Tetrahedron Letters 49 (2008) 4607–4609

Contents lists available at ScienceDirect

Tetrahedron Letters

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

First synthesis of 4,5-dihydro-3(2*H*)-pyridazinones via Zn-mediated hydrohydrazination

Karolin Alex, Annegret Tillack, Nicolle Schwarz, Matthias Beller *

Leibniz-Institut für Katalyse e.V. an der Universität Rostock, Albert-Einstein-Strasse 29a, 18059 Rostock, Germany

ARTICLE INFO

Article history:
Received 8 April 2008
Revised 18 May 2008
Accepted 19 May 2008
Available online 23 May 2008

Keywords:
Hydrazine
Hydroamination
Intermolecular
Pentynoic acid
Pyridazinone
Zinc

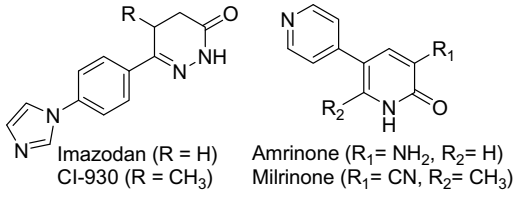
ABSTRACT

The hydrohydrazination of 4-pentynoic acid with different arylhydrazines proceeds smoothly in the presence of zinc chloride. The domino amination–amidation sequence leads to aryl-substituted 4,5-dihydro-3(2*H*)-pyridazinones.

Pyridazines represent an important class of biologically active compounds.[1] Especially pyridazinone derivatives are well known for their treatment in cardiovascular and heart diseases because of their blood pressure reduction properties as well as platelet-aggregation-inhibition and cardiotonic effects.[2] Besides, aryl-substituted 4,5-dihydro-3(2*H*)-pyridazinones such as imazodan are reported to show ionotropic properties comparable to milrinone and amrinone (Scheme 1).[3]

In general, the synthesis of 4,5-dihydro-3(2*H*)-pyridazinones proceeds via reaction of γ-ketoacids and their derivatives with alkylhydrazines or phenylhydrazines to give the corresponding hydrazones.[4] The resulting hydrazones are known to be converted by a simple condensation reaction to pyridazinones.[5] Other syntheses of pyridazinones are based for example on condensation of Wittig reagents with arylhydrazones or condensation of α-keto-esters with hydrazinocarbonyl-acetic acid esters.[6]

For some time, we have been involved in catalytic intermolecular hydroamination reactions of alkynes with amines[7,8] and arylhydrazines (hydrohydrazination).[9] Notably, in these domino reactions alkynes behave somewhat similar to carbonyl compounds. Indeed, imines as well as interesting heterocycles such as indoles[9,10] and pyrazolines[11] are directly available from alkynes. Most recently, we demonstrated that zinc chloride and zinc triflate are especially well-suited as catalysts for such reactions of terminal alkynes.[12]

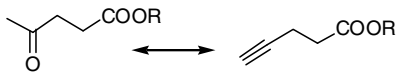


Scheme 1. Selected examples of biologically active pyridazinones.

With respect to the analogy of alkynes and carbonyl compounds, we thought that 4-pentynoic acid derivatives should behave similar to γ-ketoacid derivatives (Scheme 2).

Based on this idea, herein we describe for the first time the synthesis of different aryl-substituted 4,5-dihydro-3(2*H*)-pyridazinones from alkynes.

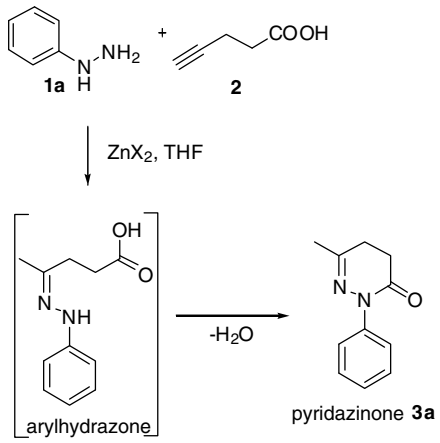
To our delight, the reaction of phenylhydrazine (**1a**) with 4-pentynoic acid (**2**) in the presence of 1 equiv $ZnCl_2$ resulted in the formation of the corresponding pyridazinone **3a** (Scheme 3). In agreement with previous work the hydrohydrazination reaction proceeds with complete regioselectivity toward the Markovnikov product.[13]



Scheme 2. Analogy of γ-ketoacids and 4-pentynoic acid.

* Corresponding author. Tel.: +49 (0)381 1281113; fax: +49 (0)381 128151113.
E-mail address: matthias.beller@catalysis.de (M. Beller).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.05.084



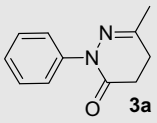
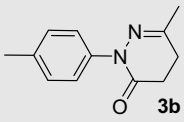
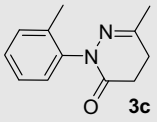
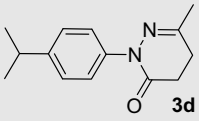
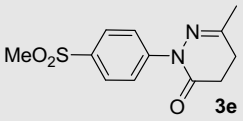
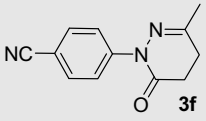
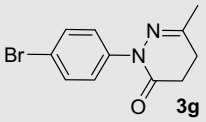
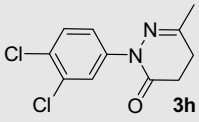
Scheme 3. Synthesis of pyridazinone **3a**.

In order to study this novel pyridazinone formation in more detail, we examined the influence of different reaction conditions (variation of Lewis acids, solvents, temperature), and changes in reaction time on the reaction of phenylhydrazine (**1a**) with 4-pentynoic acid (**2**). Selected results are presented in Table 1.

Initially, we investigated the effects of different Zn salts as well as $Yb(OTf)_3$ or $FeCl_3$ as Lewis acids. All the Zn salts showed full conversion and the best yield (81%) is obtained applying $Zn(OTf)_2$ (Table 1, entries 1–5). Increasing the amount of $Zn(OTf)_2$ from 1 equiv to 3 equiv the yield dropped down (Table 1, entries 1 and 8). Advantageously, using 3 equiv of $ZnCl_2$ the desired product is observed in 90% yield (Table 1, entry 7). It is important to note that applying catalytic amounts of zinc salts gave significantly lower yields. The necessity to apply stoichiometric amounts of the Zn salt is explained due to deactivation by the product similar to Friedel–Crafts acylation reactions.[14] As solvents, dioxane and toluene gave a much lower yield compared to tetrahydrofuran (Table 1, entries 9 and 10). In general, the alkyne is consumed relatively fast, but the best yields are obtained after 24 h (Table 1, entries 11 and 12). Apparently, the intramolecular amidation reaction seems to be the rate-determining step. By comparing the stoichiometric ratio of the starting materials the highest product yield is obtained with a slight excess of phenylhydrazine (Table 1, entries 7, 13, and 14).

Next, we studied reactions of 4-pentynoic acid (**2**) with substituted arylhydrazines **1** under optimized conditions in the presence of the cheap and easily available $ZnCl_2$. After Zn-mediated hydrohydrazination and subsequent condensation reactions, it is possi-

Table 2
Reaction of arylhydrazines **1** with 4-pentynoic acid (**2**) to various aryl-substituted pyridazinones **3**[a]

Entry	Pyridazinone **3**	Yield[b] (%)
1	 **3a**	72
2	 **3b**	61
3	 **3c**	47
4	 **3d**	64
5	 **3e**	53
6	 **3f**	67
7	 **3g**	71
8	 **3h**	57

[a] Reaction conditions: 4-pentynoic acid (1.5 mmol), arylhydrazine (1.95 mmol), 3 equiv $ZnCl_2$, THF (3 mL), 24 h, 100°C.
[b] Isolated yield.

Table 1
Reaction of phenylhydrazine (**1a**) with 4-pentynoic acid (**2**) under different conditions[a]

Entry	Lewis acid	Equiv	Solvent	Time (h)	Ratio (alkyne:hydrazine)	Conversion[b] (%)	Yield[b] (%)
1	$Zn(OTf)_2$	1	THF	24	1:1.3	100	81
2	$Zn(OAc)_2$	1	THF	24	1:1.3	100	69
3	$Yb(OTf)_3$	1	THF	24	1:1.3	89	14
4	$FeCl_3$	1	THF	24	1:1.3	32	0
5	$ZnCl_2$	1	THF	24	1:1.3	100	56
6	$ZnCl_2$	2	THF	24	1:1.3	100	74
7	$ZnCl_2$	3	THF	24	1:1.3	100	90
8	$Zn(OTf)_2$	3	THF	24	1:1.3	100	57
9	$ZnCl_2$	3	Dioxane	24	1:1.3	100	45
10	$ZnCl_2$	3	Toluene	24	1:1.3	100	35
11	$ZnCl_2$	3	THF	9	1:1.3	100	59
12	$ZnCl_2$	3	THF	16	1:1.3	100	71
13	$ZnCl_2$	3	THF	24	1:1	100	74
14	$ZnCl_2$	3	THF	24	1:2	100	56

[a] Reaction conditions: phenylhydrazine, 4-pentynoic acid, solvent (2 mL), 100 °C.
[b] Yield and conversion were determined by GC analysis with dodecane as internal standard.

ble to isolate the pyridazinone derivatives **3a–h** directly in moderate to good yields (Table 2). For example, reaction of *p*-tolylhydrazine proceeded over both steps in 61% yield (Table 2, entry 2), while the more sterical hindered *o*-tolylhydrazine gave a lower yield of 47% (Table 2, entry 3). Compared to the *p*-tolyl-substituted pyridazinone a similar yield is observed for the *p*-isopropyl-substituted pyridazinone derivative with 64% yield (Table 2, entry 4). Besides alkyl-substituted arylhydrazines, we also tested phenylhydrazines with electron-withdrawing substituents. These methylsulfonyl-, cyano-, and 4-bromophenyl-substituted pyridazinones are synthesized in up to 71% yield (Table 2, entries 5–7). In addition, the 3,4-dichloro-substituted phenylhydrazine in *para*- and *meta*-position gave the corresponding pyridazinone **3h** in 57% yield (Table 2, entry 8).

In conclusion, we have developed a novel method for the synthesis of aryl-substituted 4,5-dihydro-3(2*H*)-pyridazinones based on domino hydrohydrazination and condensation reactions. Eight substituted arylhydrazines react with 4-pentynoic acid in the presence of $ZnCl_2$ to give the corresponding pyridazinone derivatives in a one-pot process in moderate to good yields. Notably, this convenient and practical procedure does not require any special handling, unusual reagents, and proceeds without the exclusion of air or water.

Acknowledgments

This work has been funded by the State of Mecklenburg-Western Pomerania, the BMBF (Bundesministerium für Bildung und Forschung), the Deutsche Forschungsgemeinschaft (Graduiertenkolleg 1213, and Leibniz-price), and the Fonds der Chemischen Industrie (FCI). We thank Dr. W. Baumann, Dr. C. Fischer, S. Buchholz, S. Schareina, and K. Mevius for their excellent technical and analytical support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.05.084.

References and notes

1. (a) Mitchinson, A.; Blackaby, W. P.; Bourrain, S.; Carling, R. W.; Lewis, R. T. *Tetrahedron Lett.* **2006**, *47*, 2257–2260; Review (b) Lee, S.-G.; Kim, J.-J.; Kim, H.-K.; Kweon, D.-H.; Kang, Y.-J.; Cho, S.-D.; Kim, S.-K.; Yoon, Y.-J. *Curr. Org. Chem.* **2004**, *8*, 1463–1480; (c) Byth, K. F.; Cooper, N.; Culshaw, J. D.; Heaton, D. W.; Oajes, S. F.; Minshull, C. A.; Norman, R. A.; Pauptit, R. A.; Tucker, J. A.; Breed, J.; Pannifer, A.; Roswell, S.; Slanway, J. J.; Valentine, A. L.; Thomas, A. P. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2249–2252; (d) Velentza, A. V.; Wainwright, M. S.; Zadadzki, M.; Mirzoeva, S.; Schumacher, M.; Haiech, J.; Focia, P. J.; Egli, M.; Waterson, D. M. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3465–3470; (e) Contreras, J. M.; Parrot, I.; Sippl, W.; Rival, Y. M.; Wermuth, C. G. *J. Med. Chem.* **2001**, *44*, 2707–2718; (f) Katritzky, A. R.; Pleynet, D. P. M.; Yang, B.; Yao, J. *Synthesis* **1998**, 1627–1630. and references therein; Review (g) Matyus, P. *J. Heterocycl. Chem.* **1998**, *35*, 1075–1089; (h) Coates, W. J. Pyridazines and Their Benzo Derivatives. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, 1996; Vol. 6, p 191.
2. Estevez, I.; Ravina, E.; Sotelo, E. *J. Heterocycl. Chem.* **1998**, *35*, 1421–1428. and references therein.
3. (a) Sircar, I.; Duell, B. L.; Bobowski, G.; Bristol, J. A.; Evans, D. B. *J. Med. Chem.* **1985**, *28*, 1405–1413; (b) Bristol, J. A. *J. Med. Chem.* **1984**, *27*, 1099–1101.
4. (a) Campos, K. R.; Woo, J. C. S.; Lee, S.; Tillyer, R. D. *Org. Lett.* **2004**, *6*, 79–82; (b) Gouault, N.; Cupif, J. F.; Picard, S.; Lecat, A.; David, M. *J. Pharm. Pharmacol.* **2001**, *53*, 981–985; (c) Ege, S. N.; Carter, M. L. C.; Ortwine, D. F.; Chou, S.-S. P.; Richman, J. F. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1252–1257; (d) Wamhoff, H.; Korte, F. *Liebigs Ann. Chem.* **1969**, *724*, 217–220; (e) Stevens, F. J.; Griffin, T. D.; Fields, T. L. *J. Am. Chem. Soc.* **1955**, *77*, 42–44.
5. Fischer, E. *Liebigs Ann. Chem.* **1886**, *236*, 126–151.
6. Recent selected examples: (a) Murphy, D. E.; Dragovich, P. S.; Ayida, B. K.; Bertolini, T. M.; Li, L.-S.; Ruebsam, F.; Stankovic, N. S.; Sun, Z.; Zhao, J.; Zhou, Y. *Tetrahedron Lett.* **2008**, *49*, 811–815; (b) Mohamed, N. R.; El-Saidi, M. M. T.; Ali, Y. M.; Elnagdi, M. H. *J. Heterocycl. Chem.* **2007**, *44*, 1333–1337; (c) de Araujo-Junior, J. X.; Schmitt, M.; Antheaume, C.; Bourguignon, J.-J. *Tetrahedron Lett.* **2007**, *48*, 7817–7820; (d) Helm, M. D.; Plant, A.; Harrity, J. P. A. *Org. Biomol. Chem.* **2006**, *4*, 4278–4280.
7. (a) Alex, K.; Tillack, A.; Schwarz, N.; Beller, M. *ChemSusChem* **2008**, *1*, 333–338; (b) Tillack, A.; Khedkar, V.; Jiao, H.; Beller, M. *Eur. J. Org. Chem.* **2005**, 5001–5012; (c) Tillack, A.; Khedkar, V.; Beller, M. *Tetrahedron Lett.* **2004**, *45*, 8875–8878; (d) Khedkar, V.; Tillack, A.; Beller, M. *Org. Lett.* **2003**, *5*, 4767–4770; (e) Tillack, A.; Garcia Castro, I.; Hartung, C. G.; Beller, M. *Angew. Chem.* **2002**, *114*, 2646–2648; . *Angew. Chem., Int. Ed.* **2002**, *41*, 2541–2543.
8. Selected recent reviews on hydroaminations of alkynes: (a) Severin, R.; Doye, S. *Chem. Soc. Rev.* **2007**, *36*, 1407–1420; (b) Lee, A. V.; Schafer, L. L. *Eur. J. Inorg. Chem.* **2007**, 2243–2255; (c) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079–3159.
9. (a) Alex, K.; Schwarz, N.; Khedkar, V.; Sayyed, I. A.; Tillack, A.; Michalik, D.; Holenz, J.; Diaz, J. L.; Beller, M. *Org. Biomol. Chem.* **2008**, *6*, 1802–1807; (b) Sayyed, I. A.; Alex, K.; Tillack, A.; Schwarz, N.; Spannenberg, A.; Michalik, D.; Beller, M. *Tetrahedron* **2008**, *64*, 4590–4595; (c) Schwarz, N.; Alex, K.; Sayyed, I. A.; Khedkar, V.; Tillack, A.; Beller, M. *Synlett* **2007**, 1091–1095; (d) Sayyed, I. A.; Alex, K.; Tillack, A.; Schwarz, N.; Michalik, D.; Beller, M. *Eur. J. Org. Chem.* **2007**, 4525–4528; (e) Khedkar, V.; Tillack, A.; Michalik, D.; Beller, M. *Tetrahedron* **2005**, *61*, 7622–7631; (f) Tillack, A.; Jiao, H.; Garcia Castro, I.; Hartung, C. G.; Beller, M. *Chem. Eur. J.* **2004**, *10*, 2409–2420; (g) Khedkar, V.; Tillack, A.; Michalik, M.; Beller, M. *Tetrahedron Lett.* **2004**, *45*, 3123–3126.
10. (a) Banerjee, S.; Barnea, E.; Odom, A. L. *Organometallics* **2008**, *27*, 1005–1014; (b) Ackermann, L.; Born, R. *Tetrahedron Lett.* **2004**, *45*, 9541–9544; (c) Cao, C.; Shi, Y.; Odom, A. L. *Org. Lett.* **2002**, *4*, 2853–2856; (d) Walsh, P. T.; Carney, M. J.; Bergman, R. G. *J. Am. Chem. Soc.* **1991**, *113*, 6343–6345.
11. Alex, K.; Tillack, A.; Schwarz, N.; Beller, M. *Org. Lett.*, in press.
12. (a) Alex, K.; Tillack, A.; Schwarz, N.; Beller, M. *Angew. Chem.* **2008**, *120*, 2337–2340; *Angew. Chem., Int. Ed.* **2008**, *47*, 2304–2307.
13. For a recent review on Markovnikov and *anti*-Markovnikov functionalization of olefins and alkynes, see: (a) Seayad, J.; Tillack, A.; Jiao, H.; Beller, M. *Angew. Chem.* **2004**, *116*, 3448–3479; *Angew. Chem., Int. Ed.* **2004**, *43*, 3368–3398.
14. For recent review in Friedel–Crafts acylation reaction, see: Sartori, G.; Maggi, R. *Chem. Rev.* **2006**, *106*, 1077–1104.