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Synthesis of novel cyclopropylic sulfones and sulfonamides acting as glucokinase activators

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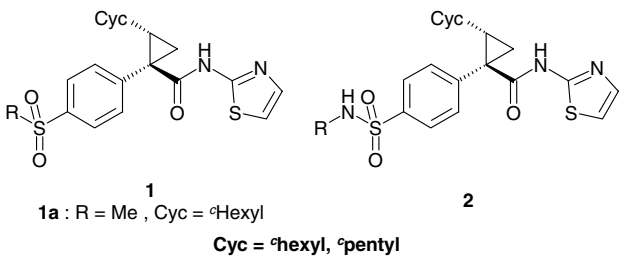
Abstract—A synthetic route towards cyclopropylic compounds, which act as glucokinase activators is described herein. The present synthesis gives easy and rapid access to a wide variety of either sulfones or sulfonamides starting from readily available late-stage intermediates.

Glucokinase (GK), a unique member of the hexokinase family, is predominantly expressed in liver and pancreas, where it catalyses the phosphorylation of glucose.[1] Unlike other hexokinases, GK demonstrates a low affinity for glucose and a sigmoidal response to glucose concentration. These properties make GK an ideal glucose sensor, the activity of GK being much higher at elevated than at normal glucose levels. In the liver, the increased GK activity at high glucose levels results in enhanced glucose utilization, whereas in the pancreas, increased GK activity results in enhanced insulin secretion.[2] Therefore, it is proposed that activation of GK should result in better control of blood glucose levels via both hepatic and pancreatic effects, whereas the glucose-dependency of GK activation may decrease the possibility of hypoglycaemia during treatment. In fact, several groups including this one have described various small-molecule GK activators (GKAs), which function through binding to an allosteric site.[3] By in-house efforts we found that compound **1a** (LY2121260) potently activates GK whereas its enantiomer ***ent*-1a** is much weaker (Scheme 1).[4]

As part of our structure activity studies around **1a**,[5] we were interested in phenyl sulfones and sulfonamides of the general structure **1** and **2**, and required a robust and short synthetic route to such compounds.

Our initial synthesis (as exemplified in Scheme 2 for Cyc = cyclopentyl) started from the cycloalkyl aldehyde. Wadsworth–Horner–Emmons reaction gave the desired *E*-olefin **4** in excellent yield. The following bromination–elimination sequence[6] provided the α-brominated α,β-unsaturated ethyl ester **5**, which was readily reduced to the bromoolefin **6** using DIBAH. **6** could then be



Scheme 1. Glucokinase activating sulfones **1** and sulfonamides **2**.

Keywords: Cyclopropanes; Sulfones; Sulfonamides; Glucokinase activators; Halogen–sulfur exchange.
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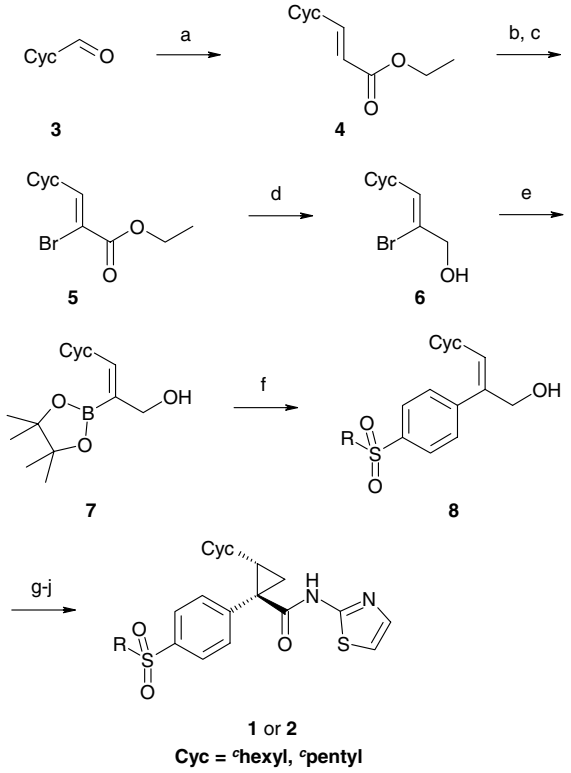
transformed to the pinacol boronic acid ester **7** employing standard conditions published by Miyaura and co-workers.[7] This boron reagent was then successfully used in Suzuki couplings with a variety of bromobenzenes in which the desired sulfone- or sulfonamide-linked functionality had been incorporated. The resulting allylic alcohols **8** could then be transformed easily into the corresponding racemic cyclopropyl methyl alcohols using Simmons–Smith conditions.[8] (Unfortunately, attempts[9] to conduct the reaction in an enantioselective manner failed to give even cyclopropane). The racemic cyclopropyl methyl alcohol was then separated into its enantiomers by chiral HPLC. Jones oxidation to the corresponding carboxylic acid and *O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU)-mediated amide coupling with 2-aminothiazole finally provided the desired target molecules **1** or **2** in good yield.

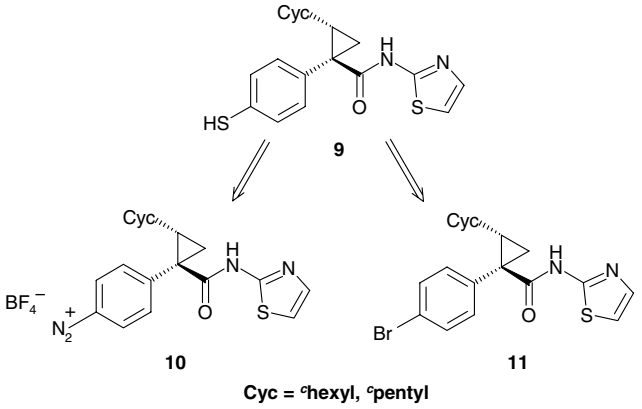
The nature of our initial synthetic route posed several problems in the exploration of the SAR. First, it was necessary to incorporate the functional groups appended via sulfone- or sulfonamide-linkages prior to the Suzuki coupling; that is, at a fairly early stage of the synthesis. Furthermore, four subsequent steps were required per desired target compound, and in addition, the route was not asymmetric. Because the interaction with GK is enantiospecific, it was necessary to separate the racemic products into their respective enantiomers for advanced studies. This was accomplished by semi-preparative chiral HPLC, but obviously lowered the yield by 50% in a late step of the reaction sequence for every final product. Therefore, the development of a new synthetic route that circumvents these issues and gives easy and rapid access to enantiopure compounds with variations in the sulfone/sulfonamide-region was highly desirable.



Scheme 2. Reagents and conditions (exemplified for Cyc = cyclopentyl, R = –NH(CH$_2$)$_2$(2-pyridyl)): cyclopentane-carbaldehyde (**3**) was prepared from cyclopentylmethanol using PCC, celite, rt, 16 h (CH_2Cl_2), 78%; (a) $(EtO)_2POCH_2CO_2Et$, NaH, 0 °C, 1 h (THF), then **3**, −78 °C to rt, 1 h (THF), 100%; (b) bromine, −10 °C, 2 h (CH_2Cl_2), not isolated; (c) NEt_3, rt, overnight (CH_2Cl_2), 76%; (d) DIBAH, −60 °C to rt, 1 h (THF/toluene), 79%; (e) bis-pinacolatodiboron, KOAc, Pd(dppf)Cl_2, dppf, 80 °C, 2 h (1,4-dioxane), 61%; (f) bromoarene, Pd(OAc)$_2$, PPh_3, Na_2CO_3, 80 °C, 16 h (^{i}PrOH/water), 74%; (g) $ZnMe_2$, CH_2I_2, 60 °C, 2 h (CH_2Cl_2/toluene), 45%; (h) chiral HPLC-separation; (i) CrO_3, H_2SO_4, 0 °C to rt, 2 h (water/acetone), 89%; (j) 2-aminothiazole, TBTU, NEt_3, 40 °C, 24 h (THF), 40%.

Being convinced that an enantiopure intermediate such as **9** as depicted in Scheme 3 would be a suitable late-stage intermediate, we first considered a protective group strategy to mask the thiophenol throughout the synthesis. Unfortunately, none of the protective groups applied withstood the cyclopropanation conditions. We then tried to synthesize **9** (Cyc = cyclopentyl) from the corresponding diazo-compound **10**, which was easily accessible from 4-nitrobromobenzene and boronic acid ester **7** via the known route, after reduction[10] of the nitro group and subsequent diazotization.[11] However, the reaction with potassium ethylxanthate[12] did not furnish the desired product.

We therefore envisioned halogen–sulfur exchange as another possibility to introduce sulfones or sulfonamides at a very late stage of the synthesis. To test the hypothesis we first performed a detailed study of a variety of literature-precedented methods using 4-halogeno- methylbenzenes as test systems (Table 1). Many of the employed methodologies[13] did not furnish the desired sulfur-containing compounds. Only potassium triisopropylsilane-thiolate [KS(TIPS)] gave the triisopropylsilyl-(TIPS)-protected thiophenol in a Pd-catalyzed coupling reaction[14] with all test systems (entries 1, 4 and 5). Furthermore, 1-iodo-4-methylbenzene (**13**) underwent the desired reaction with phenyl-methanethiol using either a mixture of copper iodide and potassium carbonate in ethyleneglycol[15] (entry 2) or copper iodide, sodium *tert*-butanolate and phenanthroline in toluene[16] (entry 3). However, utilization of these reactions for our purposes would have required a subsequent deprotection step prior to transformation of the free thiophenol



Scheme 3. Possible late-stage intermediates.

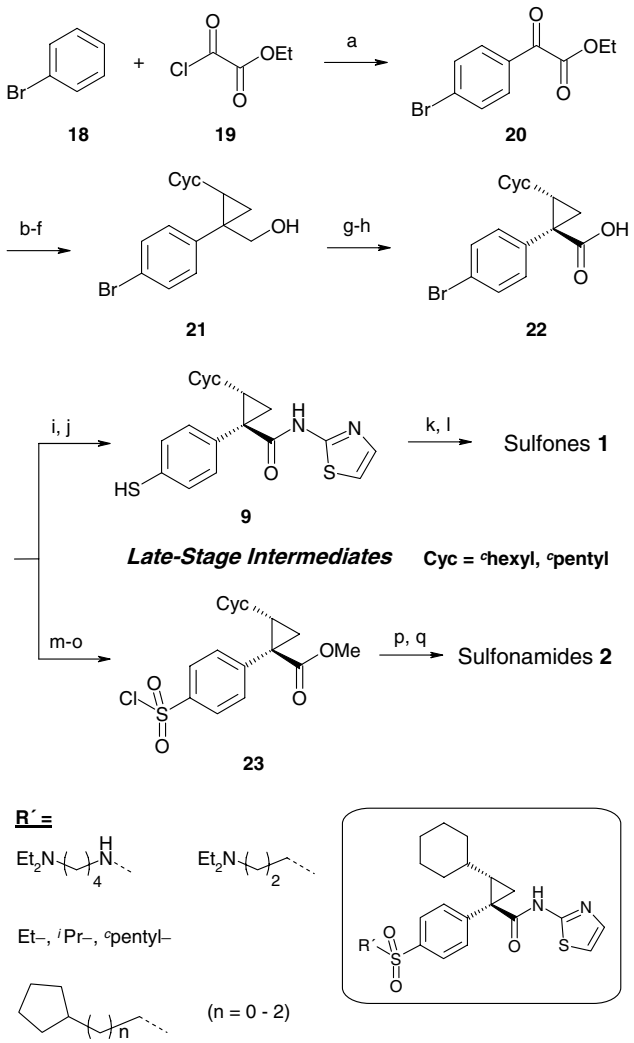
Table 1. Halogen–sulfur exchange on test systems

Entry	X =	Nucleophile	Product	Conversion[g] (%)
1[a]	Br **12**	KS(TIPS) (1 equiv)	Ar–S–TIPS **15**	100
2[b]	I **13**	BnSH (1 equiv)	Ar–S–Ph **16**	100
3[c]	I **13**	BnSH (1 equiv)	Ar–S–Ph **16**	100
4[d]	I **13**	KS(TIPS) (1 equiv)	Ar–S–TIPS **15**	100
5[e]	OTf **14**	KS(TIPS) (1 equiv)	Ar–S–TIPS **15**	100
6[f]	Br **12**	NaSMe (8 equiv)	Ar–SH **17**	100

[a] $Pd(PPh_3)_4$, 20 h (benzene/THF), reflux.
[b] CuI, K_2CO_3, 16 h (ethyleneglycol/^{i}PrOH), 80 °C.
[c] CuI, NaO^{t}Bu, phenanthroline, 20 h (toluene), 110 °C.
[d] $Pd(PPh_3)_4$, 15 min (benzene/THF), reflux.
[e] $Pd(PPh_3)_4$, 15 min (benzene/THF), reflux.
[f] (DMA), 150 °C.
[g] As determined by GC–MS.

to sulfones or sulfonamides. In this respect, a third reaction using a large excess of sodium thiomethylate in DMA at high temperatures[17] is highly remarkable as it was possible under the reaction conditions to obtain the free thiophenol directly (entry 6). Furthermore the reaction does not require the more expensive iodo precursor and transition metal-catalysis is not necessary. We therefore regarded this reaction to be well suited for our actual synthesis of GK activators.

Initial plans to start from 4-bromoiodobenzene following the known procedure shown in Scheme 2 proved not to be viable as the Suzuki coupling with boronic acid ester **7** provided a complex mixture of coupling products. We therefore envisioned an alternative route, which is depicted in Scheme 4. Friedel–Crafts acylation of bromobenzene (**18**) with **19** provided the α-keto phenylacetic acid **20** in satisfactory yield.[18] Subsequent Wittig reaction[19] furnished the expected olefin as an *E*/*Z*-mixture. Interestingly, the equilibrium could be shifted completely towards the *E*-isomer by treatment with sodium methoxide at 50 °C. In addition to causing transesterification, the methoxide apparently catalyses the *E*/*Z* equilibration via a Michael–retro-Michael addition sequence. Subsequent addition of aqueous sodium hydroxide to the reaction mixture resulted in saponification of the ester to afford the *E*-carboxylic acid exclusively.[20] Reduction with DIBAL and standard cyclopropanation gave racemic cyclopropylic alcohol **21**. Its enantiomers could be separated in multigram scale by prep. HPLC,[21] enabling the rapid synthesis of enantiomerically pure cyclopropyl carboxylic acid **22** after Jones oxidation.[22] For the preparation of sulfones



Scheme 4. Reagents and conditions (exemplified for Cyc = cyclohexyl): (a) $AlCl_3$, −10 °C to rt, 4 h (DCM), 72%; (b) (*cyc*-C_6H_{11})CH_2PPh_3I, LiHMDS, 0 °C to rt, 16 h (THF), 80%; (c) NaOMe, 50 °C, 16 h (MeOH); (d) NaOH, 50 °C, 5 h (methanol/water), 75% (two steps); (e) DIBAH, −70 °C to rt, 16 h (toluene), 86%; (f) $ZnMe_2$, CH_2I_2, 60 °C, 5 h (dichloroethane), 78%; (g) chiral HPLC-separation; (h) CrO_3, H_2SO_4, rt, 2 h (acetone/water), 90%; (i) 2-aminothiazole, TBTU, NEt_3, 0 °C to rt, 16 h (THF), 74%; (j) NaSMe, 150 °C, 16 h (DMA), 94%; (k) R′–X, K_2CO_3, rt, 16 h (acetone), 60–70%; (l) Oxone®, rt, 4 h (MeOH/water), >80% (two steps); (m) NaSMe, 150 °C, 16 h (DMA); (n) concd H_2SO_4, rt, 16 h (MeOH); (o) KNO_3, SO_2Cl_2, rt, 1 h ($CHCl_3$), 76% (three steps); (p) R′ (=R″–NH_2), NEt_3, rt, 16 h (CH_2Cl_2); (q) 2-aminothiazole, ^{i}PrMgCl, −20 °C to 60 °C, 16 h (THF), >70% (two steps).

1, **22** was converted to the desired amide prior to halogen–sulfur exchange, alkylation and oxidation.[23]

Because the thiazole was not stable to the oxidative chlorination conditions[24] used in the synthesis of the sulfonamides, it was necessary to prepare the intermediate methyl ester-containing sulfonyl chloride **23**. This could be transformed into the sulfonamides **2** by simple reaction with an amine and subsequent amidation with 2-aminothiazole, activated by deprotonation with *iso*-propyl magnesium chloride prior to addition to the methylester. All target molecules were obtained in good yields and high enantiomeric purity.[25]

In summary, we have developed a robust route to novel enantiopure small molecule GK activators that provides the desired sulfones and sulfonamides bearing a variety of functional groups in only two steps from readily available late-stage intermediates. By employing this methodology we were able to increase the rate of compound synthesis significantly and thereby accelerate the SAR-exploration in this region of the molecule. A summary of the results of this SAR study including a detailed discussion of pharmacokinetic and pharmacodynamic properties of the compounds will follow in due course.

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19. The phosphomium salt was prepared starting from bromo-methylcyclohexane (1. NaI, reflux, 6 h (acetone); 2. PPh_3, reflux, 22 h (xylene) 78% (two steps)).
20. A similar isomerization of the corresponding methylsulfone has been reported by Corbett et al. In that case, the stronger electron-withdrawing effect of the sulfone as compared to the bromide apparently increased the rate of isomerization such that treatment with methanolic aqueous base at rt for 20 h resulted in complete isomerization without competing saponification. Subsequent removal of methanol and brief heating afforded the *E*-carboxylic acid exclusively. When these conditions were applied to the bromide, a mixture of *E*/*Z* carboxylic acids was obtained. See Ref. 3a.
21. HPLC was done using a 80 mm ID dynamic axial compression (DAC) Novasep column separating up to 24 g/h of the racemic cyclopropyl alcohol. Conditions: 1 kg Daicel Chiralpak AD (20 μm), mobile phase: 100% MeCN, starting flow rate 150 ml/min, end run flow rate 320 ml/min, 260 nm.
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