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Microwave-Assisted Ullmann C−S Bond Formation: Synthesis of the P38α MAPK Clinical Candidate VX-745

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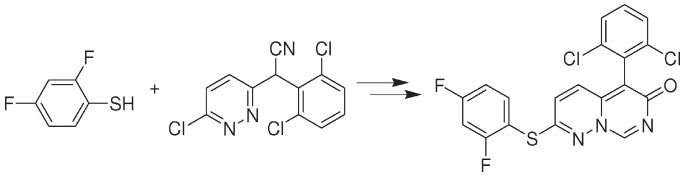

Microwave irradiation promotes the rapid and efficient reaction of a thiophenol and aryl or heteroaryl halide using a copper or palladium catalyst and a range of ligands, depending upon substrate. Of particular utility is the use of copper(I) iodide (5 mol %) and *trans*-cyclohexane-1,2-diol as ligand under basic conditions and microwave irradiation to give the corresponding sulfide in high yield. This method for C−S bond formation is applied in the four-step synthesis of the clinical candidate VX-745 in 38% overall yield. The inhibitory activity of VX-745 against p38α MAPK is confirmed in Werner syndrome dermal fibroblasts at 1.0 μM concentration by immunoblot assay.

Introduction

P38α is one member of the mitogen-activated protein kinase (MAPK) family of intracellular enzymes, which also includes ERKs (extracellular signal regulated kinases) and JNKs (c-Jun amino terminal kinases). It is part of a cell signaling cascade involved in the regulation of pro-inflammatory cytokine biosynthesis at the transcriptional and translational level.[1,2] The reduction of pro-inflammatory cytokine levels offers potential for therapeutic intervention in inflammatory disorders such as rheumatoid arthritis and Crohn's disease, and thus the design of safe and efficacious clinical candidates remains a compelling,[2,3] if elusive,[4] therapeutic goal. Following the discovery that pyridinylimidazole p38α MAPK inhibitors such as SB203580 (Figure 1) mediate multiple cellular responses,[1] including the production of pro-inflammatory cytokines, a wide variety of structurally distinct chemotypes[5,6] have been developed based upon p38α MAPK binding motifs in order to deliver effective treatments for inflammatory diseases.[7,8] Our recent studies toward therapeutic intervention in the premature aging disorder Werner syndrome (WS)[9] identified that blocking the p38α response through the use of SB203580 can rescue the pathology of WS cells.[10] This observation provided good evidence that the abbreviated life span of WS cells was linked to a stress-induced growth arrest mediated by p38α MAPK. However SB203580, while useful for research applications, lacks the kinase selectivity profile that is desirable for a therapeutic agent. Our recent report on a route to BIRB 796 and its behavior in WS cells[11] gave access to another chemotype for study with a complementary mode of action.[12,13] However, BIRB 796 has a number of similarities in cross-kinase

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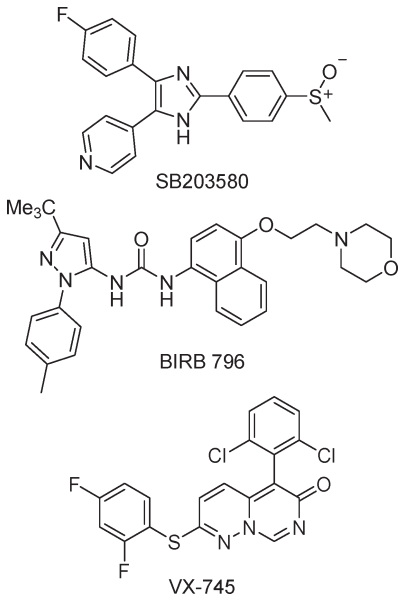
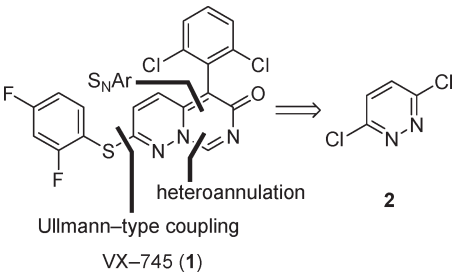


FIGURE 1. Sample P38α MAPK inhibitors.

specificity to SB203580, in particular with regard to its inhibition of the stress-activated JNK kinases.[14,15]

In 1999 Vertex Pharmaceuticals released the structure of a new clinical candidate, VX-745 (**1**), that functioned by ATP competitive inhibition of p38α MAPK.[16] This compound displayed potent activity, clinical efficacy, and an exquisite selectivity profile, effective at 5.0 nM concentration with 1000-fold selectivity over closely related kinases, including ERK1, JNK1-3, and MK2. This profile, in particular the high selectivity for p38 MAPKs over JNKs, made the evaluation of VX-745 (**1**) in WS cells compelling, and so we set out to realize the synthesis of this inhibitor to facilitate its biological study. Our approach[17,18] (Scheme 1) to the pyrimido[1,6-*b*]pyridazinone motif was mindful of the limitations recorded in the original release,[16] later shown to be poorly reproducible and low-yielding in further applications in both academic and industrial laboratories, in particular regarding the formation of the *S*−heteroaryl bond.[19] In addressing these difficulties, it was hoped that new general microwave-mediated methods, in particular for sulfide formation, could be realized that were rapid, efficient, and readily automated for analogue production. Thus the unusual central heterocyclic motif would be prepared by heteroannulation of a (phenylthio)pyridazine, prepared ultimately from 3,6-dichloropyridazine (**2**) by an Ullmann-type coupling with 2,4-difluorothiophenol that was facilitated by microwave irradiation.

SCHEME 1. Disconnective Strategy for the Synthesis of VX-745



Results and Discussion

Although microwave irradiation has received increasing attention in recent years as a valuable alternative to the use of conductive heating for accelerating transformations, in synthetic chemistry, medicinal chemistry, and the biosciences,[20] it was surprising to find that very few of the many methods[21] available for the synthesis of diaryl sulfides by S_NAr or Ullmann-type coupling[22] with copper or palladium catalysts had been investigated under microwave-assisted conditions, despite the great synthetic versatility[23] and

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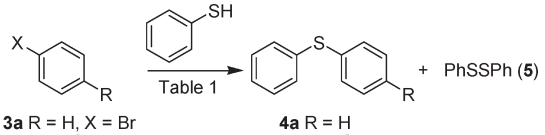
TABLE 1. Conditions for Microwave-Mediated Synthesis of Sulfides 4a−c

entry	3	reagents and conditions[a]	product (yield %)[b]
1	**3b**	CuI (5 mol %), Cs_2CO_3 (1 equiv), NMP, 195 °C (250 W), 2 h	−
2	**3b**	$Pd(OAc)_2$ (2.5 mol %), Xantphos (5 mol %), *i*-Pr_2NEt (2 equiv), 1,4-dioxane, 100 °C (150 W), 3 × 30 min	**4b** (10)
3	**3b**	$Pd(PPh_3)_4$ (5 mol %), *t*-BuONa, *i*-PrOH, 100 °C (150 W), 1 h	**4b** (12)
4	**3a**	CsOH (2 equiv), DMSO, 120 °C (200 W), 10 min	**5** (75)
5	**3a**	CsOH (2 equiv), DMSO, 120 °C (250 W), 5 min	**5** (55)
6	**3a**	CsOH (2 equiv), anhydrous DMSO, 100 °C (200 W), 10 min	**4a** (15)
7	**3b**	CsOH (2 equiv), anhydrous DMSO, 100 °C (150 W), 10 min	**4b** (11)
8	**3a**	PEPPSI-*i*Pr (2 mol %), *t*-BuONa (1.5 equiv), PhMe, 100 °C (150 W), 30 min	−
9	**3b**	PEPPSI-*i*Pr (2 mol %), *t*-BuONa (1.5 equiv), PhMe, 120 °C (150 W), 3 × 1 h	**4b** (46)
10	**3b**	PEPPSI*i*Pr (2 mol %), *t*-BuONa (1.5 equiv), LiCl (20 mol %), PhMe, 120 °C (150 W), 3 × 1 h	**4b** (74)
11	**3b**	PEPPSI-*i*Pr (2 mol %), K_2CO_3 (1.0 equiv), LiCl (20 mol %), dioxane, 120 °C (150 W), 3 × 1 h	**4b** (44)
12	**3b**	PEPPSI-*i*Pr (2 mol %), *t*-BuONa (1.5 equiv), LiCl (20 mol %), dioxane, 120 °C (150 W), 3 × 1 h	**4b** (45)
13	**3b**	PEPPSI-*i*Pr (2 mol %), *t*-BuONa (1.5 equiv), PhMe, 150 °C (120 W), 1 h	**4b** (10)
14	**3b**	PEPPSI-*i*Pr (5 mol %), LiBr (20 mol %), K_2CO_3 (1.0 equiv), dioxane, 150 °C (120 W), 2 × 1 h	**4b** (11)
15	**3b**	*t*-BuONa (1.5 equiv), PhMe, 120 °C (150 W), 90 min, then 2 × 1 h	**4b** (47)
16	**3b**	*t*-BuONa (1.5 equiv), LiCl (20 mol %), PhMe, 120 °C (150 W), 3 × 1 h	**4b** (80)
17	**3b**	CuI (10 mol %), neocuproine (10 mol %), *t*-BuONa (1.5 equiv), PhMe, 80 °C (150 W), 3 × 1 h	**4b** (61)
18	**3b**	CuI (10 mol %), neocuproine (10 mol %), *t*-BuONa (1.5 equiv), PhMe, 100 °C (150 W), 3 × 1 h	**4b** (60)
19	**3b**	neocuproine (10 mol %), *t*-BuONa (1.5 equiv), PhMe, 100 °C (150 W), 3 × 1 h	**4b** (70)
20	**3b**	*t*-BuONa (1.5 equiv), PhMe, 100 °C (150 W), 3 × 1 h	**4b** (58)
21	**3c**	PEPPSI-*i*Pr (2 mol %), *t*-BuONa (1.5 equiv), PhMe, 120 °C (150 W), 3 × 1 h	−
22	**3c**	PEPPSI-*i*Pr (2 mol %), *t*-BuONa (1.5 equiv), LiCl (20 mol %), PhMe, 120 °C (150 W), 3 × 1 h	**4c** (9)
23	**3c**	CuI (10 mol %), neocuproine (10 mol %), *t*-BuONa (1.5 equiv), PhMe, 80 °C (150 W), 2 × 1 h	**4c** (41)
24	**3c**	*t*-BuONa (1.5 equiv), PhMe, 80 °C (150 W), 2 × 1 h	−
25	**3c**	*t*-BuONa (1.5 equiv), PhMe, 120 °C (150 W), 3 × 1 h	−
26	**3b**	CuI (5 mol %), ethylene glycol (2 equiv), K_2CO_3 (2 equiv), *i*-PrOH, 120 °C (150 W), 3 × 1 h	**4b** (82)
27	**3c**	CuI (5 mol %), ethylene glycol (2 equiv), K_2CO_3 (2 equiv), *i*-PrOH, 120 °C (150 W), 3 × 1 h	**4c** (89)
28	**3c**	CuCl (5 mol %), ethylene glycol (2 equiv), K_2CO_3 (2 equiv), *i*-PrOH, 120 °C (150 W), 3 × 1 h	**4c** (20)
29	**3c**	CuI (5 mol %), (±)-*trans*-cyclohexane-1,2-diol (2 equiv), K_2CO_3 (2 equiv), *i*-PrOH, 120 °C (150 W), 3 × 1 h	**4c** (95)
30	**3c**	CuI (5 mol %), K_2CO_3 (2 equiv), *i*-PrOH, 120 °C (150 W), 3 × 1 h	**4c** (63)
31	**3c**	(±)-*trans*-cyclohexane-1,2-diol (2 equiv), K_2CO_3 (2 equiv), *i*-PrOH, 120 °C (150 W), 3 × 1 h	−

[a]All reactions were carried out using microwave dielectric heating at the given temperature in a sealed tube using a CEM Discover single-mode microwave synthesizer by moderation of the initial magnetron power (given in parentheses). [b]Isolated yield after purification by column chromatography on silica; − indicates reaction was unsuccessful and only unreacted thiophenol was obtained.

SCHEME 2. Synthesis of Aryl Sulfides 4a−c



chemotherapeutic utility of the products. Following the ground-breaking work by Buchwald and Kwong on the copper(I)-catalyzed coupling of aryl iodides and thiols using potassium carbonate as base in 2-propanol in the presence of ethylene glycol,[21a] the copper-catalyzed cross-coupling of aryl bromides and iodides has been reported using microwave heating with copper(I) iodide and cesium carbonate in NMP.[24] In this study, microwave irradiation provided notable improvements over conductive heating experiments, but the procedure still required very high temperatures (195 °C) and prolonged irradiation times (2−6 h). In order to establish the potential of a microwave-mediated approach to VX-745, the synthesis of the three simple aryl sulfides **4a−c** by the reaction of thiophenol and bromobenzene (**3a**), 4-iodonitrobenzene (**3b**), or 4-iodomethoxybenzene (**3c**), respectively, was investigated under a range of conditions using microwave heating (Scheme 2, Table 1). In each case, the identity of the product was verified by a combination of NMR spectroscopic analysis and mass spectrometry, being mindful of the formation of phenyl disulfide (**5**), which is reported to predominate in related processes in the presence of oxygen[21a] and is known to compete with sulfide formation under a range of conditions.[22] CuI−Cs_2CO_3-mediated reaction of an electron-poor iodide **3b**, used to approximate a halopyridazine substrate appropriate for the synthesis of VX-745, according to the procedure of Wu and He[24] returned unreacted thiophenol with no evidence of the desired sulfide **4b** (entry 1). The adaption of two published Pd-catalyzed methods[21i,k] to microwave heating using iodide **3b** (entries 2 and 3) did provide the product **4b**, but in very low yield in both cases. Clearly an improved and effective microwave-assisted procedure was required for this transformation, and so a range of methods was explored (entries 4−15). The use of CsOH in DMSO[21m] under microwave irradiation was unsuccessful (entries 4 and 5), giving a high yield of phenyl disulfide (**5**). When repeated under anhydrous oxygen-free conditions (entries 6 and 7), the required sulfides **4a** and **4b** were isolated but once again in very low yield. Although our initial studies with a palladium catalyst had not been very successful (entries 2 and 3), the palladium(II) *N*-heterocyclic-carbene (NHC) precatalyst PEPPSI-*i*Pr (PEPPSI = pyridine-enhanced precatalyst preparation stabilization and initiation), [1,3-bis(2,6-diisopropylphenyl)-imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride, has shown remarkable versatility[25] in particular for C−C and C−N bond formation. This low-cost precatalyst is air- and moisture-stable, robust, and highly active and so seemed a good candidate for investigation. Although irradiation at 100 °C for 30 min in PhMe in the presence of PEPPSI-*i*Pr using *t*-BuONa as base failed (entry 8), a higher

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TABLE 2. Microwave-Assisted Synthesis of 7a−c

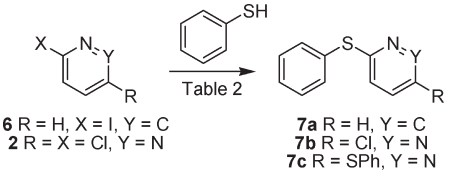
entry	2/6	reagents and conditions[a]	product (yield %)[b]
1	**6**	neocuproine (10 mol %), *t*-BuONa (1.5 equiv), PhMe, 120 °C, 3 × 1 h	**7a** (76)
2	**6**	PEPPSI-*i*Pr (2 mol %), *t*-BuONa (1.5 equiv), PhMe, 120 °C, 3 × 1 h	**7a** (64)
3	**6**	PEPPSI-*i*Pr (2 mol %), *t*-BuONa (1.5 equiv), LiCl (20 mol %), PhMe, 120 °C, 3 × 1 h	**7a** (88)
4	**6**	CuI (10 mol %), neocuproine (10 mol %), *t*-BuONa (1.5 equiv), PhMe, 80 °C, 2 × 1 h	**7a** (72)
5	**6**	CuI (10 mol %), neocuproine (10 mol %), *t*-BuONa (1.5 equiv), PhMe, 120 °C, 3 × 1 h	**7a** (96)
6	**6**	CuI (5 mol %), (±)-*trans*-cyclohexane-1,2-diol (2 equiv), K_2CO_3 (2 equiv), *i*-PrOH, 120 °C (150 W), 3 × 1 h	**7a** (91)
7	**2**	PEPPSI-*i*Pr (2 mol %), *t*-BuONa (1.5 equiv), LiCl (20 mol %), PhMe, 120 °C, 3 × 1 h	**7c** (42)
8	**2**	CuI (10 mol %), neocuproine (10 mol %), *t*-BuONa (1.5 equiv), PhMe, 120 °C, 3 × 1 h	**7c** (75)
9	**2**	*t*-BuONa (1.5 equiv), PhMe, 120 °C, 3 × 1 h	**7c** (47)

[a]All reactions were carried out using microwave dielectric heating at the given temperature in a sealed tube using a CEM Discover single-mode microwave synthesizer by moderation of the initial magnetron power (150 W). [b]Isolated yield after purification by column chromatography on silica.

temperature and prolonged reaction time gave **4b** in moderate yield (entry 9). The advantages of using LiCl or LiBr additives with this precatalyst have been described previously for Negishi reactions.[25c] In our studies, the use of LiCl (entry 10) rather than LiBr was found to have a dramatic effect, giving sulfide **4c** in good yield. The process was quite tolerant of changes in base (entry 11) or solvent (entry 12), although these both did lower the efficiency of reaction as did the use of a higher temperature (entries 13 and 14). It was apparent that for this electron-deficient aryl iodide the catalyst was having very little effect in the absence of LiCl on the course of reaction (compare entries 9 and 15). In fact, the addition of LiCl to a catalyst-free reaction (entry 16) gave an outcome similar to that of the PEPPSI-*i*Pr/LiCl-mediated transformation (entry 10), indicating that for this substrate a classical S_NAr process was probably dominant. Switching from Pd to Cu, the use of CuI-neocuproine (10 mol %) in the presence of *t*-BuONa at 80 (entry 17) or 100 °C (entry 18) gave yields of **4b** similar to those of control experiments (entries 19 and 20). Although this is not altogether surprising for the electron-deficient substrate **3b**, the use of an electron-rich iodide **3c** in the presence of PEPPSI-*i*Pr, PEPPSI-*i*Pr/LiCl, or CuI/neocuproine gave **4c** (entries 21−23) in 0, 9%, or 41% yield, respectively, whereas the control experiments (entries 24 and 25) failed to provide the product. This is probably due to the increasing involvement of a transition-metal-catalyzed mechanism, in particular for Ullmann-type sulfide formation, with an electron-rich iodide. The use of a diol ligand at increased temperature improved the yield for both electron-poor (entry 26) and electron-rich (entry 27) iodides providing CuI rather than CuCl (entry 28) was used as catalyst. The optimum conditions (entry 29) employed (±)-*trans*-cyclohexane-1,2-diol (2 equiv) as ligand and CuI (5 mol %) as catalyst to give sulfide **4c** in 95% isolated yield. In the absence of this ligand, the yield was dramatically reduced (entry 30), and without the catalyst (entry 31) no reaction was observed at all.

(25) For select examples of the use of PEPPSI-*i*Pr, see: (a) Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. *Angew. Chem., Int. Ed.* **2007**, *46*, 2768. (b) Organ, M. G.; Avola, S.; Dubovyk, I.; Hadei, N.; Kantchev, E. A. B.; O'Brien, C. J.; Valente, C. *Chem.−Eur. J.* **2006**, *12*, 4749. (c) Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. *Aldrichimica Acta* **2006**, *39*, 97. (d) O'Keefe, B. M.; Simmons, N.; Martin, S. F. *Org. Lett.* **2008**, *10*, 5301. (e) Wang, G.; Huang, Z.; Negishi, E. *Org. Lett.* **2008**, *10*, 3223. (f) Flegeau, E. F.; Popkin, M. E.; Greaney, M. F. *Org. Lett.* **2008**, *10*, 2717. (g) Perkins, J. R.; Carter, R. G. *J. Am. Chem. Soc.* **2008**, *130*, 3290. (h) Coleridge, B. M.; Bello, C. S.; Leitner, A. *Tetrahedron Lett.* **2009**, *50*, 4475. (i) Browne, D. L.; Taylor, J. B.; Plant, A.; Harrity, J. P. A. *J. Org. Chem.* **2009**, *74*, 396. (j) Mennecke, K.; Kirschning, A. *Synthesis* **2008**, 3267. (k) Valente, C.; Baglione, S.; Candito, D.; O'Brien, C. J.; Organ, M. G. *Chem. Commun.* **2008**, 735.

SCHEME 3. C−S Bond Formation Using Haloazines



6 R = H, X = I, Y = C
2 R = X = Cl, Y = N

7a R = H, Y = C
7b R = Cl, Y = N
7c R = SPh, Y = N

Following the model studies, promising experimental conditions were investigated further (Table 2). 2-Iodopyridine (**6**) or 1,4-dichloropyridazine (**2**) was reacted with thiophenol (Scheme 3) under microwave irradiation, the former as a heteroaryl model substrate and the latter for direct application in the synthesis of VX-745. In the absence of a catalyst (entry 1), the electron-deficient heteroaryl iodide **6** gave sulfide **7a** in good yield by classical S_NAr. Of our newly uncovered methods (entries 2−6), both the PEPPSI-*i*Pr- (entry 3) and Cu-mediated processes (entries 5 and 6) proved extremely efficient in sulfide formation, although the role of the transition metal may well be of lesser significance for these substrates. Using dichloropyridazine **2**, none of the desired product **7b** was obtained (entries 7−9) and instead two C−S bond-forming processes occurred to give **7c** in reasonable yield. It was apparent that, for the synthesis of VX-745, synthesis of the sulfide would need to succeed C−C bond formation, and so the order of steps was amended in the light of this observation.

The base-mediated reaction of 3,6-dichloropyridazine (**2**) and (dichlorophenyl)acetonitrile **8** (Scheme 4) has been reported to give pyridizinylacetonitrile **9**, albeit in poor yield (32%) using NaH in THF.[26] By switching to potassium *tert*-butoxide the efficiency of this reaction was improved to 73%, but this was only after exhaustive chromatographic purification to remove unreacted pyridazine **2**. Under more forcing conditions, using microwave irradiation in toluene at 120 °C for 1.5 h, conversion was complete and thus the purification of **9** was simplified considerably, although the yield was slightly reduced (62%).

From chloropyridazine **9**, the previously explored range of methods for C−S bond formation were investigated (Table 3) alongside a number of traditional conductive heating procedures. The simple S_NAr reaction of **9** with sodium 2,4-difluorothiophenoxide, prepared from thiophenol **4** by treatment with NaH, has been reported to be more efficient in DMF because of the solubility of **9**.[19a] In our hands, this process did indeed provide **10** in reasonable yield

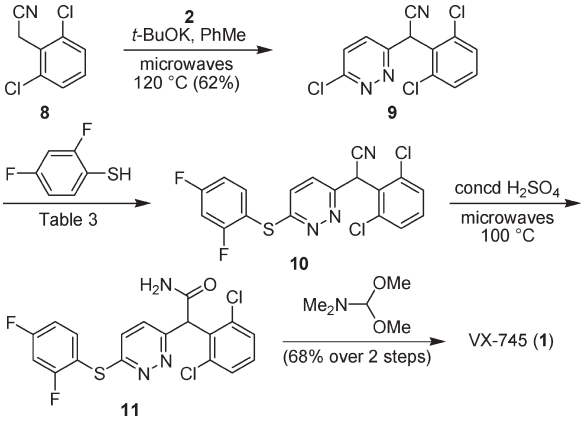
(26) The use of sodium amide as a base gives **9** in 28% yield (ref 16a), whereas the use of sodium hydride gives the product in 43% yield (ref 19a).

TABLE 3. Synthesis of Intermediate 10

entry	reagents and conditions[a]	yield %[b]
1	NaH, DMF, rt, 3 h[19a]	57
2	$Pd(OAc)_2$ (5 mol %), *t*-BuONa 1.1 equiv), DPPF (10 mol %), PhMe, reflux, 16 h	31
3	$Pd(OAc)_2$ (5 mol %), *t*-BuONa (1 equiv), DPPF (10 mol %), PhMe, microwaves, 150 °C (120 W), 1 h	–
4	$Pd(OAc)_2$ (5 mol %), *t*-BuONa (2 equiv), Xantphos (2 equiv), PhMe, microwaves, 150 °C (150 W), 3 × 1 h	44
5	$Pd(OAc)_2$ (5 mol %), *t*-BuONa (1 equiv), (S)-TolBINAP (10 mol %), PhMe, reflux, 16 h	73
6	PEPPSI-*i*Pr (2 mol %), *t*-BuONa (1 equiv), PhMe, reflux, 18 h	75
7	PEPPSI-*i*Pr (2 mol %), *t*-BuONa (1.5 equiv), PhMe, microwaves, 150 °C (120 W), 1 h	75
8	PEPPSI-*i*Pr (2 mol %), *t*-BuONa (1.5 equiv), LiCl (20 mol %), PhMe, microwaves, 120 °C (150 W), 3 × 1 h	72
9	*t*-BuONa (1.5 equiv), PhMe, microwaves, 150 °C (120 W), 1 h	54
10	*t*-BuONa (2 equiv), PhMe, microwaves, 120 °C (150 W), 3 × 1 h	69
11	CuI (10 mol %), Et_3N, dioxane, 90 °C, 16 h	82
12	CuI (10 mol %), Et_3N, dioxane, microwaves, 120 °C (100 W), 3 × 1 h	55
13	CuI (10 mol %), neocuproine (10 mol %), *t*-BuONa (1.5 equiv), PhMe, microwaves, 120 °C (150 W), 3 × 1 h	79
14	neocuproine (10 mol %), *t*-BuONa (1.5 equiv), PhMe, microwaves, 120 °C (150 W), 3 × 1 h	86
15	(±)-*trans*-cyclohexane-1,2-diol (2 equiv), K_2CO_3 (2 equiv), *i*-PrOH, microwaves, 120 °C (150 W), 3 × 1 h	92
16	CuI (5 mol %), (±)-*trans*-cyclohexane-1,2-diol (2 equiv), K_2CO_3 (2 equiv), *i*-PrOH, microwaves, 120 °C (150 W), 3 × 1 h	91

[a]Microwaves denotes reactions were carried out using microwave dielectric heating at the given temperature in a sealed tube using a CEM Discover single-mode microwave synthesizer by moderation of the initial magnetron power (given in parentheses). [b]Isolated yield after purification by column chromatography on silica; – indicates reaction was unsuccessful and **10** was not isolated. DPPF = 1,1′-ferrocenebis(diphenylphosphine); (*S*)-TolBINAP = (*S*)-(−)-2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl.

SCHEME 4. Synthesis of VX-745 (1)



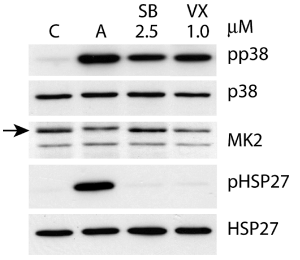


FIGURE 2. VX-745 inhibits the anisomycin induced activation of p38α MAPK in hTERT-immortalized WS dermal cells as assessed by immunoblot assay. Lane 1 (C), WS cells; lane 2 (A), WS cells/anisomycin; lane 3 (SB) WS cells/anisomycin/SB203580 (2.5 μM); lane 4 (VX), WS cells/anisomycin/VX-745 (1.0 μM). The phosphorylated forms of p38α MAPK and HSP27 are indicated by pp38 and pHSP27, respectively. MK2 is an antibody that recognizes both phosphorylated and unphosphorylated forms of MK2 (arrow); the phosphorylated form is indicated by a band shift (lane 2).

(entry 1), but contamination by unreacted starting materials once again complicated compound purification considerably. Traditional conductive heating conditions (entries 2, 5, 6 and 11) using a Pd catalyst or mediated by Cu gave sulfide **10** in improved yields (up to 82%) although only after lengthy reaction times. The use of microwave irradiation proved particularly effective for this transformation with short reaction times and considerably simplified purification procedures. Most interestingly, the addition of neocuproine (10 mol %) (entry 14) seemed to have a significant effect, an observation which was in line with the model studies (Table 1, entries 19 and 20). However, once again, the use of a diol ligand (entries 15 and 16) proved highly effective: heating chloride **9** with the thiophenol in the presence of CuI (5 mol %), (±)-*trans*-cyclohexane-1,2-diol (2 equiv), and K_2CO_3 (2 equiv) as base gave sulfide **10** in 91% isolated yield (entry 16). A near identical result was obtained in the absence of CuI (entry 15), demonstrating the broad utility of these conditions in promoting the reaction of both electron-rich and electron-poor iodides and confirming that for this substrate the transformation was predominantly a classical S_NAr process.

With a rapid route to the nitrile intermediate **10** secured, hydrolysis to the corresponding amide was carried out in concentrated sulfuric acid at 100 °C for 2 h by conductive heating or by microwave irradiation at 100 °C for 30 min giving **11** in 63% or 68% yield, respectively. Finally, heating **11** with *N*,*N*-dimethylformamide dimethyl acetal at 100 °C in toluene for 2 h, followed by an overnight stir at room temperature, facilitated heteroannulation to the pyrimido-[1,6-*b*]pyridazinone **1** in yields that ranged from 87% to >98% and completed the synthesis of VX-745. Overall our rapid route used microwave irradiation to dramatically accelerate three out of the four steps and established a reproducible and efficient route to this p38α MAPK inhibitor in 38% overall yield.

To confirm that the inhibitory properties of VX-745 were consistent with the original report[16] in a different cellular context, as well as to provide added confirmation of structure, p38 MAPK signaling in hTERT-immortalized AG03141 WS dermal cells was examined by immunoblot detection of activated versions of p38α, MK2, and HSP27 (Figure 2) as described previously.[11] Treatment with anisomycin (lane 2) caused an increase in the level of phosphorylated p38α and HSP27, when compared with untreated cells (lane 1). The increased phosphorylation of HSP27 (but not p38α) was inhibited by 2.5 μM of SB203580 (lane 3) or 1.0 μM of VX-745 (lane 4). In addition, anisomycin results in the phosphorylation

by p38α of MK2 (the main HSP27 kinase) as shown by a band-shift on the MK2 immunoblot (lane 2); this band shift is prevented using SB203580 at 2.5 μM (lane 3) and VX-745 at 1.0 μM (lane 4). These data are consistent with the mechanism of action being via inhibition of p38α as opposed to a more upstream kinase.

In conclusion, microwave irradiation has been employed to promote C−S bond formation in the synthesis of the clinical candidate VX-745, which inhibits p38α MAPK in Werner syndrome cells. Of particular utility with this mode of heating is the NHC precatalyst PEPPSI-*i*Pr, used in conjunction with the additive LiCl, the use of CuI/neocuproine, or even just the addition of neocuproine under basic conditions, the most efficient method being dependent upon the substrate. However of all the reagent combinations, microwave irradiation at 120 °C for 3 h using CuI (5 mol %) as catalyst, (±)-*trans*-cyclohexane-1,2-diol (2 equiv) as ligand, and K_2CO_3 (2 equiv) as base seems to be the most reliable method and is efficient for both electron-poor and electron-rich iodides by a classical S_NAr or Cu-mediated Ullmann process, or perhaps by a combination of the two. Overall, the synthesis benefits from carrying out a number of steps with microwave dielectric heating, in particular in terms of shorter reaction times and through simplifying compound purification, to deliver the target inhibitor in 38% overall yield, which acted as a p38α inhibitor, as anticipated, in hTERT-immortalized WS dermal cells. Studies are now underway to use this clinical candidate, prepared by the described route, to understand the accelerated aging of Werner syndrome cells in culture, and this will be reported in due course.

Experimental Section

Typical Procedure for PEPPSI-*i*Pr/LiCl-Mediated C−S Bond Formation. A solution of the aryl halide (0.50 mmol), the thiophenol (0.55 mmol), PEPPSI-*i*Pr (7 mg, 0.01 mmol), LiCl (4.5 mg, 0.1 mmol), and NaO*t*Bu (72 mg, 0.75 mmol) in dry PhMe (2 mL) was irradiated at 120 °C in a pressure-rated glass tube (10 mL) for 3 × 1 h using a CEM Discover microwave synthesizer by moderating the initial power (150 W). After cooling in a flow of compressed air, the reaction mixture was filtered through Celite and evaporated in vacuo. Purification by column chromatography on SiO_2 gave the desired product.

Typical Procedure for LiCl-Mediated C−S Bond Formation. A solution of the electron-poor aryl halide (0.65 mmol), the thiophenol (0.50 mmol), LiCl (4.5 mg, 0.1 mmol), and NaO*t*Bu (72 mg, 0.75 mmol) in dry PhMe (2 mL) was irradiated at 120 °C in a pressure-rated glass tube (10 mL) for 3 × 1 h using a CEM Discover microwave synthesizer by moderating the initial power (150 W). After cooling in a flow of compressed air, the reaction mixture was partioned between H_2O and Et_2O, and the aqueous layer was further extracted with Et_2O. The combined ethereal extracts were washed with brine, dried ($MgSO_4$), and evaporated in vacuo. Purification by column chromatography on SiO_2 gave the desired product.

Typical Procedure for CuI/Neocuproine-Mediated C−S Bond Formation. A solution of the aryl halide (1.0 mmol), the thiophenol (1.0 mmol), CuI (19 mg, 0.10 mmol), neocuproine (20 mg, 0.10 mmol), and NaO*t*Bu (144 mg, 1.5 mmol) in dry PhMe (2 mL) was irradiated at 120 °C in a pressure-rated glass tube (10 mL) for 3 × 1 h using a CEM Discover microwave synthesizer by moderating the initial power (150 W). After cooling in a flow of compressed air, the reaction mixture was filtered and evaporated in vacuo. Purification by column chromatography on SiO_2 gave the desired product.

Typical Procedure for Cu- and Pd-Free C−S Bond Formation. A solution of the electron-poor aryl halide (0.50 mmol), the thiophenol (0.55 mmol), neocuproine (10 mg, 0.05 mmol), and NaO*t*Bu (72 mg, 0.75 mmol) in dry PhMe (2 mL) was irradiated at 120 °C in a pressure-rated glass tube (10 mL) for 3 × 1 h using a CEM Discover microwave synthesizer by moderating the initial power (150 W). After cooling in a flow of compressed air, the reaction mixture was filtered through Celite and evaporated in vacuo. Purification by column chromatography on SiO_2 gave the desired product.

Typical Procedure for CuI/(±)-*trans*-Cyclohexane-1,2-diol-Mediated C−S Bond Formation. A mixture of the aryl halide (0.50 mmol), the thiophenol (0.50 mmol), CuI (5 mg, 25 μmol), (±)-*trans*-cyclohexane-1,2-diol (0.12 g, 1.0 mmol), and K_2CO_3 (0.14 g, 1.0 mmol)) in 2-propanol (2 mL) was irradiated at 120 °C for 3 × 1 h in a pressure-rated glass tube (10 mL) using a CEM Discover microwave synthesizer by moderating the initial power (150 W). After cooling in a flow of compressed air, the reaction mixture was filtered and evaporated in vacuo. Purification by column chromatography on SiO_2 gave the desired product.

6-Chloro-α-(2,6-dichlorophenyl)-3-pyridazineacetonitrile (9). A solution of (2,6-dichlorophenyl)acetonitrile (**8**) (6.0 g, 32 mmol) in dry THF (20 mL) was added to a stirred suspension of KO*t*Bu (4.0 g, 36 mmol) in dry THF (20 mL), at room temperature. After 15 min, a solution of 3,6-dichloropyridazine (**2**) (4.8 g, 32 mmol) in dry THF (10 mL) was added dropwise, and the solution was stirred for a further 2 h. The mixture was partitioned between saturated aqueous NH_4Cl solution (20 mL) and EtOAc (20 mL). The aqueous layer was further extracted with EtOAc (2 × 20 mL), and the combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), filtered, and evaporated in vacuo to give a red oil. Purification by column chromatography on SiO_2, eluting with EtOAc−hexane (1:1), and recrystallization (EtOH), gave the title compound as orange needles (7.1 g, 73%), mp 122−124 °C (lit.[19a] mp 124−131 °C). (Found: MH^+, 297.9633. $C_{12}H_7{}^{35}Cl_3N_3$ [MH] requires 297.9627); IR (KBr) ν/cm^{-1} 3116, 2923, 2853, 2184, 1617, 1572, 1157, 783; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (1H, d, *J* 8.8), 7.53 (1H, d, *J* 8.8), 7.38−7.34 (2H, m), 7.26 (1H, dd, *J* 7, 9), 6.43 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.6 (C), 155.5 (C), 135.9 (2C), 131.2 (CH), 129.6 (C), 129.4 (CH), 129.1 (CH), 128.8 (CH), 127.5 (CH), 115.2 (C), 38.5 (CH); MS (EI) *m*/*z* (rel intensity) 300 ($C_{12}H_7{}^{37}Cl^{35}Cl_2N_3{}^+$, 92%), 298 ($C_{12}H_7{}^{35}Cl_3N_3{}^+$, 100).

In an alternative procedure, a solution of (2,6-dichlorophenyl)acetonitrile (**8**) (100 mg, 0.54 mmol), KO*t*Bu (66 mg, 0.59 mmol), and 3,6-dichloropyridazine (**2**) (80 mg, 0.54 mmol) in dry THF (2 mL) was irradiated at 120 °C for 1.5 h in a pressure-rated glass tube (10 mL) using a CEM Discover microwave synthesizer by moderating the initial power (150 W). After cooling in a flow of compressed air, the reaction mixture was filtered, and the solvent was evaporated in vacuo. Purification by column chromatography on SiO_2, eluting EtOAc−hexane (1:1), and recrystallization (EtOH) gave the title compound as orange needles (99 mg, 62%), with identical physical and spectroscopic properties.

α-(2,6-Dichlorophenyl)-6-[(2,4-difluorophenyl)thio]-3-pyridazineacetonitrile (10). (Table 3, entry 16) According to the typical procedure, 6-chloro-α-(2,6-dichlorophenyl)-3-pyridazineacetonitrile (**9**) (75 mg, 0.25 mmol) was added to a stirred solution of (±)-*trans*-cyclohexane-1,2-diol (58 mg, 0.5 mmol), CuI (2.4 mg, 13 μmol), K_2CO_3 (69 mg, 0.5 mmol), and 2,4-difluorothiophenol (30 μL, 0.25 mmol), in propan-2-ol (2 mL). The solution was irradiated at 120 °C in a pressure-rated glass tube (10 mL) for 3 × 1 h using a CEM Discover microwave synthesizer by moderating the initial power (150 W). After cooling in a flow of compressed air, the reaction mixture was filtered on SiO_2, washing with MeOH, and evaporated in vacuo. Purification by

column chromatography on SiO_2, gradient eluting with Et_2O−hexane (1:5 to 1:1), gave the title compound as an orange solid (93 mg, 91%), mp 143−145 °C. (Found: $M^{\bullet+}$, 406.9857. $C_{18}H_9{}^{35}Cl_2F_2N_3S$ [M] requires 406.9862); IR (KBr) ν/cm^{-1} 3084, 2880, 2168, 1618, 1597, 1564, 1422, 1398, 1270, 1141, 967, 783; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57−7.54 (1H, m), 7.53−7.51 (1H, d *J* 9), 7.34−7.33 (1H, m), 7.32−7.30 (1H, d *J* 9), 7.23−7.12 (2H, m), 6.91−6.87 (2H, m), 6.35 (1H, s); ^{13}C NMR (125 MHz, DMSO) δ 164.3 (C, dd, J_{C-F} 250, 12), 162.8 (C, dd, J_{C-F} 250, 13), 154.5 (C), 146.2 (C), 138.7 (CH, d, J_{C-F} 10), 137.5 (C), 135.6 (C), 132.4 (C), 131.4 (CH), 130.1 (CH, d, J_{C-F} 3), 129.3 (CH, d, J_{C-F} 10), 126.9 (CH), 120.2 (C), 113.4 (CH, dd, J_{C-F} 22, 3), 111.6 (C, dd, J_{C-F} 19, 3), 105.7 (CH, t, J_{C-F} 26), 38.9 (CH); MS (APcI) *m*/*z* (rel intensity) 409 ($C_{18}H_9{}^{37}Cl^{35}ClF_2N_3S^+$, 70%), 408 ($C_{18}H_{10}{}^{35}Cl_2F_2N_3S^+$, 100).

5-(2,6-Dichlorophenyl)-2-[(2,4-difluorophenyl)thio]-6*H*-pyrimido-[1,6-*b*]pyridazin-6-one (VX-745) (1). A solution of α-(2,6-dichlorophenyl)-6-[(2,4-difluorophenyl)thio]-3-pyridazineacetonitrile (**10**) (123 mg, 0.3 mmol) in concentrated H_2SO_4 (2 mL) was irradiated at 100 °C for 0.5 h in a pressure-rated glass tube (10 mL) using a CEM Discover microwave synthesizer by moderating the initial power (100 W). After cooling in a flow of compressed air, the mixture was slowly poured into water (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed successively with saturated aqueous $NaHCO_3$ solution (10 mL) and brine (10 mL), dried ($MgSO_4$), and evaporated in vacuo to give carboxamide **11** as a yellow oil, which was used without further purification. The residue was added to a solution of *N*,*N*-dimethylformamide dimethyl acetal (55 μL, 0.4 mmol) in anhydrous toluene (2 mL) and irradiated at 100 °C for 1 h in a pressure-rated glass tube (10 mL) using a CEM Discover microwave synthesizer by moderating the initial power (120 W). After cooling in a flow of compressed air, the solvent was removed in vacuo. Purification by column chromatography on SiO_2, gradient eluting with EtOAc−hexane (7:3) to EtOAc, gave the title compound as a yellow solid (90 mg, 68%), mp 261−264 °C. (Found: MH^+ 435.9873, $C_{19}H_{10}N_3O^{35}Cl_2F_2S$ [MH] requires 435.9890); IR (KBr) υ/cm^{-1} 3048, 1612, 1597, 1579, 1422, 1240, 1138, 1107, 787; ^{1}H NMR (500 MHz, d_6-DMSO) δ 8.87 (1H, s), 7.86 (1H, ddd, *J* 8.4, 8.4, 6.4), 7.62 (2H, d, *J* 8), 7.58 (1H, app td, *J* 9.3, 2.6), 7.51 (1H, dd, *J* 8, 8), 7.31 (1H, td, *J* 8.8, 2.8), 7.06 (2H, s); ^{13}C NMR (125 MHz, d_6-DMSO) δ 165.8 (C), 164.8 (C, dd, J_{C-F} 251, 11.5), 163.1 (C, dd, J_{C-F} 253.8, 13.8), 154.4 (C), 150.7 (CH), 139.1 (CH, d, J_{C-F} 10), 137.9 (C), 136.1 (C), 131.7 (CH), 130.5 (C), 129.4 (CH), 128.9 (CH), 123.9 (CH), 113.8 (CH, dd, J_{C-F} 22, 3.5), 111.8 (C), 109.6 (C, dd, J_{C-F} 18.8, 5), 106 (CH, t, J_{C-F} 26.7); MS (ES) *m*/*z* 436 (MH^+, 100%).

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for all compounds, details of general experimental methods, and supplementary experimental procedures for Tables 1−3. This material is available free of charge via the Internet at http://pubs.acs.org.