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A convenient synthesis of 5-arylamino-4*H*-pyran-4-ones using palladium-catalyzed amination

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ABSTRACT

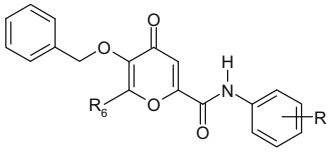
A concise approach to 5-arylamino-4*H*-pyran-4-ones is described via palladium-catalyzed amination reaction. The methodology involved in this Letter is based on protection/deprotection protocols and on manipulation of the 5-hydroxy group of readily available kojic acid. It would provide a new entry to a range of 5-arylamino-4*H*-pyran-4-ones via Buchwald–Hartwig-type amination reaction on 4*H*-pyran-4-one unit.

Six-membered heterocyclic compounds containing oxygen such as 4*H*-pyran-4-ones constitute an important class of biologically active natural and synthetic products, playing a fundamental role in bioorganic chemistry and continuing to attract interest.[1] A large number of natural products containing a γ-pyranone unit have been isolated which show interesting biological activities.[2] In connection with our studies toward the design and synthesis of ATP-competitive Src inhibitors focused on 6-substituted-5-benzyloxy-4-oxo-4*H*-pyran-2-carboxamides[3] (Fig. 1), we became interested in the use of the readily available kojic acid as a starting material to study the replacement of its 5-hydroxyl group by a wide variety of 5-arylamino substituents. To the best of our knowledge, no such reaction has been yet described in the literature. Moreover, thanks to this methodology, we decided to synthesize new Dasatinib[4] analogues (an oral dual Bcr/Abl and Src family tyrosine kinases inhibitor approved for use in patients with chronic myelogenous leukemia and Philadelphia chromosome-positive acute lymphoblastic leukemia, Fig. 2) where the thiazole moiety was replaced by a 4*H*-pyran-4-one skeleton.

First, we attempted to synthesize a series of 5-arylamino-4*H*-pyran-4-ones via nucleophilic substitution of the corresponding 5-tosyloxy-4*H*-pyran-4-one **3** prepared in two steps starting from kojic acid **1** (Scheme 1). After a selective tosylation and an oxidation reaction, the carboxylic acid **2** was converted to the amide[5] intermediate **3**. Despite the preparation of this derivative, we were unable to obtain the desired product resulting from the displacement of the tosyl group by various amines (aniline and benzylamine), but we were only able to obtain the formation of the imine compound **4** in the case of the condensation of benzylamine in the presence of triethylamine in a sealed tube (Scheme 1). No reaction or degradation was observed with aniline.

Recently, a new synthetic method based on the applications of metal-mediated carbon–carbon bond formation reactions such as Heck, Suzuki, and Stille couplings to obtain 5-substituted-4*H*-pyran-4-ones has received increasing attention.[6] This post-derivatization strategy allows efficient preparation of a large number of derivatives from a single precursor bearing a triflate function. Based on this knowledge, we decided to apply the same strategy to achieve a palladium-catalyzed carbon–nitrogen bond formation reaction.

According to the protocol developed by Kamino et al.,[6] a first route was envisaged (Scheme 2) with the preparation of the triflate derivative **7**, considering that this compound could serve as a versatile intermediate for introducing various substituents at C-5 position. Bis-*tert*-butyldimethylsilyl ether **5** was obtained by using an excess of *tert*-butyldimethylsilyl chloride and triethylamine with a



R = H ; 2-Cl ; 2,6-diCl ; 2,6-diCH$_3$; 2,6-ClCH$_3$
R$_6$ = H ; CH$_3$; CH$_2$CH(CH$_3$)$_2$; CH$_2$OP(O)(OC$_2$H$_5$)$_2$

Figure 1. Structure of 5-benzyloxy-4-oxo-4*H*-pyran-2-carboxamides.

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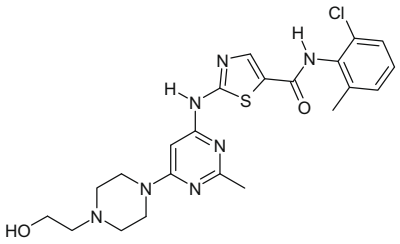


Figure 2. Structure of Dasatinib.

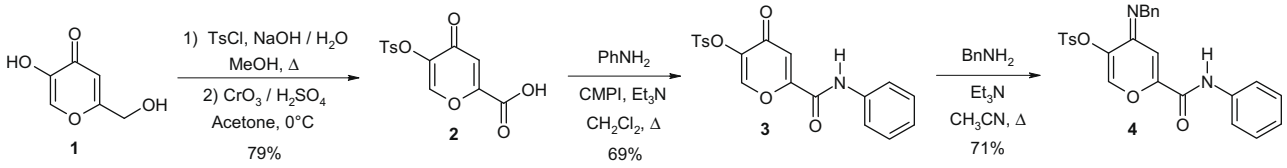
catalytic amount of 4-dimethylaminopyridine in dichloromethane. A selective deprotection as described by Jiang[7] following by reaction of triflic anhydride afforded the desired triflate derivative **7** in high yield. Palladium-catalyzed amination of the triflate **7** with aniline in the presence of Pd_2dba_3, xantphos, and cesium carbonate in toluene afforded the arylaminopyran-4-one **8**. Further, deprotection was realized but direct oxidation of alcohol function using Jones reagent at low temperature was unsuccessful due to extensive degradation of the starting material (Scheme 2).

It reasonably appears that the introduction of the 5-arylamino function must be realized at the end of the sequence in order to prevent this drawback.

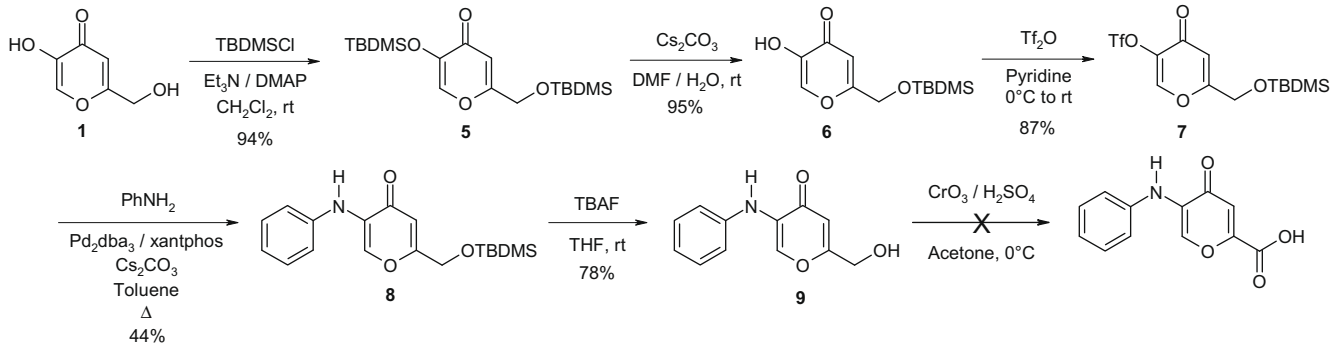
Then, we examined a second route by attempting the preparation of triflates **13a–e** in four steps starting from kojic acid (Scheme 3).

Primary alcohol function of kojic acid **1** was firstly selectively protected[8] using 3,4-dihydro-*2H*-pyran with catalytic quantities of *p*-toluenesulfonic acid monohydrate before addition of triflic anhydride in pyridine and subsequent deprotection under acidic conditions. Then, carboxylic acid **12**[9] was obtained by oxidation of alcohol **11**[10] in high yield according to previously used conditions and carboxamides **13a–e** were synthesized by reaction of variously substituted anilines.[3] Among all reagents available in our laboratory and tested, we found that a combination employing phenyl dichlorophosphate as the coupling reagent and triethylamine in dichloromethane provided good yields of carboxamides in few minutes[11] (Table 1, entries 1–5).

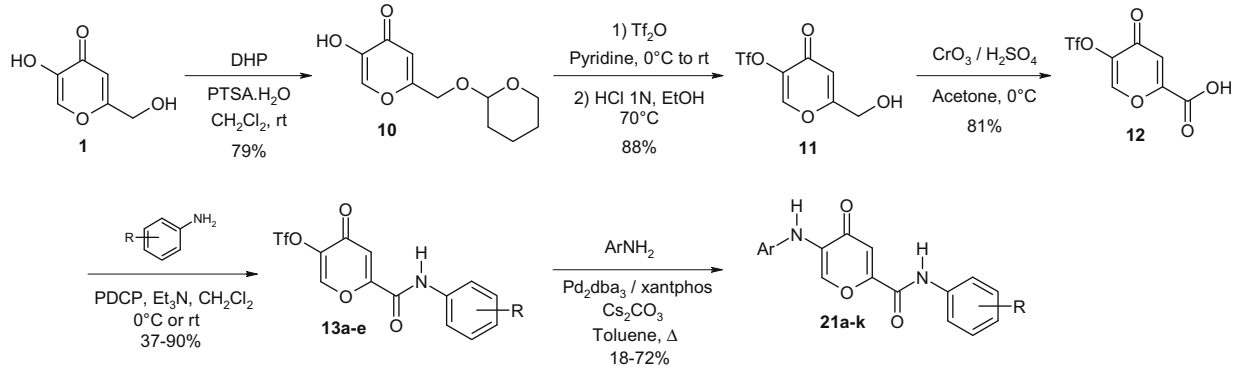
To determine an efficient method for Buchwald/Hartwig amination[12] on 4*H*-pyran-4-one moiety, we undertook an intensive screening of a variety of palladium catalysts, ligands, bases, and solvents. We found that a combination employing Pd_2dba_3, xantphos (a chelating ligand developed by van Leeuwen[13]), and cesium carbonate in toluene provided the most generally successful results. Indeed, use of xantphos as ligand was found to be critical to afford the desired arylamines **21a–k** (other diphosphine-based ligands such as BINAP were totally ineffective). This observation



Scheme 1. Preparation of 5-tosyloxy-4*H*-pyran-4-one **3** and formation of imine derivative **4.**



Scheme 2. Attempts for the synthesis of 5-arylamino-4*H*-pyran-4-ones by route 1.



Scheme 3. Synthesis of 5-arylamino-4*H*-pyran-4-ones by route 2.

Table 1
Amide bond formation

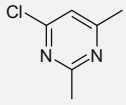
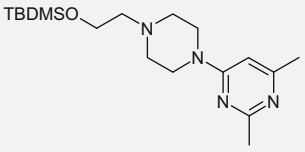
Entry	R	Conditions	Yield(%)
1	H	PDCP, Et_3N, CH_2Cl_2, rt	**13a**: 90
2	2-Cl	PDCP, Et_3N, CH_2Cl_2, 0 °C	**13b**: 79
3	2,6-DiCl	PDCP, Et_3N, CH_2Cl_2, 0 °C	**13c**: 37
4	2,6-DiCH_3	PDCP, Et_3N, CH_2Cl_2, rt	**13d**: 72
5	2-Cl-6-CH_3	PDCP, Et_3N, CH_2Cl_2, 0 °C	**13e**: 90

was in strong correlation with Lee and Cho's protocol on α-pyranone.[14]

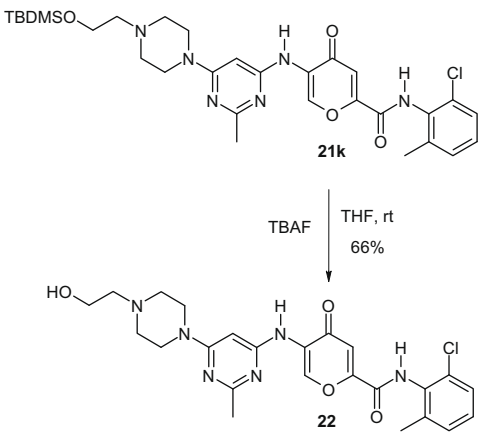
Following our generally successful protocol,[15] palladium-amination of triflates **13a–e** proceeded smoothly with aniline in the presence of a sub-stoichiometric quantity of Pd_2dba_3 (10 mol %), xantphos (20 mol %), and cesium carbonate in toluene (Table 2). The best result was obtained when using **13d** as the starting material (Table 2, entry 4). Only a trace and a low yield of the desired coupling products were observed with **13b** and **13c** due to degradation of the starting material (Table 2, entries 2 and 3).

As part of our ongoing research program on new Dasatinib analogues, pyrimidines **18** and **20** were prepared as described in Scheme 4. The condensation of acetamidine hydrochloride with diethylmalonate afforded the 4,6-dihydroxypyrimidine **16**,[16] which was converted to the dichloro compound **17.**[17] A regioselective nucleophilic substitution with aqueous ammoniac gave the 4-amino-6-chloro-2-methylpyrimidine **18.**[17] Further, the reaction of **18** with 1-(2-hydroxyethyl)piperazine in acetonitrile/DMF under microwave activation afforded the pyrimidine **19**. Protection of the hydroxyl group of **19** was necessary for the palladium-coupling. Then, the two pyrimidines **18** and **20** were also coupled according to the same method to afford various functionalized 5-substituted-4*H*-pyran-4-ones. Further, deprotection of the *tert*-butyldimethylsilyl group of **21k** was also possible as demonstrated in Scheme 5 to afford a Dasatinib analogue **22**[18] bearing a 4*H*-pyran-4-one moiety.

Table 2
Palladium-catalyzed amination reaction

Entry	R	Ar	Yield[a] (%)
1	H		**21a**: 44
2	2-Cl		**21b**: Trace
3	2,6-DiCl		**21c**: 18
4	2,6-DiCH_3		**21d**: 72
5	2-Cl-6-CH_3		**21e**: 61
6	H		**21f**: 38
7	2,6-DiCH_3		**21g**: 35
8	2-Cl-6-CH_3		**21h**: 36
9	H		**21i**: 18
10	2,6-DiCH_3		**21j**: 32
11	2-Cl-6-CH_3		**21k**: 30

[a] All compounds were fully characterized by spectroscopic methods including, IR, ^1H and ^{13}C NMR, and mass spectrometry.



Scheme 5. Deprotection of 5-arylamino-4*H*-pyran-4-one **21k**.

In summary, we have developed a novel series of triflates (following selective protection, oxidation, and amide bond formation reactions) as key intermediates for 5-substituted-4*H*-pyran-4-ones. They were coupled with various aryl amines under original and unreported palladium-catalyzed Buchwald/Hartwig amination demonstrating the synthetic potential of these derivatives in C–N bond formation.

Acknowledgment

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Supplementary data

Supplementary data (experimental procedure and characterization data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.07.139.

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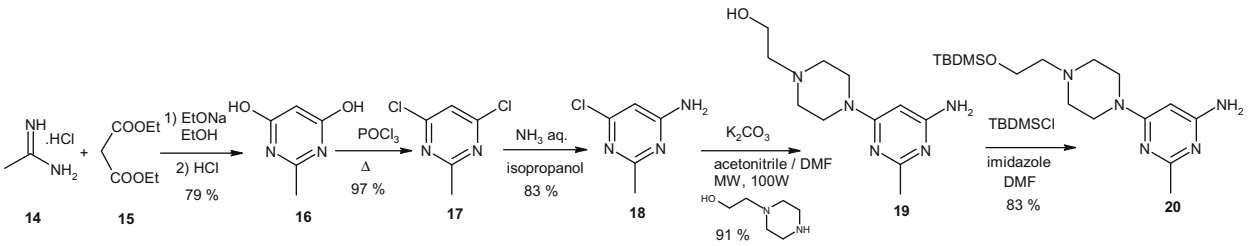

Scheme 4. Synthesis of pyrimidines **18** and **20**.

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9. Mp 206–207 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.25 (s, 1H, **H$_3$**), 9.26 (s, 1H, **H$_6$**). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 117.4 (J = 319.0 Hz), 118.9, 141.6, 152.3, 154.9, 160.0, 170.8. IR (KBr): 3096, 2928, 1746, 1648, 1620, 1429, 1229, 1142 cm^{-1}. MS-ES$^+$ (MeOH): *m/z* 288.
10. Mp 56–57 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 4.42 (d, 2H, C**H$_2$**OH, J = 5.9 Hz), 5.89 (t, 1H, CH$_2$O**H**, J = 5.9 Hz), 6.63 (s, 1H, **H$_5$**), 9.12 (s, 1H, **H$_2$**). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 59.3, 112.8, 118.2 (J = 319.0 Hz), 140.6, 151.6, 170.5, 170.9. IR (KBr): 3432, 3076, 2922, 1664, 1631, 1429, 1217, 1133, 844 cm^{-1}. MS-ES$^+$ (MeOH): *m/z* 274.
11. *Typical procedure for synthesis of* **13e**: To a solution of 0.6 g (2.08 mmol) of 4-oxo-5-{[(trifluoromethyl)sulfonyl]oxy}-4*H*-pyran-2-carboxylic acid (**12**), 370 μL (2.29 mmol) of phenyl dichlorophosphate, and 281 μL (2.29 mmol) of 2-chloro-6-methylaniline in 30 mL of anhydrous dichloromethane at 0 °C are added 870 μL (6.24 mmol) of triethylamine dropwise. After being stirred for 15 min under nitrogen atmosphere, the reaction mixture was hydrolyzed and extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated to dryness by rotary evaporation. Further purification by column chromatography on silica gel (dichloromethane/methanol 99/1) furnished **13e** as a yellow solid in 90% yield.
Mp 166–167 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.26 (s, 3H, C**H$_3$**), 7.33–7.35 (m, 2H, 2**H$_{Ph}$**), 7.34 (s, 1H, **H$_5$**), 7.43–7.48 (m, 1H, **H$_{Ph}$**), 9.31 (s, 1H, **H$_2$**), 10.74 (s, 1H, N**H**). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 18.3, 117.2, 118.2 (J = 319 Hz), 127.3, 129.1, 129.4, 132.0, 132.3, 138.6, 141.6, 152.0, 156.6, 156.7, 170.6. IR (KBr): 3257, 3091, 2978, 1692, 1670, 1427, 1220, 1137 cm^{-1}. MS-ES$^+$ (MeOH): *m/z* 411.
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14. Lee, J.-H.; Cho, C.-G. *Tetrahedron Lett.* **2003**, *44*, 65–67.
15. *Typical procedure for synthesis of* **21k**: A sealed tube was charged with 200 mg (0.486 mmol) of 6-[(2-chloro-6-methylphenyl)carbamoyl]-4-oxo-4*H*-pyran-3-yl trifluoromethanesulfonate (**13e**), 45 mg (10 mol %) of Pd_2dba_3, 56 mg (20 mol %) of xantphos, and 238 mg (0.729 mmol) of cesium carbonate. After adding 4 mL of toluene, the mixture was degassed and backfilled with argon where upon were added 205 mg (0.583 mmol) of 6-{4-[2-(*tert*-butyldimethylsilyloxy)ethyl]piperazin-1-yl}-2-methyl pyrimidin-4-ylamine (**20**). After stirring for 90 min at 110 °C, the reaction mixture was cooled to room temperature, diluted with dichloromethane, filtered through Celite, and concentrated. The crude material was purified by using column chromatography (dichloromethane/methanol 98/2) to give the product **14k** as a yellow solid in 30% yield.Mp 176–177 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 0.09 (s, 6H, 2C**H$_3$**), 0.91 (s, 9H, 3C**H$_3$**), 2.27 (s, 3H, **C**H$_3$), 2.41 (s, 3H, C**H$_3$**), 2.51–2.54 (m, 6H), 3.50–3.53 (m, 4H), 3.76 (t, 2H, J = 6.1 Hz), 6.55 (s, 1H), 7.10 (s, 1H, **H$_3$**), 7.33–7.35 (m, 2H), 7.44–7.48 (m, 1H), 8.42 (s, 1H, N**H**), 9.78 (s, 1H, **H$_6$**), 10.65 (s, 1H, N**H**CO). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) −5.1, 18.1, 18.3, 26.0, 26.2, 43.9, 53.1, 60.1, 61.1, 84.3, 112.1, 127.3, 128.9, 129.3, 131.8, 132.1, 132.6, 138.6, 141.6, 154.3, 157.6, 160.4, 162.7, 165.7, 172.3. IR (KBr): 3308, 2927, 1692, 1641, 1594, 1508, 1251, 1103, 836 cm^{-1}. MS-ES$^+$ (MeOH): *m/z* 613.
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18. Mp 225–226 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.27 (s, 3H, C**H$_3$**Ph), 2.41 (s, 3H, C**H$_3$**), 2.43–2.54 (m, 6H), 3.53–3.58 (m, 6H), 4.48 (t, 1H, O**H**, J = 5.3 Hz), 6.54 (s, 1H), 7.10 (s, 1H, **H$_3$**), 7.32–7.35 (m, 2H), 7.42–7.48 (m, 1H), 8.42 (s, 1H, N**H**), 9.77 (s, 1H, **H$_6$**), 10.65 (s, 1H, N**H**CO). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 18.3, 26.2, 43.8, 52.9, 58.7, 61.4, 84.2, 112.1, 127.3, 128.9, 129.4, 131.8, 132.2, 132.6, 138.6, 141.7, 154.3, 157.7, 160.4, 162.7, 165.7, 172.3. IR (KBr): 3390, 3326, 2927, 1697, 1646, 1595, 1512, 1210 cm^{-1}. MS-ES$^+$ (MeOH): *m/z* 498.