Synthesis of 5-Aroyldihydropyrimidinones via Liebeskind–Srogl Thiol Ester–Boronic Acid Cross-Couplings

Hana Prokopcová, Leonardo Pisani, C. Oliver Kappe*

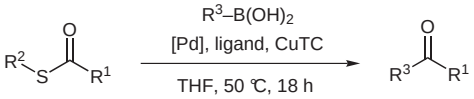
Christian Doppler Laboratory for Microwave Chemistry and Institute of Chemistry, Karl-Franzens-University Graz, Heinrichstraße 28, 8010 Graz, Austria
Fax +43(316)3809840; E-mail: oliver.kappe@uni-graz.at
Received 6 August 2006

Abstract: A novel and efficient two-step synthesis of 5-aroyl-3,4-dihydropyrimidin-2-ones is reported. These privileged ketone structures are readily generated by microwave-assisted Liebeskind–Srogl-type coupling of boronic acids with the corresponding pyrimidone thiol esters. The thiol esters themselves are easily prepared using Biginelli multicomponent chemistry.

Key words: transition metals, cross-coupling, catalysis, ketones, heterocycles

Transition-metal-catalyzed carbon–carbon cross-coupling procedures have revolutionized the art and practice of organic synthesis in the last two decades.[1] The typically mild reaction conditions, high functional group tolerance and broad availability of starting materials have contributed to the growing success of e.g. palladium-catalyzed carbon–carbon bond formation methods. Apart from the well-known Suzuki–Miyaura biaryl cross-coupling,[2] a growing number of related transition-metal-catalyzed carbon–carbon[1,3] and carbon–heteroatom coupling protocols[4] have been reported in the recent literature, underpinning the versatility and importance of transition-metal-mediated reactions for organic synthesis.

Recently, Liebeskind and Srogl developed a novel carbon–carbon cross-coupling protocol, involving the Pd(0)-catalyzed, Cu(I)-mediated coupling of thiol esters with boronic acids to form ketones under neutral conditions (Scheme 1).[5] A key feature of this protocol, and of closely related procedures involving thioethers,[6,7] is the requirement of stoichiometric amounts of a Cu(I) carboxylate [e.g. Cu(I) thiophene-2-carboxylate, CuTC][8] as metal cofactor. Due to the higher thiophilicity of the soft Cu(I) metal, selective sulfide coupling under Liebeskind–Srogl conditions can be performed even in the presence of a, for example, Suzuki-active bromide.[9] A variety of palladium precatalysts/ligand systems such as $Pd_2(dba)_3$/tris(2-furyl)phosphine (TFP) are effective in this transformation (Scheme 1), and moderate to excellent yields of the desired ketones can typically be achieved by coupling of aromatic and aliphatic *S*-alkyl and *S*-aryl thiol esters with different boronic acids.[5]



Scheme 1 Palladium-catalyzed Liebeskind–Srogl ketone synthesis

Despite the apparent attractiveness of this general and mild transition-metal-mediated protocol reported by Liebeskind and Srogl in 2000,[5] there are surprisingly few applications of this ketone synthesis for the preparation of more complex target structures.[10] In continuation of our interest in the generation of diversely substituted and novel types of privileged scaffolds based on 3,4-dihydropyrimidin-2-one (DHPMs),[11–14] we herein report the efficient synthesis of 5-aroyldihydropyrimidinones **1** (Figure 1) via Liebeskind–Srogl ketone synthesis starting from the corresponding DHPM-5-carboxylic acid thiol esters **2**.

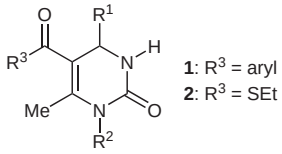


Figure 1 General structure of target 5-aroyldihydropyrimidin-2-ones **1**

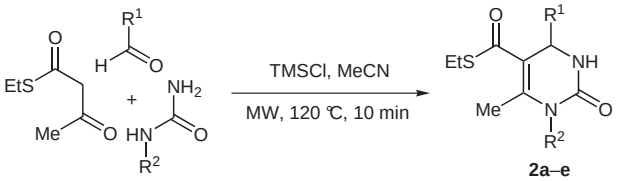
Our strategy toward ketones **1** first required an efficient access to the corresponding DHPM thiol ester precursors **2**. To the best of our knowledge there is only one reference to the synthesis of a DHPM-5-carboxylic acid thiol ester in the literature, utilizing a Biginelli-type three-component cyclocondensation involving ethyl thioacetoacetate, an aromatic aldehyde and urea under acidic conditions.[15]

For Biginelli multicomponent reactions of this type a plethora of highly efficient synthetic methods is available in the literature,[14] including protocols that make use of controlled microwave irradiation.[11,16] In contrast to many of the recently reported methods involving the use of an expensive Lewis acid catalyst such as $Yb(OTf)_3$,[11] we have utilized trimethylsilyl chloride (TMSCl) in the current protocol as an inexpensive mediator of the Biginelli reaction.[17] Gratifyingly, a high yield of DHPM-5-carboxylic acid *S*-ethyl thiol ester **2a** was obtained by microwave heating[16] (120 °C, 10 min) of a mixture of ethyl thioacetoacetate, benzaldehyde and urea (1:1:3) in MeCN with

SYNLETT 2007, No. 1, pp 0043–0046
Advanced online publication: 20.12.2006
DOI: 10.1055/s-2006-958443; Art ID: D23806ST

one equivalent of TMSCl in a sealed reaction vessel (Table 1). The isolated yield of 90% obtained from these optimized conditions compared very favorably with microwave experiments using 10 mol% of $Yb(OTf)_3$ as catalyst (86% yield),[11] and with room temperature protocols involving TMSCl as a mediator requiring several hours of reaction time.[17] The high-speed microwave method proved applicable for a variety of different substrates, including the use of sterically demanding *ortho*-substituted aromatic aldehyde **2c** as well as *N*-alkylureas **2d**,**e** as building blocks (see Table 1). Although the required key precursor for this synthesis, ethyl thioacetoacetate, is not commercially available, it can be rapidly prepared in large quantities starting from inexpensive starting materials,[18] therefore allowing efficient access to DHPM-5-carboxylic acid thiol esters of type **2** in sufficient quantities.

Table 1 Synthesis of Dihydropyrimidine-5-carboxylic Acid Thiol Esters **2** via Microwave-Assisted Biginelli Reaction



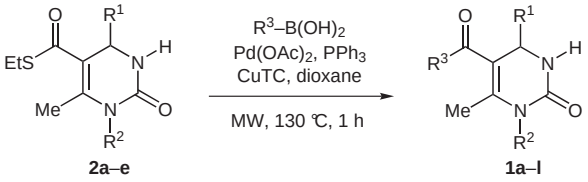
DHPM **2**	R^1	R^2	Yield (%)[a]
2a	Ph	H	90
2b	3-BrC_6H_4	H	86
2c	2-$CF_3C_6H_4$	H	66
2d	3,4-$(F)_2C_6H_3$	Et	53
2e	Thiophen-2-yl	Me	62

[a] Isolated yields of pure product.

With the required DHPM thiol esters **2** in hand, we next set out to evaluate the suitability of these multifunctionalized heterocycles to serve as starting materials in the Liebeskind–Srogl ketone synthesis. As a model system for our optimization studies, the reaction of thiol ester **2a** with phenylboronic acid was selected (Table 2).

Under controlled single-mode microwave heating in sealed vessels,[16] the reaction conditions were refined with respect to the solvent, the type and concentration of the Pd(0) catalyst, the number of equivalents of the CuTC cofactor, the amount of boronic acid, the reaction temperature and irradiation time. Since coordinating solvents such as DMF are not useful in this protocol,[5–7] our attention focused on the use of THF and dioxane as solvents. In our hands the highest yields were typically obtained by using anhydrous dioxane as solvent. As far as the Pd catalyst is concerned, most of the catalyst/ligand systems reported by Liebeskind and Srogl for this and related thioorganics–boronic acid cross-couplings [e.g. $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, $Pd(OAc)_2/P(t\text{-}Bu)_3$, $Pd(dba)_2/PPh_3$, $Pd(PPh_3)_4/Zn(OAc)_2$, Hermann's catalyst/dppf, $Pd_2dba_3{\cdot}CHCl_3$/TFP, $PdCl_2$(dppf)/TFP] were found to be useful for this transformation. We do find that for the specific carbon–carbon coupling discussed herein, the use of comparatively inexpensive $Pd(OAc)_2$ as a precatalyst and PPh_3 as a ligand consistently provided the best results and was most convenient to work with. Our optimized reaction conditions utilized 2.0 equivalents of phenylboronic acid, 10 mol% of $Pd(OAc)_2$, 20 mol% of PPh_3 and 3.0 equivalents of CuTC in anhydrous dioxane as solvent, applying an Ar atmosphere. Lower catalyst loadings (e.g. 1–5 mol%) led to significantly decreased yields. The cleanest conversions **2a** → **1a** (monitored by HPLC) were achieved by exposing the reaction mixture to controlled microwave heating at 130 °C for one hour. Higher reaction temperatures resulted in more by-product formation, while shorter reaction times led to incomplete conversions. Purification of the crude reaction mixture by column chromatography provided the desired DHPM ketone **1a** in 86% isolated yield. Comparison studies using traditional heating in an oil bath (reflux, 110 °C) required 12 hours to reach completion and provided a 63% isolated product yield under otherwise identical reaction conditions.

Table 2 Microwave-Assisted Liebeskind–Srogl Thiol Ester–Boronic Acid Coupling for the Synthesis of 5-Aroyldihydropyrimidinones **1**



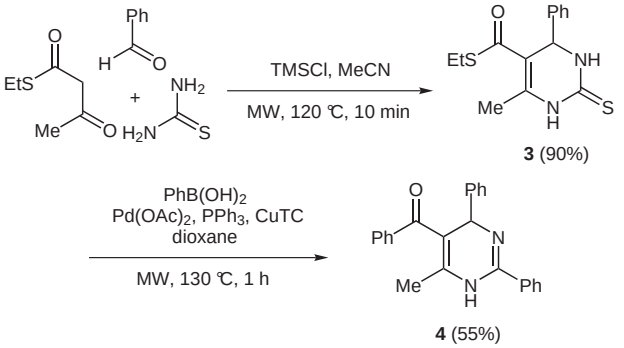
DHPM **1**	R^1	R^2	R^3	Yield (%)[a]
1a	Ph	H	Ph	86
1b	Ph	H	3-ClC_6H_4	80
1c	Ph	H	4-MeC_6H_4	78
1d	Ph	H	3-$MeOC_6H_4$	74
1e	Ph	H	3,4-$(F)_2C_6H_3$	88
1f	3-BrC_6H_4	H	Ph	66
1g	3-BrC_6H_4	H	4-MeC_6H_4	61
1h	3-BrC_6H_4	H	3,4-$(F)_2C_6H_3$	68
1i	2-$CF_3C_6H_4$	H	Ph	65
1j	2-$CF_3C_6H_4$	H	3-ClC_6H_4	70
1k	Thiophen-2-yl	Me	Ph	82
1l	3,4-$(F)_2C_6H_3$	Et	Ph	73

[a] Isolated yields of pure product after column chromatography.

In order to explore the general scope of this novel 5-aroyl-DHPM synthesis a small collection of 12 ketone products was generated, using a combination of the five DHPM thiol esters **2a**–**e** discussed above (Table 1) and five boronic acids (see R^3 in Table 2). As can be seen from the isolated yields presented in Table 2 the reaction is very general, allowing different substitution patterns on the DHPM scaffold (R^1, R^2), but also tolerating both electron-rich and electron-poor aryl boronic acids (R^3) as coupling partners. Without any further optimization of the reaction conditions, good product yields (61–88%) were obtained for all cases.

Importantly, the completely neutral, base-free conditions used here allow total selectivity for the Liebeskind–Srogl carbon–carbon bond formation (ketone synthesis), without any Suzuki coupling (biaryl synthesis) being observed for cases where 'Suzuki-active' aryl bromides are incorporated on the scaffold (DHPMs **1f**–**h**).[9,19]

Finally, we were interested in performing Liebeskind–Srogl-type bis-couplings on a DHPM substrate that contained two independent carbon–sulfur connections. In a recent study, we demonstrated that direct Pd(0)-catalyzed/Cu(I)-mediated carbon–carbon cross-coupling of 3,4-dihydropyrimidine-2-thiones and boronic acids under Liebeskind–Srogl conditions leads to 2-aryl-1,4-dihydropyrimidines.[13] In order to evaluate the potential to combine both carbon–carbon bond-forming events in a one-pot reaction, a suitable 2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid thiol ester was synthesized and treated with excess of phenylboronic acid using our standard Liebeskind–Srogl conditions (Scheme 2). In the event, microwave irradiation of a reaction mixture containing pyrimidine-2-thione thiol ester **3**, 4.0 equivalents of phenylboronic acid, 15 mol% of $Pd(OAc)_2$, 30 mol% of PPh_3 and 5.0 equivalents of CuTC in anhydrous dioxane provided bis-coupling product **4** in 55% (non-optimized) isolated yield after purification by column chromatography.



Scheme 2 Liebeskind–Srogl-type bis-couplings

In conclusion, we have developed a two-step protocol for the synthesis of diversely substituted 5-aroyl-3,4-dihydropyrimidine-2-ones **1**, combining a Biginelli multicomponent approach with the transition-metal-catalyzed Liebeskind–Srogl ketone synthesis. This novel method uses commercially available building blocks (aldehydes, boronic acids, ureas) to generate diversity on the DHPM scaffold that is otherwise not easily available.[20] Both steps can be carried out efficiently throug the use of controlled microwave irradiation.

Typical Procedure for the Microwave-Assisted TMSCl-Promoted Biginelli Reaction (Table 1)

In a 10 mL Pyrex microwave process vial, the appropriate aldehyde (0.5 mmol), urea (1.5 mmol), (*S*)-ethyl thioacetoacetate (0.5 mmol), and MeCN (0.75 mL) were placed. After the addition of TMSCl (0.5 mmol) the vessel was sealed and subsequently irradiated for 10 min at 120 °C with magnetic stirring. After cooling to ambient temperature, the mixture was poured onto crushed ice (10 g) and allowed to stand at r.t. for 18 h. The resulting precipitated solid was collected by filtration and washed with a cold 1:1 mixture of EtOH–H_2O, providing the desired DHPM products **2a**–**e** in 53–90% yield and high purity (>98% by HPLC).

Typical Procedure for the Liebeskind–Srogl DHPM Ketone Synthesis (Table 2)

A dry microwave process vial was charged with the corresponding DHPM **2** (0.15 mmol), the appropriate boronic acid (0.3 mmol), CuTC (0.45 mmol), $Pd(OAc)_2$ (10 mol%) and PPh_3 (20 mol%). Then the reaction vessel was sealed and flushed with Ar. Through the septum of the microwave vessel, anhyd and degassed dioxane (1 mL) was added and the mixture was subsequently heated for 1 h at 130 °C using microwave irradiation. After cooling to ambient temperature, the solvent was evaporated and the crude mixture diluted with EtOAc (50 mL) and extracted with 10% aq NH_3 (3 × 15 mL). The organic layer was dried over $MgSO_4$ and then concentrated under reduced pressure to afford a semisolid that was subsequently purified by silica gel column chromatography, using a 5:1 mixture of $CHCl_3$–acetone or $CHCl_3$–PE eluent. This procedure provides the pure ketones **1a**–**l** in 61–88% yield. Spectroscopic data for **1a**: $C_{18}H_{16}N_2O_2$, white solid, mp 212–213 °C (lit.[20e] mp 214–216 °C). ^{1}H NMR (360 MHz, DMSO-d_6): δ = 1.66 (s, 3 H), 5.29 (s, 1 H), 7.19–7.24 (m, 3 H), 7.28–7.33 (m, 2 H), 7.42–7.43 (m, 4 H), 7.49–7.53 (m, 1 H), 7.80 (s, 1 H), 9.17 (s, 1 H). MS (pos APCI): *m/z* = 353. All compounds were fully identified by NMR and MS analysis.

Acknowledgment

This work was supported by the Austrian Academic Exchange Service (OeAD). L. P. thanks the University of Bari for financial support. We thank also Biotage AB (Uppsala, Sweden) for the provision of the Emrys Synthesizer and Initiator Eight.

References and Notes

(1) (a) *Transition Metals for Organic Synthesis*; Beller, M.; Bolm, C., Eds.; Wiley-VCH: Weinheim, **2004**. (b) *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A.; Diederich, F., Eds.; Wiley-VCH: Weinheim, **2004**.
(2) Suzuki, A.; Miyaura, N. *Chem. Rev.* **1995**, *95*, 2457.
(3) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359.
(4) Ley, S. V.; Thomas, A. W. *Angew. Chem. Int. Ed.* **2003**, *42*, 5400.
(5) (a) Liebeskind, L. S.; Srogl, J. *J. Am. Chem. Soc.* **2000**, *122*, 11260. (b) Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2000**, *2*, 3229.

(6) (a) Liebeskind, L. S.; Srogl, J. *Org. Lett.* **2002**, *4*, 979. (b) Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2000**, *2*, 3229. (c) Kusturin, C.; Liebeskind, L. S.; Neumann, W. L. *Org. Lett.* **2002**, *4*, 983. (d) Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2001**, *3*, 91. (e) Alphonse, F. A.; Suzenet, F.; Keromnes, A.; Lebret, B.; Guillameut, G. *Synlett* **2002**, 447.
(7) For reviews, see: (a) Lory, P.; Gilbertson, S. R. *Chemtracts* **2005**, *18*, 569. (b) Fukuyama, T.; Tokuyama, H. *Aldrichimica Acta* **2004**, *37*, 87.
(8) Innitzer, A. *Synlett* **2005**, 2405.
(9) Kusturin, C.; Liebeskind, L. S.; Rahman, H.; Sample, K.; Schweitzer, B.; Srogl, J.; Neumann, W. L. *Org. Lett.* **2003**, *5*, 4349.
(10) (a) Rodriguez-Cendejas, C. G.; Liebeskind, L. S.; Pena-Cabrera, E. *ARKIVOC* **2005**, *(vi)*, 250. (b) Achab, S.; Diker, K.; Potier, P. *Tetrahedron Lett.* **2001**, *42*, 8825. (c) Nambu, H.; Hata, K.; Matsugi, M.; Kita, Y. *Chem. Eur. J.* **2005**, *11*, 719.
(11) Stadler, A.; Kappe, C. O. *J. Comb. Chem.* **2001**, *3*, 624.
(12) (a) Dallinger, D.; Kappe, C. O. *Synlett* **2002**, 1901. (b) Dallinger, D.; Gorobets, N. Yu.; Kappe, C. O. *Org. Lett.* **2003**, *5*, 1205. (c) Dallinger, D.; Gorobets, N. Yu.; Kappe, C. O. *Mol. Diversity* **2003**, *7*, 229. (d) Khanetskyy, B.; Dallinger, D.; Kappe, C. O. *J. Comb. Chem.* **2004**, *6*, 884. (e) Wannberg, J.; Dallinger, D.; Kappe, C. O.; Larhed, M. *J. Comb. Chem.* **2005**, *7*, 574. (f) Desai, B.; Kappe, C. O. *J. Comb. Chem.* **2005**, *7*, 641. (g) Desai, B.; Dallinger, D.; Kappe, C. O. *Tetrahedron* **2006**, *62*, 4651.
(13) Lengar, A.; Kappe, C. O. *Org. Lett.* **2004**, *6*, 771.
(14) For reviews on DHPMs, see: (a) Kappe, C. O. *Tetrahedron* **1993**, *49*, 6937. (b) Kappe, C. O. *Acc. Chem. Res.* **2000**, *33*, 879. (c) Kappe, C. O. *Eur. J. Med. Chem.* **2000**, *35*, 1043. (d) Kappe, C. O.; Stadler, A. *Org. React.* **2004**, *63*, 1.
(15) Kadis, V.; Stradins, J.; Khanina, E. L.; Dubурs, G.; Muceniece, D. *Khim. Geterotsikl. Soedin.* **1985**, 117.
(16) For recent reviews on microwave synthesis, see: (a) De La Hoz, A.; Diaz-Ortiz, A.; Moreno, A. *Chem. Soc. Rev.* **2005**, *34*, 164. (b) Kappe, C. O. *Angew. Chem. Int. Ed.* **2004**, *43*, 6250. (c) Hayes, B. L. *Aldrichimica Acta* **2004**, *37*, 66. (d) Kappe, C. O.; Dallinger, D. *Nature Rev. Drug Discov.* **2006**, *5*, 51.
(17) (a) Zhu, Y.; Pan, Y.; Huang, S. *Synth. Commun.* **2004**, *34*, 3167. (b) Zhu, Y.; Huang, S.; Pan, Y. *Eur. J. Org. Chem.* **2005**, 2354. (c) Zhu, Y.; Pan, Y.; Huang, S. *Heterocycles* **2005**, *65*, 133.
(18) Wilson, G. E.; Hess, A. *J. Org. Chem.* **1980**, *45*, 2766.
(19) For base-catalyzed Suzuki reactions of 3-bromophenyl-DHPMs with boronic acids, see ref. 12e.
(20) The synthesis of DHPMs of type **1** by direct Biginelli condensation involving benzoylacetone has been described, but is limited to the availability of the 1,3-dicarbonyl compounds: (a) Ma, Y.; Qian, C.; Wang, L.; Yang, M. *J. Org. Chem.* **2000**, *65*, 3864. (b) Ranu, B. C.; Hajra, A.; Jana, U. *J. Org. Chem.* **2000**, *65*, 6270. (c) Varala, R.; Alam, M. M.; Adapa, S. R. *Synlett* **2003**, 67. (d) Zigeuner, G.; Nischk, W.; Juraszovits, B. *Monatsh. Chem.* **1966**, *97*, 1611. (e) Chi, Y.-F.; Wu, Y.-L. *Huaxue Xuebao* **1956**, *22*, 184.