for the synthesis of various heterocycles including quinolones,[6] indoles,[7] indolo[2,3-*b*]quinoxalines,[8] isatoric anhydrides,[9] and spiro-fused heterocyclic structures.[10,11] Although the first synthesis of isatin was reported back in 1840 by Erdmann[12] and Laurent,[13] the great versatility of isatins has led to the continuous development of new and more efficient procedures for their synthesis. To date, a variety of protocols for isatin production have included *i*) oxidation of indoles,[14] *ii*) C–H activation protocols with anilines,[15] 2-oxo-*N*-arylacetamides,[16] or α-haloamides,[17] *iii*) intramolecular oxidative cyclization using preexisting *ortho*-substituents such as methyl ketones,[18,19] primary amides,[10] and double/triple bonds,[20] and finally *iv*) a direct double carbonylation with subsequent cyclization via C–H activation chemistry,[21] (Scheme 1). However, despite the numerous routes to isatins, these approaches suffer from a number of disadvantages: *i*) elevated reaction temperatures are required, *ii*) regioselective issues can be observed in the C–C bond forming step to the aromatic ring, and *iii*) these methods are only applicable to the synthesis of *N*-substituted isatins.

Herein, we report a mild, high-yielding transformation of 2-iodoanilines to isatins. The detailed approach entails a room temperature Pd-catalyzed double carbonylation using near stoichiometric amounts of carbon monoxide (CO) followed by an acid-promoted cyclization. This procedure generates isatins in good to excellent yields and readily enables isotopic labeling opportunities.



Scheme 1. Literature precedented methods for isatin production.

Results and Discussion

Preliminary studies were undertaken to investigate the Pd-catalyzed double carbonylation of 2-iodoaniline with *n*-hexylamine.[22] Successful amino double carbonylations employing a CO atmosphere at room temperature were earlier reported by Kondo,[23] and then further adapted by us[24] applying near-stoichiometric amounts of CO generated *ex situ* from the solid precursor 9-methylfluorene-9-carbonyl chloride (COgen).[25,26] Subjecting 2-iodoaniline to *n*-hexylamine, $Pd(dba)_2$, $HBF_4P(tBu)_3$, DBU and CO (3 equiv.) in THF, provided the corre-

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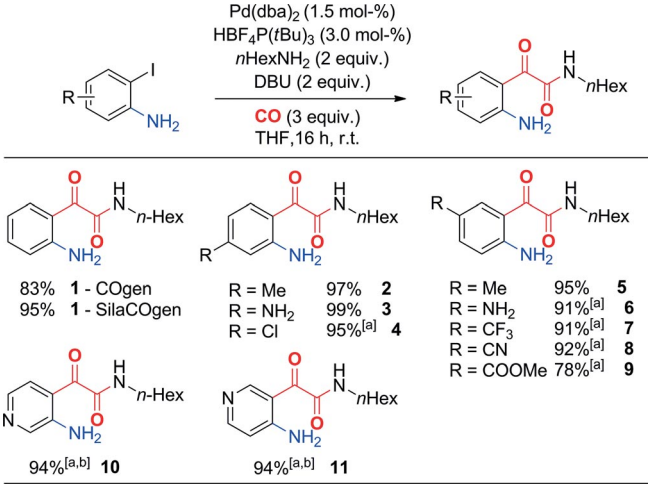
sponding α-ketoamide **1** in 83 % yield (Scheme 2). However, by exchanging COgen with another CO-surrogate, methyldiphenylsilanecarboxylic acid (SilaCOgen), which releases CO at a faster rate at room temperature,[27] we were able to increase the yield of **1** to 95 % (Scheme 2). At this point, substrate scope studies were conducted to assess functional group tolerances for the reaction. As expected, aryl iodides possessing electron-donating groups resulted in desired α-ketoamides **2**, **3** and **5** in excellent yields.[28] At slightly higher catalyst loadings, full conversion of 2-iodoanilines with electron-deficient substituents was also possible providing compounds **4**, **7**–**9** in yields of 78–95 %.

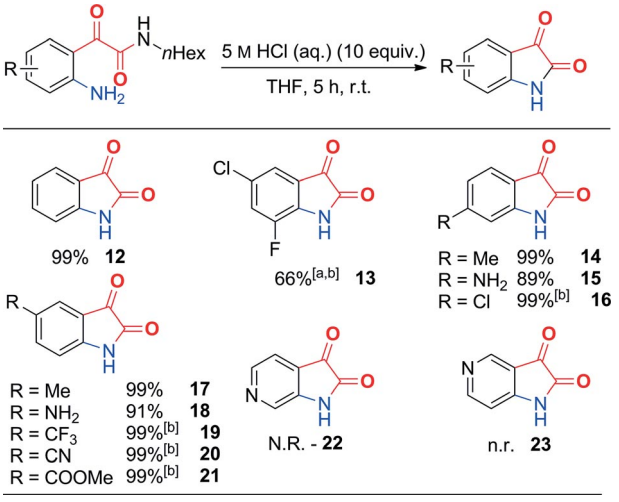


Scheme 2. The scope of the Pd-catalyzed double carbonylation with 2-iodoanilines. **Reaction conditions**: **Chamber A**: Aryl iodide (0.50 mmol), $Pd(dba)_2$ (2 mol-%), $HBF_4P(tBu)_3$ (4 mol-%) dry THF (4 mL), *n*-hexylamine (1.00 mmol), and DBU (1.00 mmol) in that order at room temperature for 16 h. **Chamber B**: SilaCOgen (1.50 mmol), dry THF (3 mL), and KF (approx. 1.00 mmol) in that order at room temperature for 16 h. [a] $Pd(dba)_2$ (5 mol-%) and $HBF_4P(tBu)_3$ (10 mol-%) used. [b]THF (3 mL) and MeCN (1 mL) as solvent.

Inspired by the literature,[29] compound **1** was cyclized upon treatment with 5 M hydrochloric acid through a *trans*-amidation, yielding isatin **12** in nearly quantitative yield after 5 h at room temperature (Scheme 3). For substrates carrying electron-deficient substituents, an increase in temperature to 60 °C was necessary to effect cyclization.

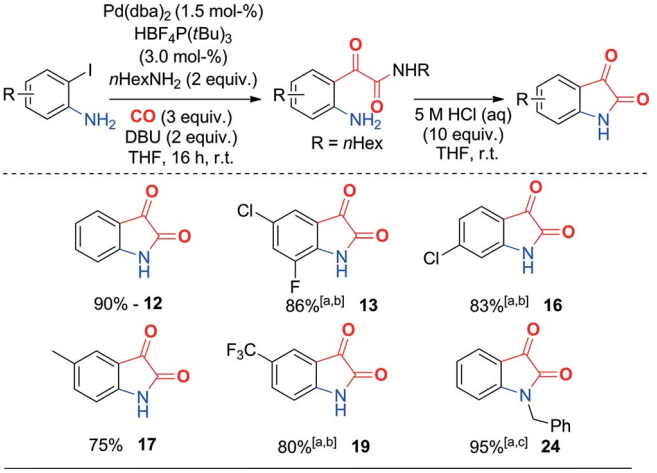
The corresponding isatins could, using this approach, be obtained in yields ranging from 66 % to 99 %. Two pyridines were successfully coupled in a double carbonylative manner and identical yields of 94 % were obtained for compounds **10** and **11** (Scheme 2). However, these structures were recalcitrant to cyclization under a variety of acidic and basic conditions (See Supporting Information).

We next investigated the possibility of carrying out such chemistry in a one-pot procedure. Gratifyingly, we found that simple isatin **12** could be prepared in a 90 % yield (Scheme 4) via a one-pot approach. However, in some cases this procedure resulted in a decreased yield, and therefore an acidic wash was introduced between the two steps. This increased the yield for 5-methylindoline-2,3-dione (**17**) from 75 % to 93 % (Scheme 5). Using this sequential procedure, 2-iodoanilines with electron-deficient substituents still yielded corresponding isatins in



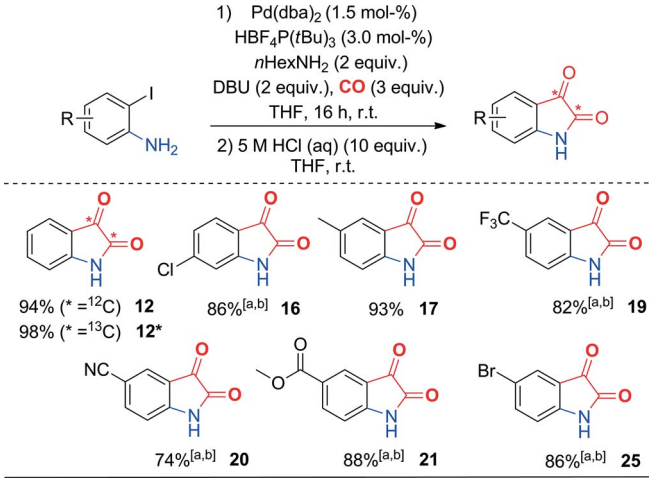
Scheme 3. Acid-mediated cyclization to Isatins. [a] Yield reported over two steps. [b] Reaction at 60 °C.

yields of 74–88 % (Scheme 5, compounds **16**, **19**–**21** and **25**). Additionally, 4-bromo-2-iodoaniline was readily transformed to its corresponding isatin, **25** in 86 % yield, thereby enabling further manipulation of the aryl bromide.



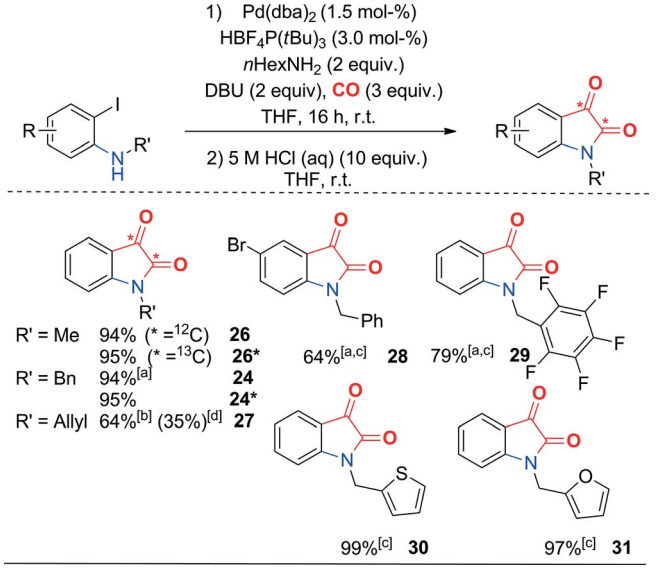
Scheme 4. The scope of the one-pot procedure. **Reaction conditions: Chamber A**: Aryl iodide (0.50 mmol), $Pd(dba)_2$ (2 mol-%), $HBF_4P(tBu)_3$ (4 mol-%) dry THF (4 mL), *n*-hexylamine (1.00 mmol), and DBU (1.00 mmol) in that order at room temperature for 16 h. **Chamber B**: SilaCOgen (1.50 mmol), dry THF (3 mL), and KF (approx. 1.00 mmol) in that order at room temperature for 16 h. [a] $Pd(dba)_2$ (5 mol-%) and $HBF_4P(tBu)_3$ (10 mol-%) used. [b] Cyclization run at 60 °C. [c] Cyclization run at 70 °C.

Furthermore, by switching to Sila^{13}COgen, it was possible to introduce two ^{13}C-carbon labels into the isatin structure in a yield comparable to that obtained for compound **12** (Scheme 5). The transformation of 2-iodoaniline could also be executed outside the glovebox under an argon atmosphere, yielding 83 % of compound **12**. Finally, we found that performing the reaction of 2-iodoaniline with substoichiometric amounts of CO (1.5 equiv.) provided **12** in a yield of 90 % based on the added CO (Results not shown, see Supporting Information section). To further expand the scope of this reaction we investigated whether or not *N*-substituted 2-iodoanilines could



Scheme 5. The scope of the sequential procedure. Reaction conditions: **Chamber A**: Aryl iodide (0.50 mmol), $Pd(dba)_2$ (2 mol-%), $HBF_4P(tBu)_3$ (4 mol-%) dry THF (4 mL), *n*-hexylamine (1.00 mmol), and DBU (1.00 mmol) in that order at room temperature for 16 h. **Chamber B**: SilaCOgen (1.50 mmol), dry THF (3 mL), and KF (approx. 1.00 mmol) in that order at room temperature for 16 h. [a] $Pd(dba)_2$ (5 mol-%) and $HBF_4P(tBu)_3$ (10 mol-%) used. [b] Cyclization at 60 °C.

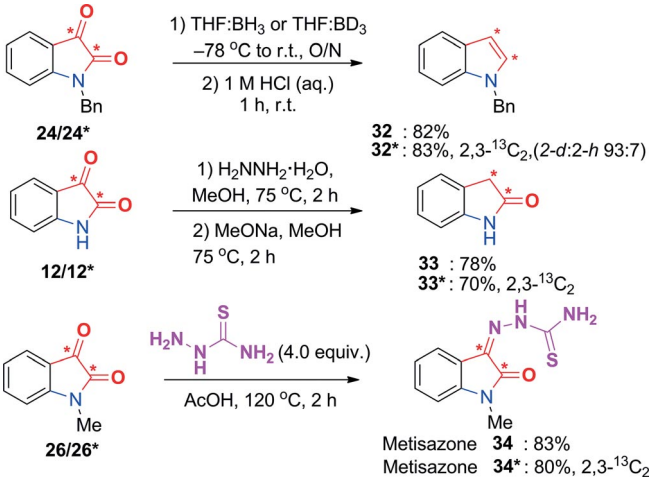
undergo conversion to their corresponding *N*-substituted isatins. Gratifyingly, a series of mono *N*-substituted 2-iodoanilines subjected to the reaction conditions used in Scheme 5 afforded products **24**, **26**–**31** in good to excellent yields (Scheme 6).



Scheme 6. The scope of substrates with *N*-substitution. Reaction conditions: **Chamber A**: Aryl iodide (0.50 mmol), Pd(dba)2 (2 mol-%), $HBF_4P(tBu)_3$ (4 mol-%) dry THF (4 mL), *n*-hexylamine (1.00 mmol), and DBU (1.00 mmol) in that order at room temperature for 16 h. **Chamber B**: SilaCOgen (1.50 mmol), dry THF (3 mL), and KF (approx. 1.00 mmol) in that order at room temperature for 16 h. [a] $Pd(dba)_2$ (5 mol-%) and $HBF_4P(tBu)_3$ (10 mol-%) used. [b] Cyclization step performed at 60 °C. [c] Cyclization step performed at 70 °C. [d] Unmodified isatin isolated.

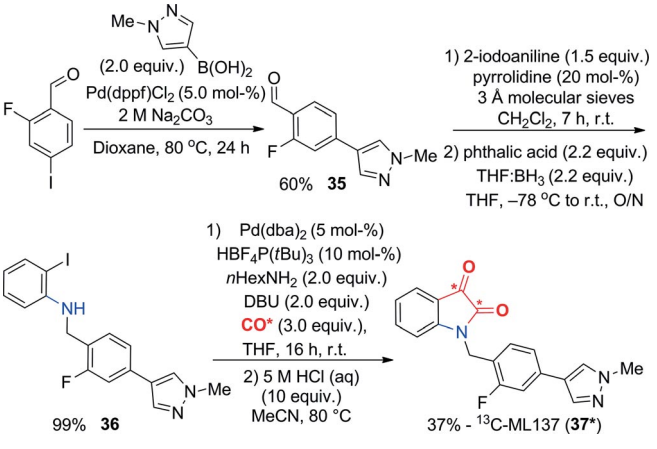
N-Methyl-2-iodoaniline could be transformed into corresponding *N*-methyl isatin in excellent yields for both the ^{12}C and ^{13}C versions, **26** and **26***, respectively. The presence of larger *N*-substituents on the aniline necessitated an increase in temperature to 60–70 °C for the α-ketoamides to cyclize into compounds **24** and **27**–**31**. Notably, *N*-thiophenylmethyl and *N*-furanylmethyl substituents did not retard the reaction and products **30** and **31** were isolated in excellent yields.

To illustrate the versatility of the reaction, we turned our attention to synthetic transformations of isatins and decided to first explore the possibility of obtaining double ^{13}C-isotope labeled indoles. It was found that reduction of free isatin employing $THF:BH_3$ was troublesome. However, when using compound **24**, reduction was readily achieved to provide *N*-benzylindole (**32**) in 82 % yield. Reduction of *N*-benzylisatin-2,3-$^{13}C_2$ (**24***) was performed using $THF:BD_3$ to afford a 93:7 mixture of *N*-benzylindole-2,3-$^{13}C_2$-2-*d* and *N*-benzylindole-2,3-$^{13}C_2$ in a comparable yield of 83 % (for **32***). Wolff–Kishner reduction[30] of ^{12}C- and ^{13}C-isatin generated 2-oxindoles **33** and **33*** in yields of 78 % and 70 %, respectively. Additionally, the antiviral drug metisazone (**34**) was synthesized with isotopic labeling by treating *N*-methylisatin-2,3-$^{13}C_2$ with thiosemicarbazide (Scheme 7).[20]



Scheme 7. Chemical transformations of isatins.

Finally, our protocol was applied to the synthesis and ^{13}C-labeling of ML137, a potent M5-positive allosteric modulator (Scheme 8).[31,32] Hence, it was possible to synthesize ^{13}C-iso-



Scheme 8. Synthesis of ^{13}C-ML137.

topically labeled ML137 (**37***) in a total yield of 22 % over three steps from commercially available 2-iodoaniline (Scheme 8).

Conclusions

In conclusion, a new procedure for the facile formation of both free and *N*-substituted isatins has been presented starting from 2-iodoanilines. Using a sequential Pd-catalyzed double carbonylation with subsequent acid-mediated cyclization, it was possible to obtain isatins in good to excellent yields. The carbonylation reaction makes possible the installation of two ^{13}C-carbon isotopes. These products can, in turn, be transformed into a triply labeled indole through reduction by THF:BD_3. This approach was applied to generate selected examples of bioactive isatins.

Experimental Section

α-Keto Amides

Chamber A*:** In an glovebox with argon atmosphere, to chamber A, was added aryl iodide (0.50 mmol), $Pd(dba)_2$ (4.44 mg, 0.01 mmol), $HBF_4P(tBu)_3$ (4.35 mg, 0.02 mmol) dry THF (4 mL), *n*-hexylamine (0.13 mL, 1.00 mmol), and DBU (0.15 mL, 1.00 mmol) in that order. The chamber was sealed with a screwcap fitted with a Teflon seal. ***Chamber B: To chamber B was added SilaCOgen (363.52 mg, 1.50 mmol), dry THF (3 mL), and KF (approx. 60 mg, 1.00 mmol) in that order. The chamber was sealed with a screwcap fitted with a Teflon seal and the loaded two-chamber system was removed from the glovebox and stirred at room temperature for 16 h. The pH of the reaction was adjusted to pH = 3 using 2 M HCl (aq) and H_2O (10 mL) was added. The reaction was extracted with CH_2Cl_2 (3 × 10 mL), washed with brine (10 mL) and dried with $MgSO_4$. Solvents were removed in vacuo and flash column chromatography yielded the desired product.

Isatins: The α-keto amide (0.1 mmol) was dissolved in THF (0.8 mL) and 5 M HCl (aq) (0.2 mL, 1.00 mmol) was added. The reaction was stirred at room temperature for 2 h and H_2O (2 mL) was added. The product was extracted with EtOAc (3 × 5 mL) and concentrated in vacuo, yielding the desired compound without further purification.

Isatins (One-Pot Procedure)

Chamber A*:** In an glovebox with argon atmosphere, to chamber A, was added aryl iodide (0.50 mmol), $Pd(dba)_2$ (4.44 mg, 0.01 mmol), $HBF_4P(tBu)_3$ (4.35 mg, 0.02 mmol) dry THF (4 mL), *n*-hexylamine (0.13 mL, 1.00 mmol), and DBU (0.15 mL, 1.00 mmol) in that order. The chamber was sealed with a screwcap fitted with a Teflon seal. ***Chamber B: To chamber B was added SilaCOgen (363.52 mg, 1.50 mmol), dry THF (3 mL), and KF (approx. 60 mg, 1.00 mmol) in that order. The chamber was sealed with a screwcap fitted with a Teflon seal and the loaded two-chamber system was removed from the glovebox and stirred at room temperature for 16 h. 5 M HCl (1 mL, 5 mmol) was added and the reaction was stirred for 5 h H_2O (10 mL) was added and the reaction was extracted with EtOAc (3 × 10 mL), washed with brine (10 mL) and dried with $MgSO_4$. Solvents were removed in vacuo and flash column chromatography yielded the desired product.

Isatins (Sequential Procedure)

Chamber A: In an glovebox with argon atmosphere, to chamber A, was added aryl iodide (0.50 mmol), $Pd(dba)_2$ (4.44 mg, 0.01 mmol), $HBF_4P(tBu)_3$ (4.35 mg, 0.02 mmol) dry THF (4 mL), *n*-hexylamine (0.13 mL, 1.00 mmol) and DBU (0.15 mL, 1.00 mmol) in that order. The chamber was sealed with a screwcap fitted with a Teflon seal. ***Chamber B:*** To chamber B was added SilaCOgen (363.52 mg, 1.50 mmol), dry THF (3 mL) and KF (approx. 60 mg, 1.00 mmol) in that order. The chamber was sealed with a screwcap fitted with a Teflon seal and the loaded two-chamber system was removed from the glovebox and stirred at room temperature for 16 h. The pH of the reaction was adjusted to pH = 3 using 2 M HCl (aq) and H_2O (10 mL) was added. The reaction was extracted with CH_2Cl_2 (3 × 10 mL), and concentrated in vacuo. The crude material was transferred to an 8 mL vial using THF (4 mL) and 5 M HCl (aq) (1 mL, 5 mmol) was added. The reaction was stirred for 5 h after which H_2O (10 mL) was added. The reaction was extracted with EtOAc (3 × 10 mL), washed with brine (10 mL) and dried with $MgSO_4$. Solvents were removed in vacuo and flash column chromatography yielded the desired product.

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[1] K. Han, Y. Zhou, F. Liu, Q. Guo, P. Wang, Y. Yang, *Bioorg. Med. Chem. Lett.* **2014**, *24*, 591–594.
[2] A. Cane, M. C. Tournaire, D. Barritault, M. Crumeyrolle-Arias, *Biochem. Biophys. Res. Commun.* **2000**, *276*, 379–384.
[3] K. L. Vine, J. M. Locke, M. Ranson, K. Benkendorff, S. G. Pyne, J. B. Bremner, *Bioorg. Med. Chem.* **2007**, *15*, 931–938.
[4] M. Verma, S. N. Pandeya, K. N. Singh, J. P. Stables, *Acta Pharm.* **2004**, *54*, 49–56.
[5] U. Pindur, *Arch. Pharm.* **1981**, *314*, 342–346.
[6] J. Deng, N. Li, H. Liu, Z. Zuo, O. W. Liew, W. Xu, G. Chen, X. Tong, W. Tang, J. Zhu, J. Zuo, H. Jiang, C. Yang, J. Li, W. Zhu, *J. Med. Chem.* **2012**, *55*, 6278–6293.
[7] A. C. Pinto, F. Soares, Q. Silva, B. Silva, *Tetrahedron Lett.* **1994**, *35*, 8923–8926.
[8] A. V. Ivashchenko, A. G. Drushlyak, V. V. Titov, *Chem. Heterocycl. Compd.* **1984**, *20*, 537–542.
[9] G. Reißenweber, D. Mangold, *Angew. Chem. Int. Ed.* **1980**, *19*, 222–223; *Angew. Chem.* **1980**, *92*, 196.
[10] J. Sun, B. Liu, B. Xu, *RSC Adv.* **2013**, *3*, 5824–5827.
[11] T. Nakamura, S. Shirokawa, S. Hosokawa, A. Nakazaki, S. Kobayashi, *Org. Lett.* **2006**, *8*, 677–679.
[12] O. L. Erdmann, *J. Prakt. Chem.* **1840**, *19*, 321–362.
[13] A. Laurent, *Ann. Chim. Phys.* **1840**, *3*, 393–434.
[14] J. S. Yadav, B. V. Subba Reddy, C. S. Reddy, A. D. Krishna, *Synthesis* **2007**, *5*, 693–696.
[15] T. Liu, H. Yang, Y. Jiang, H. Fu, *Adv. Synth. Catal.* **2013**, *355*, 1169–1176.
[16] B. Tang, R. Song, C. Wu, Y. Liu, M. Zhou, W. Wei, G. Deng, D. L. Yin, J. H. Li, *J. Am. Chem. Soc.* **2010**, *132*, 8900–8902.
[17] Q. Gui, F. Dai, J. Liu, P. Chen, Z. Yang, X. Chen, Z. Tan, *Org. Biomol. Chem.* **2014**, *12*, 3349–3353.
[18] A. Ilangovan, G. Satish, *Org. Lett.* **2013**, *15*, 5726–5729.
[19] F. F. Gao, W. J. Xue, J. G. Wang, A. X. Wu, *Tetrahedron* **2014**, *70*, 4331–4335.
[20] G. Satish, A. Polu, T. Ramar, A. Ilangovan, *J. Org. Chem.* **2015**, *80*, 5167–5175.

[21] W. Li, Z. Duan, X. Zhang, H. Zhang, M. Wang, R. Jiang, H. Zeng, C. Liu, A. Lei, *Angew. Chem. Int. Ed.* **2015**, *54*, 1893–1896; *Angew. Chem.* **2015**, *127*, 1913.

[22] Initial efforts to perform the double carbonylation and concommitant ring closure directly with the aniline nitrogen were unsuccessful.

[23] M. Iizuka, Y. Kondo, *Chem. Commun.* **2006**, 1739–1741.

[24] D. U. Nielsen, K. Neumann, R. H. Taaning, A. T. Lindhardt, A. Modvig, T. Skrydstrup, *J. Org. Chem.* **2012**, *77*, 6155–6165.

[25] P. Hermange, A. T. Lindhardt, R. H. Taaning, K. Bjerglund, D. Lupp, T. Skrydstrup, *J. Am. Chem. Soc.* **2011**, *133*, 6061–6071.

[26] For a mechanistic investigation of the double-carbonylation, see: V. M. Fernandez-Alvarez, V. de la Fuente, C. Godard, S. Castillón, C. Claver, F. Maseras, J. J. Carbó, *Chem. Eur. J.* **2014**, *20*, 10982–10898, and references cited therein.

[27] S. D. Friis, R. H. Taaning, A. T. Lindhardt, T. Skrydstrup, *J. Am. Chem. Soc.* **2011**, *133*, 18114–18117.

[28] F. Ozawa, H. Yanagihara, A. Yamamoto, *J. Org. Chem.* **1986**, *51*, 415–417.

[29] V. M. Fernández-Alvarez, V. De la Fuente, C. Godard, S. Castillón, C. Claver, F. Maseras, J. J. Carbó, *Chem. Eur. J.* **2014**, *20*, 10982–10989.

[30] D. Soriano, *J. Chem. Educ.* **1993**, *70*, 332.

[31] T. M. Bridges, J. P. Kennedy, M. J. Noetzel, M. L. Breininger, P. R. Gentry, P. Jeffrey Conn, C. W. Lindsley, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1972–1975.

[32] A. Abdul-Ridha, L. López, P. Keov, D. M. Thal, S. N. Mistry, P. M. Sexton, J. R. Lane, M. Canals, A. Christopoulos, *J. Biol. Chem.* **2014**, *289*, 6067–6079.

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