Organic Process Research & Development

Communication

pubs.acs.org/OPRD

Lewis Acid-Catalyzed Synthesis of 4-Aminopyrimidines: A Scalable Industrial Process

Ulla Létinois,*[,‡] Jan Schütz,[‡] Ralph Härter,[§] Rinke Stoll,[‡] Florian Huffschmidt,[‡] Werner Bonrath,[‡] and Reinhard Karge[‡,†]

[‡]Process Research and Development and [§]OPS-MT, DSM Nutritional Products Ltd., P.O. Box 2676, CH-4002 Basel, Switzerland

Supporting Information

ABSTRACT: Pyrimidine synthesis starting from acrylonitrile has been known since the 1960s. The new Lewis acid-catalyzed condensation reaction allows the synthesis of 4-aminopyrimidines starting from the easily accessible chemical acrylonitrile without the need for carcinogenic chemicals and costly derivatization in up to 90% yield. The method is versatile and applicable for industrial-scale synthesis of biologically relevant substances such as vitamin B1 and trimethoprim.

INTRODUCTION

Aminopyrimidines are key intermediates for the synthesis of biologically active substances such as vitamin B_1 (thiamin **1**),[1] its natural antagonist bacimethrin **2**,[2] pesticides (amprolium **3**),[3] and chemotherapeutic agents (trimethoprim **4**).[4] Grewe diamine **5** is the key building block in all industrial syntheses of vitamin B_1 (Figure 1).[5] Although various synthetic protocols

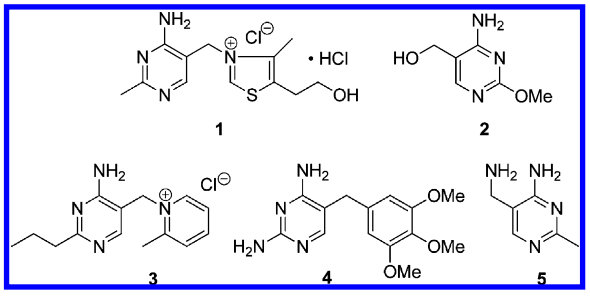


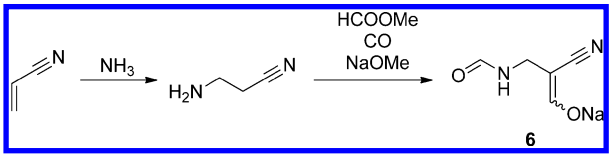
Figure 1. Examples of biologically active 4-aminopyrimidines.

are available for the synthesis of 4-aminopyrimidines,[5] reports on industrially applicable syntheses remain scarce.[5] Commonly, major challenges in designing industrially attractive processes for fine chemicals include the development of low-cost, atom-efficient processes that are easily scalable, nonhazardous, and at the same time highly selective.[6]

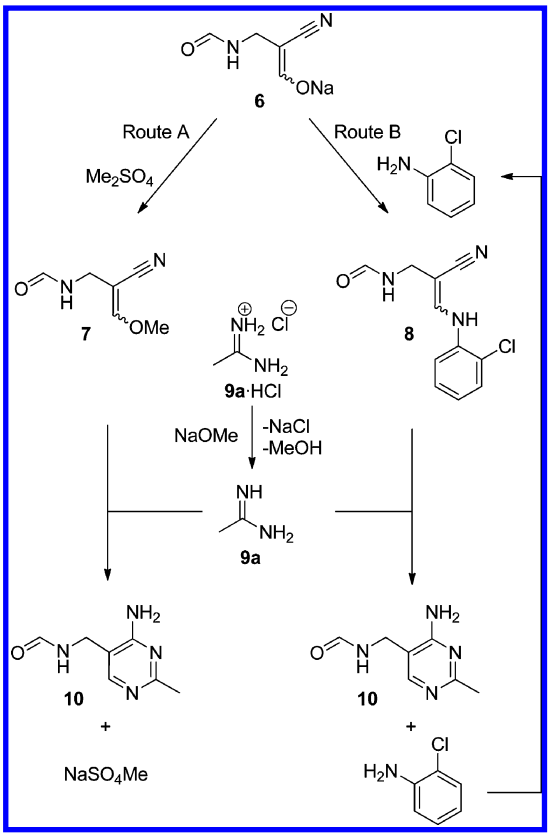
From the known syntheses to 4-aminopyrimidines, the industrially relevant syntheses use the sodium enolate **6** as a common intermediate, which can be obtained from the bulk chemical acrylonitrile (C_3-synthon) in a two-step synthesis.[7] The industrial access to **6** has been largely improved recently (Scheme 1).[8]

The acid-sensitive enolate **6** is transformed either to an enol ether **7** with dimethylsulfate (Scheme 2, Route **A**)[9] or to the

Scheme 1. Preparation of sodium enolate 6 from acrylonitrile



Scheme 2. Industrially relevant syntheses of 4-aminopyrimidines starting from sodium enolate 6



enamine **8** with *o*-chloroaniline (Scheme 2, Route **B**).[10] Major drawbacks of these procedures are the use of carcinogenic reagents (dimethylsulfate, *o*-chloroaniline) and the related formation of sodium methylsulfate waste and loss of *o*-

Received: July 16, 2012

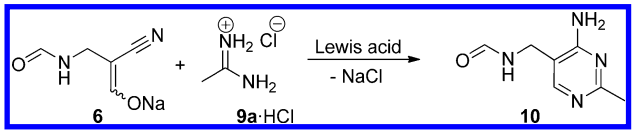
   dx.doi.org/10.1021/op300190s | *Org. Process Res. Dev.* XXXX, XXX, XXX−XXX

chloroaniline due to incomplete recycling. Moreover, additional workup and purification procedures are necessary in order to recycle the *o*-chloroaniline and minimize the contamination of the final product.

Subsequent condensation of enol ether **7** or enamine **8** with acetamidine **9a** leads to the desired pyrimidine **10**. Both procedures (Routes **A** and **B**) use acetamidine **9a** (free base). In general, amidines are commercially available as hydrochloride salts due to the moderate stability of the free base. Consequently, in the above syntheses the amidine hydrochloride needs to be neutralized with a strong base (e.g., alkoxides) prior to the condensation. Disadvantages are salt production, instability of free acetamidine, and the additional cost of sodium methoxide.

A patent application by BASF, which has later been actively withdrawn, describes the uncatalyzed reaction of **6** and **9a**·HCl.[11] Yields of approximately 50% are claimed. A catalyzed, high-yielding variant of a direct reaction of enolate **6** with amidine hydrochlorides to 4-aminopyrimidines, thus circumventing both derivatization of **6** and neutralization of the hydrochloride salt would greatly simplify the process and has not been reported to date to the best of our knowledge.

Scheme 3. Synthesis of 4-aminopyrimidines from cyanoenolates



RESULTS AND DISCUSSION

As a part of our efforts towards the design of greener and more economic syntheses of vitamins and fine chemicals, we were interested in the development of such a reaction. We report here the first catalyzed, scalable access to 4-aminopyrimidines via direct condensation of enolates of type **6** with amidinium chlorides. The method is readily applicable for large-scale industrial production of 4-aminopyrimidines.[12] Both starting materials are easily soluble in methanol, ethanol, DMSO, DMF, and NMP, but both also undergo rapid decomposition in these solvents. In other solvents such as ethers, esters, and alcohols with more than three carbons the solubility is very low. A suspension of enolate **6** and **9a**·HCl in either toluene, 3-pentanone, or dioxane resulted in a greyish-brown suspension, which stuck to the flask walls at elevated temperatures.[a] In spite of the formation of the sticky mass, we were pleased to find that the desired pyrimidine **10** formed after one hour at 100 °C (detected by HPLC). Further screening of reaction conditions allowed increasing the yield to 37% (Table 1, entry 1). We found that the condensation reaction could be carried out in a temperature range of 75−110 °C. DSC analysis showed that **6** starts to decompose at 115 °C.

In order to further optimize the reaction, several additives were tested. H_2SO_4 (20 mol %) gave 45% yield (Table 1, entry 2), but the benefit of this additive is rather limited compared to the uncatalyzed experiment (entry 1). Brønsted acid NH_4Cl had a negative influence on the yield (entry 3). Addition of alanine, a bifunctional amino acid, resulted in 40% yield (entry 4). Strong Brønsted base $NaOCH_3$ did not lead to any product formation (entry 5), but triethylamine with a pK_a >10 in toluene[13] gave 42% yield (entry 6). The addition of oxophilic Lewis acids[14] chosen from the third main group ($AlCl_3$ and $GaCl_3$) led to decomposition of the starting material (entries 7 and 8), whereas Lewis acids from the fourth transition group (TiO_2 and $TiCl_4$) resulted in a moderate increase of the yield to 55% and 52%, respectively (entries 9 and 10). The addition of aminophilic Lewis acids[14] was more successful. Iron chlorides improved the yield to 63% and 43% (entries 11 and 12). Surprisingly, $FeCl_2$, which is considered a weak aminophilic Lewis acid, gave better results than the strong aminophilic $FeCl_3$. We were happy to find that the addition to the reaction mixture of salts of metals from the transition groups 8 and 9 (metal salts such as Ru(COD)Cl_2 and $CoCl_2$) led to the formation of pyrimidine **10** in 70% and 72% yield, respectively (entries 13 and 14), while in the presence of CuCl the yield increased to 87% (entry 15). With pentahydrate of $CuSO_4$ and dihydrate of $CuCl_2$ respective yields of 60 and 63% were achieved (entries 16 and 17). Zinc halides $ZnCl_2$ and $ZnBr_2$ gave yields of 80 and 74% (entries 18 and 19). In conclusion, copper(I) chloride was the most effective Lewis acid in this reaction (87%, entry 15). During further investigations, we chose to concentrate our attention on zinc chloride and copper(I) chloride as the most suitable Lewis acids.

Table 1. Screening of various additives in the condensation reaction of 6 and 9b (see Scheme 3)[a]

entry	catalyst	yield [%][b]
1	–	37
2	H_2SO_4	45
3	NH_4Cl	13
4	alanine	40
5	NaOMe	0
6	Et_3N	42
7	$AlCl_3$	0
8	$GaCl_3$	7
9	TiO_2	55
10	$TiCl_4$	52
11	$FeCl_2$	63
12	$FeCl_3$	43
13	Ru(COD)Cl_2[c]	70
14	$CoCl_2$	72
15	CuCl	87
16	$CuSO_4$·5 H_2O	60
17	$CuCl_2$·2 H_2O	63
18	$ZnCl_2$	80
19	$ZnBr_2$	74

[a]Reagents and conditions: Enolate **6** (57 mmol), **9a**·HCl (66.9 mmol, 1.17 equiv), catalyst (10.8 mmol, 0.2 equiv), 3-pentanone (54 mL, 1 M), 85 °C, 16 h, full conversion of **6**. [b]wt % HPLC. [c]COD = 1,5-cyclooctadiene.

In this first screening of additives it was shown that the condensation of enolate **6** with acetamidine hydrochloride, **9a**·HCl, proceeded in yields >70% in the presence of aminophilic Lewis acids. For a process with industrial applicability, however, process research and reaction development are not finished after optimization of reaction yields. The next steps of our investigations concerned the downstream processes such as separation of the product from the reaction mixture, product purification, and adequate waste treatment.[15] In all of the above examples, the reaction mixture was a sticky slurry, which might complicate the handling of the material, especially if carried out at industrial scale. Therefore, various

dx.doi.org/10.1021/op300190s | *Org. Process Res. Dev.* XXXX, XXX, XXX−XXX

reaction solvents were tested, which on the one hand circumvent a sticky reaction mixture and on the other hand do not facilitate the decomposition of the reactants. Due to economic reasons, we chose to concentrate only on the Zn-catalyzed condensation. In solvents DMF, NMP or DMSO and C_1–C_3 alcohols where sticking did not occur, the starting materials decomposed. After a detailed investigation of the physicochemical properties of the solvent, an isopropanol/toluene mixture was found to be a suitable solvent for the process, limiting decomposition to a minimum. However, upon variation of the ratios of reactants and catalyst an additional problem was noticed. Not only the ratio of isopropanol and toluene but also the stoichiometry of **9a**·HCl as well as the stoichiometry of $ZnCl_2$ had an influence on the stirrability. In an isopropanol–toluene mixture (65:35 v/v) 0.95 equiv of **9a**·HCl and 0.3 equiv of $ZnCl_2$ gave a nonstirrable mixture. The same observation is valid for 1.4 equiv of **9a**·HCl and 0.15 equiv of $ZnCl_2$. The mixture became stirrable in the same solvent mixture when the amount of $ZnCl_2$ was higher than 0.2 equiv and that of **9a**·HCl was higher than 1.1 equiv. We carried out a design of experiments (DoE, method of least-squares)[16] with variation of the parameters (a) percentage of isopropanol in toluene (65–90 wt %), (b) equivalents of acetamidine hydrochloride (0.95–1.40 equiv), and (c) equivalents of zinc chloride (0.15–0.30 equiv) in order to determine the most suitable stoichiometry of reactants and solvents. The result of the experimental design is shown in Figure 2. The green dots

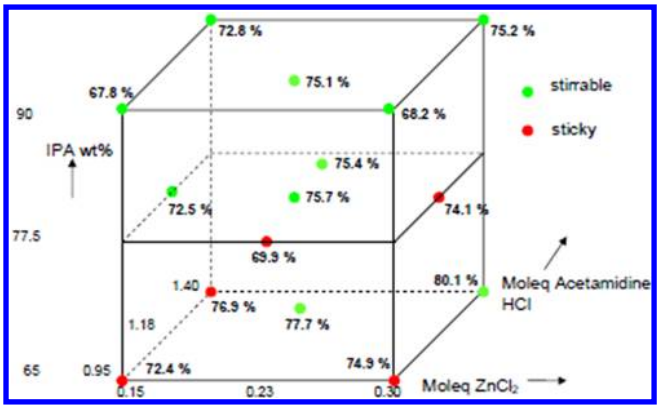
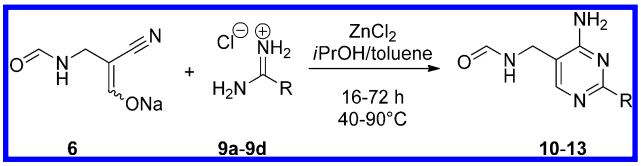


Figure 2. Evaluation of optimal reaction parameters by DoE. The numbers next to the dots indicate the isolated yield of pyrimidine **10** obtained experimentally using the corresponding ratio of reagents and solvents.

indicate reaction mixtures that are stirrable, and the red dots define mixtures that are not stirrable. The goodness of fit R^2 of the model was 0.96. The yields predicted by the DoE under optimal conditions corresponded well with the experimental results (±1%). A suitable reaction mixture that did not stick to the flask walls and provided optimal yields consisted of 1.4 equiv of acetamidine hydrochloride and 0.26 equiv of $ZnCl_2$ in a mixture of 65 wt % isopropanol in toluene.[b] This mixture is sufficiently polar to avoid sticking of the substrates, while side-reactions are minimized. We were able to scale the process to m^3-scale including saponification of **10** to **5** leading to 75% isolated yield of **5** starting from sodium enolate **6**.

The new procedure can be used to prepare several types of aminopyrimidines. Besides acetamidine hydrochloride (**9a**·HCl), commercially available formamidine hydrochloride (**9b**), guanidine hydrochloride (**9c**), and *O*-methylisourea hydrochloride (**9d**) were successfully applied in the condensation reaction. Reaction of *β*-cyano enolate **6** (1.0 equiv) with amidine hydrochlorides **9a–9d** (1.0–1.4 equiv) in the presence of $ZnCl_2$ (0.2–0.3 equiv) in isopropanol–toluene furnished the corresponding aminopyrimidines in 37–83% yield (Table 2).

Table 2. Synthesis of various pyrimidines using substituted amidine hydrochlorides



entry	amidine	R	pyrimidine	yield [%][a]
1	**9a**·HCl	CH_3	**10**	83
2	**9b**·HCl	H	**11**	52
3	**9c**·HCl	NH_2	**12**	72
4	**9d**·HCl	OMe	**13**	37

[a]Isolated yield.

We point out that this procedure also works especially well for the synthesis of *N*-((2,4-diaminopyrimidin-5-yl)methyl)-formamide (**12**) (entry 3), a key building block in the synthesis of trimethoprim (**4**).[17]

In addition, further extension of this methodology was achieved by varying the nature of the sodium enolates. To this end, *β*-cyano enolates **14a** and **14b** were conveniently prepared similarly to enolate **6** via *α*-formylation of the corresponding nitriles. Alternatively, enolates **14c–14e** could be obtained by ring-opening of the corresponding isoxazoles in the presence of $NaOCH_3$ and subsequent filtration of the precipitate (Figure 3).[18]

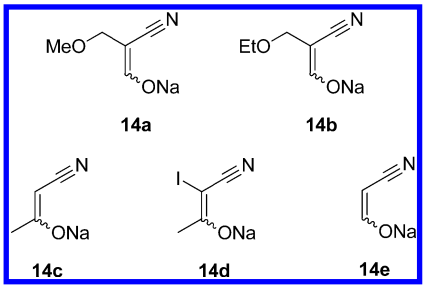
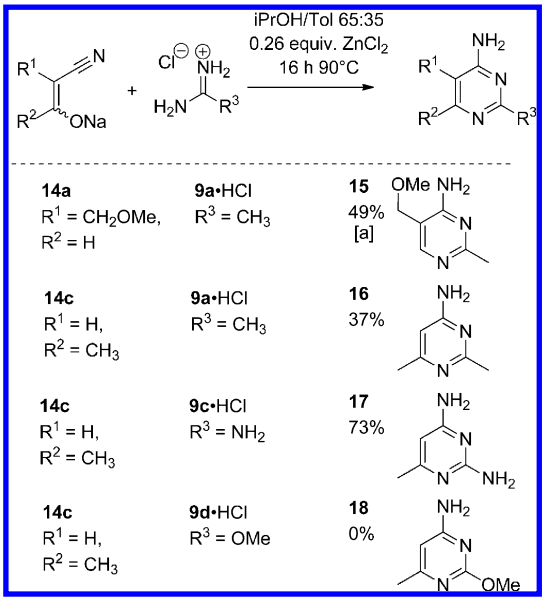


Figure 3. Prepared cyanoenolates for condensation reactions to pyrimidines.

Sodium enolates **14a–e** reacted with various amidine hydrochlorides in the presence of $ZnCl_2$ (Scheme 4). We were pleased to note that keto enolate **14c** gave the pyrimidine derivative in 73% yield in the condensation with guanidine hydrochloride (**9c**) and in 37% yield with acetamidine hydrochloride (**9a**·HCl). However, the condensation of **14c** with **9d** was not successful. We have found that the reaction temperature is crucial for the conversion. Generally, no conversion was observed below 75 °C. In the case of **14a** and **14b**, decomposition occurred due to the limited stability of these enolates under the reaction conditions. While they were stable below 30 °C, only decomposition was observed above this temperature under the reaction conditions used. We observed that the condensation reaction of **14a** and **9a**·HCl

dx.doi.org/10.1021/op300190s | Org. Process Res. Dev. XXXX, XXX, XXX–XXX

Scheme 4. Synthesis of aminopyrimidines from cyano enolates 14 and amidine hydrochlorides 9

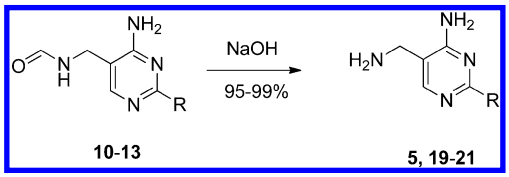


[a]0.26 equiv of NEt_3 was used instead of $ZnCl_2$.

took place in 49% yield at 80 °C, when triethylamine (1.0 equiv) was used as additive instead of a Lewis acid. Enolates **14d** and **14e** could not react with amidines. Decomposition of the enolates occurred when the reactions were catalyzed either with Lewis acids or Lewis bases.

Removal of the *N*-formyl protecting group of the corresponding pyrimidines **10**−**13** was easily accomplished in high yields following standard conditions (Scheme 5).[19]

Scheme 5. Deprotection of pyrimidines 10−13



Workup procedures, critical in industrial-scale processes, were also studied in detail, allowing the facile separation of Lewis acid and pyrimidine. Pyrimidines are known as suitable ligands for various metal salts, including zinc[20] and copper.[21] The biological activity of vitamin B_1 is related to complexation with zinc,[22] the activity of trimethoprim is enhanced by complexation of copper.[23] Therefore, we anticipated that an efficient method is necessary to separate the pyrimidine−metal complex in order to isolate product that complies to transition-metal specifications (<100 ppm). We decided to take advantage of the physicochemical behaviour of pyrimidines under basic conditions. It was found that the separation of zinc(II) can be achieved by precipitation of the corresponding hydroxide. Amphoteric $Zn(OH)_2$ exhibits low solubility in water at pH 9.[24] Aqueous workup of the reaction mixture with pH adjusted to 9 with sodium hydroxide, followed by filtration of the precipitated zinc hydroxide, furnished the crude *N*-formyl Grewe diamine **10** with a zinc content below 100 ppm.[25] However, filtration at pH 9 led to partial hydrolysis of the pyrimidine. In order to avoid the handling of a product mixture containing formamide **10** and Grewe diamine **5**, the reaction conditions were adjusted to allow a complete hydrolysis. The hydrolysis was carried out at pH 11 followed by stirring of the reaction mixture at 80 °C for 2 h. The resulting Grewe diamine (**5**) was then separated from inorganic salts by countercurrent extraction.[19] In the case where CuCl was used as a Lewis acid (Table 1, entry 16), the workup could not be performed in the same way due to the formation of a colloidal precipitate of copper hydroxide in alkaline solutions.[26] Instead, copper was converted to the stable, water-soluble tetraammine complex by addition of ammonia. Subsequently, the pH was adjusted to pH 9, allowing the crystallization of pyrimidine **10**, which was easily isolated by filtration. The final product **10** contained less than 100 ppm of Cu (see Supporting Information).[25]

CONCLUSION

In summary we have succeeded in developing a novel procedure for the synthesis of 4-aminopyrimidines, catalyzed by Lewis acids. Thus Grewe diamine **5**, key building block in the synthesis of vitamin B1, was successfully prepared in 60% overall yield in four steps starting from acrylonitrile. Efficient separation of the product from the catalyst was achieved, allowing the process to be easily scaled to industrial volumes.

EXPERIMENTAL SECTION

Procedure for the Cyclization Reaction of 6 with 9a·HCl to 10. Detailed example for the cyclization reaction of **6** and **9a**·HCl in the presence of zinc chloride consists of the following:

The reactor, which is equipped with a heating jacket, is charged with 2.14 kg of toluene, and then 1.5 kg of **6** (89%, 9.055 mol) as well as 1.13 kg of **9a**·HCl (11.95 mol, 1.32 equiv) is slowly added, followed by isopropanol (3.96 kg) and $ZnCl_2$ (0.323 kg, 2.37 mol, 0.26 equiv). The reactor is heated to an inner temperature of 82 °C. When the reaction temperature of 82 °C is reached, the mixture is stirred for 16 h.

After 16 h, the jacket temperature is decreased to 65 °C. An in-process control indicated a cyclization yield of 80% based on **6**. Then 6 kg of water is added. The mixture is stirred until complete dissolution of the solid material is observed. Stirring is stopped, and the two liquid phases separate. The aqueous phase is discharged. The toluene phase is washed twice at 60 °C with 1.5 kg water and is then discharged.

All water phases are combined and transferred into the reactor. The pressure is lowered, and isopropanol is distilled off until a content of <2% is reached. The reactor is heated to 75 °C inner temperature (83 °C jacket temperature), and 0.87 kg of 28% aqueous NaOH solution (6.09 mol NaOH) is added, leading to pH 9 at 75 °C. Upon precipitation of $Zn(OH)_2$ the reaction mixture is filtered over a 1 μm Pall filter. The reactor is washed with water, and the aqueous phases are combined and recharged into the reactor. Aqueous 42.8% NaOH solution (1.9 kg, 20.33 mol NaOH) is added, and the content is heated to 80 °C inner temperature. After one hour, the saponification of **10** to **5** is finished, and the reactor content is transferred to a countercurrent extractor where **5** is extracted from the water phase with 1-butanol at 60 °C inner temperature. After the extraction, 1-butanol is evaporated under reduced pressure, leading to 1.008 kg **5** (6.8 mol, 75% yield, 93% purity).

dx.doi.org/10.1021/op300190s | *Org. Process Res. Dev.* XXXX, XXX, XXX−XXX

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures for all synthesized compounds and spectroscopical identification. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: ulla.letinois@dsm.com

Present Address

[†]DSM Biotechnology Centre China, 476 Li Bing Road, Shanghai-Pudong 201203, Peoples Republic of China.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Dr. Gerhard Schiefer and Dieter Gossweiler for analytical support, and Dr. René Stemmler and Dr. Jonathan Medlock for fruitful discussion.

■ ADDITIONAL NOTES

[a]The conditions as disclosed in the BASF patent application have also been tried, leading to 35% yield. Unfortunately, under these conditions the reaction mixture also sticks to the flask walls, and the final product mixture is not homogeneous. The inhomogeneity of the crude product may be the reason why yields of >50% are reported in the patent application but not found in our study.

[b]One reviewer asked if 0.26 equiv of zinc- or copper salts is acceptable in fine chemical synthesis. According to several patents, the use of 20 mol % or more of zinc- or copper salts is quite common in the production of fine chemicals. For example, in vitamin E production, copper salts are used in 50 mol % or more in the oxidation of trimethylphenol to trimethyquinone (see patents from various vitamin E manufacturers such as BASF in EP 1132367, 0.75 equiv $CuCl_2$ and in DE 4029198, from Mitsubishi Gas Chemical Company in EP 127888, 1 mol equiv $CuCl_2$; from Eisai in EP 294584, 0.5 equiv $CuCl_2$. High loadings of zinc salts are used in the condensation of trimethylhydroquinone (see U.S. patent 6,020,505 from Eisai). Recycling and handling of the transition metal waste is not the subject of the current manuscript, and therefore this point is not explained in the text.

■ REFERENCES

(1) Stahl, A.; Heseker, H. *Ernährungsumschau* **2008**, *55*, 420.

(2) Zilles, J. L.; Croal, L. R.; Downs, D. M. *J. Bacteriol.* **2000**, *182*, 5606.

(3) Somogyi, J. C. *Ernährung* **1998**, *22*, 405.

(4) Goodman, L. S., Limbird, L. E., Milinoff, P. B., Ruddon, R. W., Gilman, A. G., Eds.; *Goodman and Gilman's: The Pharmacological Basis of Therapeutics*; McGraw-Hill: New York, 1996.

(5) Eggersdorfer, M.; Adam, G.; John, M.; Hähnlein, W.; Labler, L.; Baldenius, K.; von dem Bussche-Hünnefeld, L.; Hilgemann, E.; Hoppe, P.; Stürmer, R.; Weber, F.; Rüttimann, A.; Moine,, G. ; Hohmann,, H.-P.; Kurth, R.; Paust, J.; Hähnlein, W.; Pauling, H.; Kaesler, B.; Oster, B.; Fechtel, U.; Kaiser, K.; de Potzolli, B. ; Casutt, M.; Koppe, T.; Schwarz, M.; Weimann, B.-J.; Hengartner, U.; de Saizieu, A.; Wehrli, C.; Blum, R. *Ullmann's Encyclopedia of Industrial Chemistry*; Wiley-Blackwell: New York, 2000; Vol. *A27*, pp 77−7810.1002/14356007.a27_443.

(6) Bonrath, W.; Netscher, T. *Appl. Catal., A* **2005**, *280*, 55.

(7) (a) Bewert, W. D.; Kiefer, H. D. (BASF AG). EP 0205131, 1986. (b) Bewert, W. D. ; Littmann, D. W. (BASF AG). EP 0001760, 1979.

(8) Felber, A.; Spruijtenburg R. (DSM Nutritional Products). WO/2003/087041, 2003.

(9) Nishihira, K. C. U. C. F.; Fujikawa, S. C. U. C. F.; Yamashita, M. C. T. M. O. (Ube Industries Ltd.). EP 0279556, 1988.

(10) (a) Bewert, W.; Littmann, W. (BASF AG). DE 2748153, 1979. (b) Littmann, W. DE 2818156, 1979. (c) Ernst, H.; Littmann, W.; Paust, J. (BASF AG). DE 3431270, 1986.

(11) Ernst, H.; Paust, J. (BASF AG). DE 3511273, 1985.

(12) Bonrath, W.; Härter, R.; Karge, R.; Létinois, U. (DSM Nutritional Products). WO/2008/087021, 2008.

(13) Values in water; scale according to Smith, M. B.; Mar, J. *March's Advanced Organic Chemistry*, 5th ed.; Wiley Interscience: New York, 2001; pp 329.

(14) Classification according to Kobayashi: Kobayashi, S.; Busujima, T.; Nagayama, S. *Chem. Eur. J.* **2000**, *6*, 3491.

(15) Anastas, P. T.; Kirchhoff, M. M. *Acc. Chem. Res.* **2002**, *35*, 686.

(16) The program, *STAVEX*, 5.1; Aicos Technologies AG: Basel, Switzerland, wasused for this purpose.

(17) Ege, G.; Pross, M. DE 4333688, 1995; Harada, K.; Choshi, T.; Sugino, E.; Sato, K.; Hibino, S. *Heterocycles* **1994**, *38*, 1119. Gluncic, B.; Kovacevic, K. (PLIVA Tvornica Farmaceutskih i Kemijskih Proizvoda). DE 2248631, 1973.

(18) Alberola, A.; González, A. M.; González, B.; Laguna, M. A.; Pulido, F. J. *Tetrahedron Lett.* **1986**, *27*, 2027.

(19) Bonrath, W.; Fischesser, J.; Giraudi, L.; Karge, R. (DSM Nutritional Products). WO/2006/079504, 2006.

(20) (a) Akalin, E.; Akyuz, S. *Vib. Spectrosc.* **2008**, *48*, 233. (b) Näther, C.; Bhosekar, G.; Jess, I. *Eur. J. Inorg. Chem.* **2007**, 5353.

(21) Prince, B. J.; Turnbull, M. M.; Willett, R. D. *J. Coord. Chem.* **2003**, *56*, 441.

(22) (a) Malandrinos, G.; Louloudi, M.; Koukkou, A. I; Sovago, I.; Drainas, C.; Hadjiliadis, N. *J. Biol. Inorg. Chem.* **2000**, *5*, 218. (b) Talbert, P. T.; Weaver, J. A.; Hambright, P. *J. Inorg. Nucl. Chem.* **1970**, *32*, 2147.

(23) (a) Habib, U.; Badshah, A.; Flörke, U.; Qureshi, R.; Mirza, B.; Nazar-ul-Islam, A. K. *J. Chem. Crystallogr.* **2009**, *39*, 730. (b) Kulkarni, D. R.; Mulay, M. R.; Rodge, J. K.; Deshpande, M. N.; Ardhapurkar, S. S. *Int. J. Pharm. Biosci.* **2010**, *1*, 1.

(24) Reichle, R. A.; McCurdy, K. G.; Hepler, L. G. *Can. J. Chem.* **1975**, *53*, 3841.

(25) Elementary analysis by AAS.

(26) Patterson, J. W.; Boice, R. E.; Marani, D. *Environ. Sci. Technol.* **1991**, *25*, 1780.