Tetrahedron Letters 52 (2011) 3849–3852

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Efficient synthesis of highly functionalized tetrahydropyridopyrimidines by a novel three-component coupling reaction

Izzat T. Raheem *, John D. Schreier, Michael J. Breslin

Department of Medicinal Chemistry, Merck Research Laboratories, West Point, PA 19486, USA

ARTICLE INFO

Article history:
Received 3 February 2011
Revised 12 May 2011
Accepted 16 May 2011
Available online 23 May 2011

Keywords:
Three-component coupling
Tetrahydropyridopyrimidine
Pharmacophore
Reaction optimization

ABSTRACT

We report the development of a novel three-component coupling reaction (3CC) for the synthesis of alkoxy tetrahydropyridopyrimidines. Systematic optimization of reaction parameters identified 3CC conditions tolerant of a wide array of functionality at all three sites of diversity, providing densely functionalized products in moderate to excellent yields. The newly developed chemistry has since been applied to the lead optimization process on a novel drug discovery program, facilitating rapid compound advancement.

1. Introduction

The ability to rapidly assemble densely functionalized heterocyclic pharmacophores provides a significant advantage within the drug discovery lead optimization space. Multiple-component couplings (MCCs) comprise a family of convergent reactions in which three or more starting materials react to form a single product, with nearly all of the atoms involved contributing to the structure of the newly formed product.[1] In medicinal chemistry, the application of MCCs toward the synthesis and optimization of leading structural series often provides facile variation of two or more structural diversity elements and facilitates efficient development of SAR and subsequent program advancement. Herein, we describe a novel three-component coupling (3CC) reaction for the synthesis of highly functionalized alkoxy tetrahydropyridopyrimidines.

The tetrahydropyridopyrimidine core is a key pharmacophore in several reported preclinical drug candidates, including selective $P2X_7$ receptor antagonists,[2] inhibitors of platelet aggregation,[3] gastric anti-lesion agents,[4] and phosphodiesterase 10 inhibitors.[5] While a number of stepwise approaches toward the synthesis of this heterocycle exists, only one multi-component reaction has been reported involving the acid-catalyzed condensation of a piperidinone with 2 equivalents of a functionalized nitrile.[6] Although highly convergent, this approach allows for the installation of only a single functionality off of the aromatic portion of the heterocycle, limiting product versatility.

In our laboratories, we recently became interested in synthesizing analogs with a 4-alkoxy-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine scaffold. The original three-step synthesis of the core involved (1) cyclocondensation between an amidine and a piperidinone ester, (2) chlorination with PPh_3/NCS, and (3) nucleophilic aromatic substitution (Fig. 1). While this synthetic route was robust and versatile, typically providing products in overall yields ranging from 10% to 30%, we were attracted to the possibility of employing a more convergent synthesis that harnessed the nucleophilic character of the intermediate pyrimidinone oxygen. This would allow for a potential one-step assembly of the fully functionalized heterocyclic framework. We reasoned that as long as the reaction medium remained devoid of complicating nucleophilic species until the formation of the pyrimidinone, we could fine tune the reaction parameters to facilitate construction of the

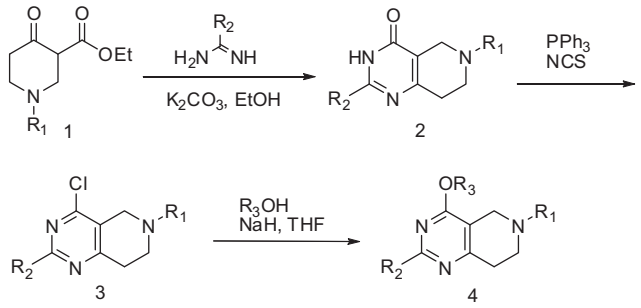
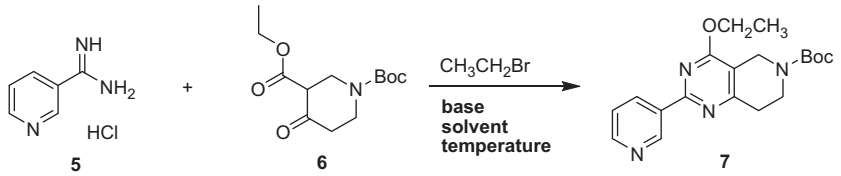


Figure 1. First generation synthesis of 4-alkoxy tetrahydropyridopyrimidines.

* Corresponding author.
E-mail address: izzat_raheem@merck.com (I.T. Raheem).

0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.05.071

Table 1
Optimization of reaction parameters[a]



Entry[a]	Base	Solvent	Temp. (°C)	Conv.[b] (%)
1	K_2CO_3	CH_2Cl_2	50	<5
2	K_2CO_3	THF	50	<5
3	K_2CO_3	DMF	50	87
4	K_2CO_3	DMSO	50	100[c]
5	K_2CO_3	Toluene	50	<5
6	K_2CO_3	EtOH	50	100[d]
7	K_2CO_3	DMF	30	40
8	K_2CO_3	DMF	70	100
9	K_2CO_3	DMF	90	100
10	None	DMF	70	<5
11	Cs_2CO_3	DMF	70	100
12	TEA	DMF	70	<5
13	$NaHCO_3$	DMF	70	<5

[a] Screening reaction conditions: 1.1 equiv **5**, 1 equiv **6**, 2.5 equiv CH_3CH_2Br, 2.5 equiv base, 0.15 M solvent, 2 h reaction time.
[b] Determined by HPLC at 254 nm.
[c] Significant decomposition.
[d] Trace conversion to fully alkylated product; reaction stalls at the pyrimidinone intermediate.

heterocycle as a 3CC by introducing the alkoxy functionality as an electrophile rather than a nucleophile.

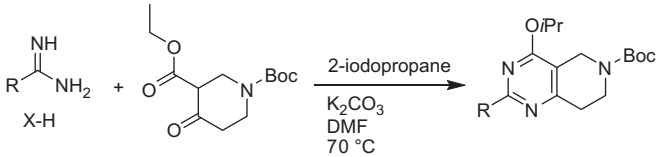
As a model system, we examined the 3CC of 3-pyridylamidinium hydrochloride (**5**), *N*-Boc-piperidinone ester **6**, and 2-bromopropane in the presence of K_2CO_3 (Table 1). Not surprisingly, the identity of the solvent proved crucial, as only polar aprotic solvents provided conversion to the desired product, likely due in part to the poor solubility of the intermediate pyrimidinone (Table 1, entries 1–6). CH_2Cl_2, THF, and toluene afforded only trace product, while EtOH furnished only the pyrimidinone intermediate. Gratifyingly, both DMSO and DMF provided high conversion at only 50 °C, with DMF affording a significantly more favorable overall reaction profile. The reaction temperature was examined next (Table 1, entries 7–9), with full conversion achieved in reasonable time at temperatures above 50 °C. We selected 70 °C as the optimal temperature as it afforded the best compromise between reaction profile and reaction rate. Finally, the identity of the base was examined (Table 1, entries 10–13). Inorganic carbonate bases provided complete conversion, while only trace conversion was achieved with bicarbonate and amine bases; K_2CO_3 was selected as optimal for this transformation. Importantly, the use of powdered K_2CO_3 was crucial, as the use of granular inorganic bases provided low and variable yields.

With a set of optimal reaction conditions in hand, we examined the scope of the 3CC with respect to all three reaction components.[7] We were pleased to find that the reaction tolerated a wide array of amidines, including aromatic, heteroaromatic, straight-chain aliphatic, cyclic aliphatic, and benzylic substitution patterns, providing the desired products in moderate to good yields (Table 2, entries 1–8). Additionally, the 3CC was tolerant of formamidine and dimethylguanidine, providing both the unsubstituted (entry 9) and amino-substituted (entry 10) products, albeit with compromised yields.

The amino substituent was examined next with a representative set of functional groups. Apart from the carbamate group employed in the above chemistry (Table 3, entry 1), both amide and urea functionalities were tolerated at this position (entries 2–4). This flexibility allows one to obviate the need for a protecting group by installing the final required functionality in the first step. Surprisingly, no conversion was observed in the presence of benzylic functionality, highlighting the importance of amine basicity, with tertiary amines too basic to be employed in the reaction (entry 5).

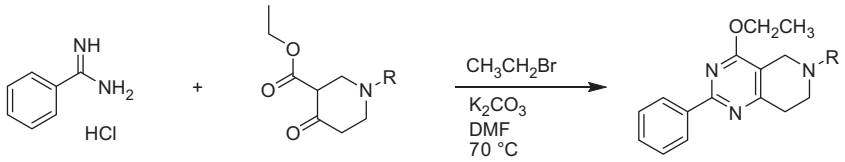
Finally, we examined the scope of the alkyl halide component (Table 4). The chemistry was again tolerant of a wide variety of functionality, including strain-chain and branched aliphatic (entries 1–3), heteroaromatic (entry 4), as well as both cyclic and acyclic heteroaliphatic functionalities (entries 5–7). Not surprisingly, the identity of the leaving group was found to be very important. When activated electrophiles such as allylic or benzylic halides were employed, the bromide leaving group proved too reactive for the 3CC, providing unfavorable reaction profiles with low conversion to the desired products. This is likely due to the competing alkylation of the amidine species. For these substrates, the corresponding chloride was found to be optimal, as in the cases of both

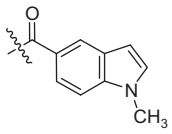
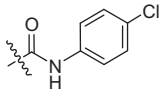
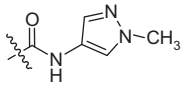
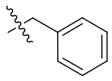
Table 2
Scope of amidine component



Entry	R	Product	X	Yield (%)
1	C_6H_5	**4a**	Cl	79
2	3-BrC_6H_4	**4b**	Cl	61
3	4-Pyridyl	**4c**	Cl	57
4	3-Thienyl	**4d**	Cl	38
5	2-Methyl-1,3-thiazol-4-yl	**4e**	Cl	61
6	Propyl	**4f**	OAc	74
7	Benzyl	**4g**	Br	70
8	Cyclopropyl	**4h**	Cl	81
9	H	**4i**	Cl	33
10	$N(CH_3)_2$	**4j**	Cl	52

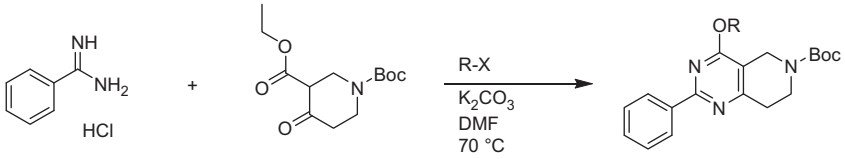
Table 3
Scope of amine component

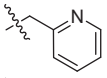
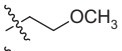
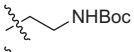
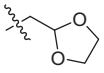
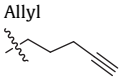
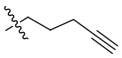


Entry	R	Product	Yield (%)
1	Boc	**4k**	82
2		**4l**	62
3		**4m**	71
4		**4n**	61
5		**4o**	0[a]

[a] No significant conversion of starting material was observed.

Table 4
Scope of alkyl halide component



Entry	R	Product	X	Yield (%)
1	Methyl[a]	**4p**	Br	53
2	*n*-Propyl	**4q**	Br	87
3	Cyclopentyl	**4r**	Br	73
4		**4s**	Br	28
5		**4t**	Br	54
6		**4u**	Br	51
7		**4v**	Br	47
8	Benzyl	**4w**	Cl	61
9	Allyl	**4x**	Cl	77
10[b]		**4y**	Br	87
11[c]		**4y**	Cl	29

[a] Due to volatility, 5 equiv CH_3Br was added as a 2.0 M solution in TBME.
[b] Reaction time = 2 h; reaction temp. = 70 °C.
[c] Reaction time = 4 h; reaction temp. = 100 °C.

benzyl and allyl chloride (entries 8–9). When unactivated electrophiles were employed, the reaction proceeded most efficiently with a bromide leaving group. However, with elevated temperatures and extended reaction times, the less reactive corresponding chlorides could be employed (Table 3, entries 10–11).

2. Conclusion

We have introduced a novel 3CC reaction that assembles densely functionalized tetrahydropyridopyrimidines in a single efficient transformation. Systematic optimization of reaction parameters

identified a protocol that is both operationally simple and tolerates a wide array of functional groups. In the context of our own drug discovery program, this reaction has not only streamlined our lead optimization process, but has also significantly impacted our scale-up efforts as the transformation has been repeatedly executed on >25-gram scale with excellent results. Current efforts are aimed at expanding the substrate scope at both the amine and alkoxy positions, as well as better understanding the pK_a dependence of the reaction. Our results will be disclosed in due course.

Acknowledgments

The authors thank the Merck West Point NMR and Mass Spectrometry facilities for assistance in characterizing the compounds presented in this manuscript. Dr. Chris Cox and Mr. Thomas Steele are also gratefully acknowledged for useful interactions.

References and notes

1. For representative reviews of MCCs see: (a) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123–131; (b) Uqi, I. *Pure Appl. Chem.* **2001**, *73*, 187–191; (c) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168; (d) Dömling, A. In *Multicomponent Reactions*; Zhu, J., Bienayme, H., Eds.; Wiley-VCH: Weinheim, 2005; p 76; (e) Biggs–Houck, J. E.; Ashkaan, Y.; Shaw, J. T. *Curr. Opin. Chem. Biol.* **2010**, *14*, 371–382.
2. Carroll, W. A.; Donnelley-Roberts, D.; Jarvis, M. F. *Purinergic Signalling* **2009**, *5*, 63–73.
3. U.S. Patent US005405848A; filed April 11, 1995.
4. Sanfilippo, P. J.; Urbanski, M.; Williams, L.; Press, J. B.; Katz, L. B.; Shriver, D. A.; Fernandex, J. A.; Shatynski, D.; Offord, S. J. *Eur. J. Med. Chem.* **1992**, *27*, 655–661.
5. U.S. Patent Application WO2010138430; filed December 2, 2010.
6. Herrera, A.; Martinez-Alvarez, R.; Chioua, R.; Almy, J. *Tetrahedron Lett.* **2006**, *47*, 5463–5465.
7. *Representative experimental procedure: tert*-butyl-2-phenyl-4-(prop-2-en-1-yloxy)-7,8-dihydropyrido[4,3-*d*]pyrimidine-6(5*H*)-carboxylate (**4x**). A 10 mL round bottom flask was charged with phenylamidinium hydrochloride (31.7 mg, 0.203 mmol), 3-carbethoxy-4-piperidone hydrochloride (50 mg, 0.184 mmol), powdered K_2CO_3 (63.7 mg, 0.461 mmol), and a stirbar. The flask was sealed and charged with DMF (1.23 mL) followed by allyl chloride (37.9 μL, 0.461 mmol). With vigorous stirring, the reaction mixture was heated to 70 °C for 2 h, and reaction progress was monitored by LCMS. Upon completion of the reaction, the reaction mixture was diluted with EtOAc (10 mL), and washed with sat. aq $NaHCO_3$ (10 mL) and brine (10 mL). The combined aqueous phases were back-extracted with EtOAc (5 mL), and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting residue was purified by gradient elution on silica gel (0–25% EtOAc/hexanes) to afford the title compound as a colorless oil that slowly solidified upon standing (52.3 mg, 77%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.36–8.44 (m, 2H), 7.40–7.48 (m, 3H), 6.05–6.17 (m, 1H), 5.44 (d, J = 17.3 Hz, 1H), 5.29 (d, J = 10.5 Hz, 1H), 5.05 (b s, 2H), 4.50 (b s, 2H), 3.75 (t, J = 5.5 Hz, 2H), 2.94 (b s, 2H), 1.51 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.34, 161.65, 154.81, 137.64, 132.76, 130.39, 130.37, 128.38, 128.01, 118.03, 80.26, 66.89, 41.38, 40.50, 31.66, 28.46; HRMS (ES) calculated M+H for $C_{20}H_{21}N_7O_2S$: 368.1963l; found:368.1969.