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Stereoselective Synthesis of *cis*-1,3-Disubstituted Cyclobutyl Kinase Inhibitors

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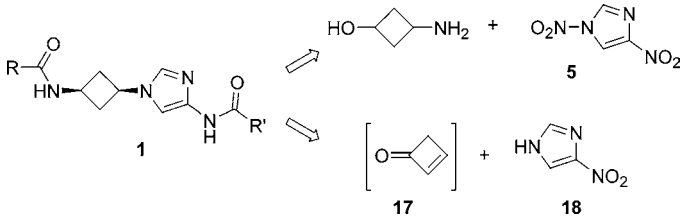
ABSTRACT



Two synthetic routes to a series of structurally novel kinase inhibitors containing a *cis*-1,3-disubstituted cyclobutane are described. The first route utilized addition of 3-aminocyclobutanol to 1,4-dinitroimidazole 5 as the crucial step in preparing 1, whereas the second route employed a novel 1,4-addition of 4-nitroimidazole 18 to in situ generated cyclobutenone 17 as the key reaction. This allowed for a stereoselective and shorter synthesis that eliminated the use of potentially explosive 1,4-dinitroimidazole 5.

We recently disclosed compounds of formula **1** as kinase inhibitors (Figure 1).[1] The *cis* orientation of substituents on

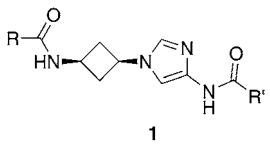


Figure 1. Target compound.

the cyclobutyl ring is essential for optimal activity. These novel structures required the development of methods to attach the imidazole to the cyclobutane as well as efficient strategies to generate the *cis*-stereochemistry. This paper details two synthetic routes utilized to generate **1**.

Our first approach was initiated by heating a neat 1:1 mixture of epichlorohydrin and benzyl bromide in the presence of catalytic mercury(II) chloride to afford 2-benzyloxy-1-bromo-3-chloropropane **2** following distillation (Scheme 1).[2]

Alkylation of diethylmalonate with **2** gave the substituted cyclobutane **3** which was purified by distillation. Hydrolysis of **3** to the diacid with potassium hydroxide in water/ethanol at reflux followed by extractive workup and then gradual warming to ca. 185 °C in vacuo (5 mmHg, °C) yielded the pure monoacid as a 1:1 mixture of *cis*−*trans* isomers. Conversion of the acid to the acyl azide with diphenylphosphoryl azide (DPPA) and triethylamine in toluene at room temperature followed by Curtius rearrangement at 70 °C and trapping of the resulting isocyanate by the addition of ethanol and continued heating at 80 °C gave the carbamate after silica gel chromatography. Subsequent hydrolysis with solid potassium hydroxide in methanol provided after workup and chromatographic purification 3-amino-1-benzyloxyxcyclobutane **4**. Hydrogenolysis of the benzyl group under acidic

(1) Ahlijanian, M. K.; Cooper, C. B.; Helal, C. J.; Lau, L.-F.; Menniti, F.; Sanner, M. A.; Seymour, P. A.; Villalobos, A. WO Patent 02/10141 A1, 2002.

(2) Intermediate **4** was prepared via the method outlined in the literature with the exception of the procedure used for acyl azide formation/Curtius rearrangement: Avram, M.; Nenitzescu, C. D.; Maxim, M. *Chem. Ber.* **1957**, *90*, pp 1424−1432.

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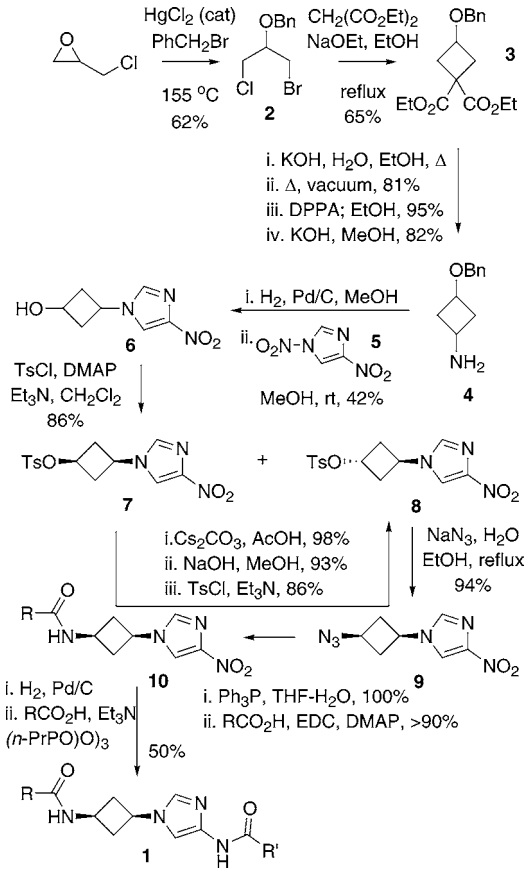
Scheme 1

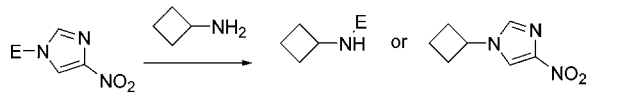


conditions, filtration, and neutralization with solid potassium hydroxide gave 3-aminocyclobutanol in methanol. This solution was added to a slurry of 1,4-dinitroimidazole **5**[3] (1,4-DNI) in methanol. Reaction between 3-aminocyclobutanol and 1,4-DNI proceeds via nucleophilic addition of the amine to the imidazole 5-position, ring opening, and then ring closure with expulsion of NO_2NH_2 to afford **6** as a solid following chromatography.[4] Tosylation of **6** followed by chromatographic separation (1:1 to 3:1 EtOAc−hexanes) gave the pure *cis* and *trans* isomers (**7** and **8**, respectively, 1:1 ratio). The *cis* isomer **7** was converted to the *trans* isomer **8** in a high-yielding three-step sequence consisting of (1) tosylate displacement with in situ formed cesium acetate at reflux in acetonitrile, (2) acetate hydrolysis at room temperature with 1 equiv of sodium hydroxide in methanol, and (3) alcohol tosylation with triethylamine as base and catalytic DMAP in methylene chloride. Reaction of the *trans* isomer **8** with sodium azide cleanly afforded *cis* azide **9** without purification. The selective reduction of the azide to the amine under Staudinger conditions was followed by coupling the crude amine with a carboxylic acid to afford amide **10** following chromatographic purification. The nitro group of **10** was reduced using catalytic hydrogenation in ethyl acetate. Due to instability of the 4-aminoimidazole, the reaction mixture was filtered through Celite and was treated with triethylamine, a carboxylic acid, and 1-propanephosphonic acid cyclic anhydride from 0 °C to room temperature, giving the desired final compound **1** after silica gel chromatography.[5]

In preparation for scaling the synthesis, a thermal and impact stability analysis of 1,4-DNI was carried out. Thermal analysis by differential scanning calorimetry (DSC) performed at 4 °C/min indicated two exotherms. The first exotherm was rather broad, beginning near 55 °C and continuing to 250 °C. This was followed by a second exotherm of 1650 J/g starting at 274 °C and ending near 350 °C. When tested by accelerating rate calorimetry (ARC), the results suggested the potential for self-heating from 35 °C that could lead to explosion. Under low heat-loss conditions the first exotherm can merge with the second exotherm. In fact, the ARC test cell containing 2 g of material exploded violently during the thermal runaway. Although impact testing did not indicate a sensitivity to impact by drop hammer it should be considered a self-reactive substance based on the thermal testing. Based on these data, we urge caution when handling this material; this compound should be stored in a freezer and only in small quantities.

The risk associated with the use of 1,4-DNI forced us to search for a safer 1,4-DNI replacement. The instability of the NO_2−N bond of 1,4-DNI was presumed to be responsible for its highly energetic nature as intermediates containing a single nitro group such as 4-nitroimidazole and **8** did not display thermal or impact instability. We thus sought to replace the nitro with other electron-withdrawing groups. *o*-Nitrophenylsulfonyl, for example, has been reported to activate 4-nitroimidazole to nucleophilic attack by anilines, resulting in 1-aryl-4-nitroimidazoles.[6] Our investigation of the reaction between activated 4-nitroimidazoles and cyclobutylamine is detailed in Table 1.

Table 1. Reactions of Activated 4-Nitroimidazoles



12 13 14

starting material	E−	major product
12a	NO_2−	**14** (81% yield)
12b	N≡C−	**14** (81% yield)
12c	$(2\text{-}NO_2C_6H_4)SO_2$−	**13c**
12d	$(2,4,6\text{-}^iPrC_6H_2)SO_2$−	**13d**
12e	$(CH_3)_3OC(=O)$−	**13e**
12f	$Ph_2P(=O)$−	**13f**

Attack on the imidazole ring (in analogy to 1,4-DNI) to afford **14** is observed when E is cyano in low yield. The

(3) Bulusu, S.; Damavarapu, R.; Autera, J. R.; Behrens, R., Jr.; Minier, L. M.; Villanueva, J.; Jayasuriya, K.; Axenrod, T. *J. Phys. Chem.* **1995**, *99*, 5009−5015.

(4) Suwinski, J.; Szczepankiewicz, W. *Tetrahedron: Asymmetry* **1991**, *2*, 941−942.

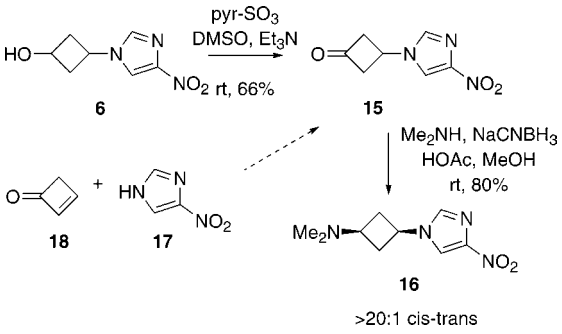
(5) Detailed experimental procedures for the conversion of **4** to **1** are found in ref 1.

(6) Suwinski, J.; Salwinska, E. *Tetrahedron* **1994**, *50*, 5741−5752.

only product observed when E is arylsulfonyl, alkoxycarbonyl, or phosphonyl is **13**, due to 4-nitroimidazole acting as the leaving group.

The challenge in finding a 1,4-DNI replacement and the fact that this route was nonstereoselective led us to formulate an alternative synthesis. Previous work in our laboratory had demonstrated that oxidation of alcohol **6** to cyclobutanone **15** followed by reductive amination with a secondary amine afforded predominantly the *cis*-product **16** (>20:1) (Scheme 2).

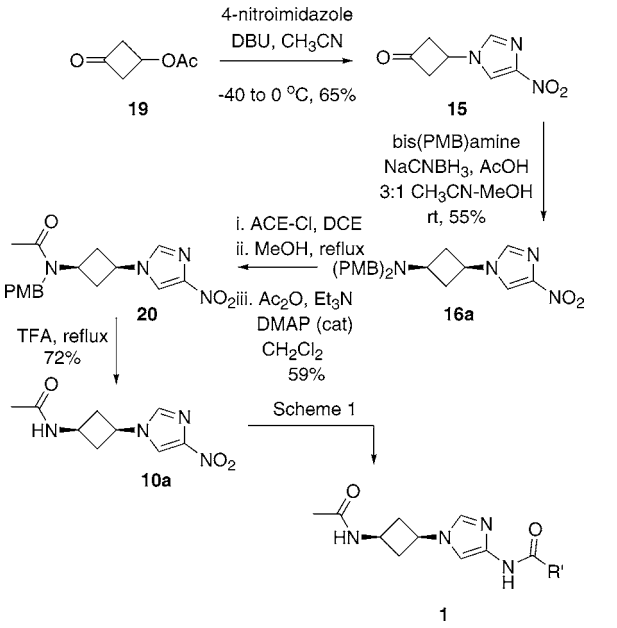
Scheme 2



Access to **15**, however, was restricted due to the requirement of using 1,4-DNI for the synthesis of **6** (Scheme 1). An alternative synthesis of **15** would be via Michael addition of 4-nitroimidazole **17** to cyclobutenone **18**.[7] The first reported synthesis of cyclobutenone,[8] from 3-chloro- or 3-bromocyclobutanone via elimination of HX, however, indicates that this material polymerizes rapidly even at −78 °C. Nonetheless, the report does state that cyclobutenone "probably can be formed and reacted *in situ* conveniently," and it was this strategy that we chose to explore.[9]

A solution of 3-acetoxycyclobutanone **19**[10] was added to a solution of 4-nitroimidazole **17** and 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) in acetonitrile at −40 °C followed by warming to 0 °C to provide the desired cyclobutanone **15** in 65% yield after silica gel chromatography (Scheme 3).[11] We presume that the 4-nitroimidazole anion (DBU salt) is sufficiently basic to eliminate acetate, generating cyclobutenone, which reacts quickly with the excess 4-nitroimidazole anion present in the reaction mixture. Direct S_N2 displacement of the acetate was ruled out based upon the poor reactivity of 4-nitroimidazole anion with electrophiles such as cyclobutyltosylate from room temperature to 150 °C. When the reaction solution was warmed above 0 °C, was allowed to sit for >2 h at 0 °C, or insufficient acid was added

Scheme 3



during the quenching step, some production of the undesired imidazole *N*-3 alkylation isomer resulted. The order of reagent addition was found to be critical as the addition of DBU to a mixture of 4-nitroimidazole and 3-acetoxycyclobutanone in acetonitrile at −40 °C gave variable yields, possibly due to reaction of the DBU with 3-acetoxycyclobutanone versus the poorly soluble 4-nitroimidazole. The reaction of 3-benzyloxycyclobutanone[12] or 3-phthalimidocyclobutanone[13] with 4-nitroimidazole/DBU under various conditions gave no product, indicating the importance of having an appropriate leaving group at the cyclobutanone 3-position.

The route was completed by introducing the *cis*-amine group via reductive amination of **15** with bis(*p*-methoxybenzyl)amine which afforded **16a** as a single stereoisomer. Reductive amination with *p*-methoxybenzylamine was not selective (2.5:1 *cis*/*trans*). Selective dealkylation of **16a** with 1-chloroethyl chloroformate (ACE-Cl) in refluxing 1,2-dichloroethane (DCE), removal of solvent, and then metha-

(7) For examples of the 1,4-addition of azoles to α,β-unsaturated systems, see: (a) Horvath, A. *Tetrahedron Lett.* **1996**, *37*, 4423−4426. (b) Horvath, A. *Synthesis* **1995**, *17*, 1183−1189.

(8) Sieja, J. B. *J. Am. Chem. Soc.* **1971**, *93*, 2481−2483.

(9) For two reports of the use of cyclobutenone in organic synthesis, see: (a) Martin, H.-D.; Iden, R.; Mais, F.-J.; Kleefeld, G.; Steigel, A.; Fuhr, B.; Rummele, O.; Oftring, A.; Schwichtenberg, E. *Tetrahedron Lett.* **1983**, *24*, 5469−5472. (b) Martin, H.-D.; Oftring, A.; Iden, R.; Schwichtenberg, E.; Schiwek, H.-J. *Tetrahedron Lett.* **1982**, *23*, 841−844.

(10) Prepared in two steps from vinyl acetate, see: Dehmlow, E. V.; Buker, S. *Chem. Ber.* **1993**, *126*, 2759−2763.

(11) **1-(3-Oxocyclobutyl)-4-nitroimidazole (15).** A solution of 4-nitroimidazole **17** (520 mg, 4.6 mmol) and DBU (687 uL, 4.6 mmol) in acetonitrile (23 mL) cooled to −40 °C was treated with a solution of 3-acetoxycyclobutanone **19** (300 mg, 2.34 mmol) in acetonitrile (2 mL). The reaction temperature was increased to 0 °C for 45 min, and then HCl (2.6 mmol, 1 M in methanol, freshly prepared) was added. The solvent was removed in vacuo, and the solid was tritutrated with methylene chloride and was filtered. The filtrate was concentrated in vacuo, and the residue was purified by silica gel chromatography (30:1 chloroform−methanol) to afforded 65% yield (274 mg) of the title compound: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.73 (d, J = 1.7 Hz, 1H), 8.09 (d, J = 1.2 Hz, 1H), 5.14 (m, 1H), 3.69 (m, 2H), 3.57 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 203.36, 137.68, 121.17, 55.89, 43.47; MS (AP/CI) 182.01 $(M + H)^+$; HRMS calcd 182.0566 (M + H), obsd 182.0572 (M + H); FTIR (cm^{-1}) 3123, 2357, 2331, 1790, 1544, 1488, 1290, 1144, 1107.

(12) Ogura, K.; Yamashita, M.; Suzuki, M.; Furukawa, S.; Tsuchihashi, G. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1637−1642.

(13) Prepared via reaction between *N*-vinylphthalimide and *N*,*N*-dimethylketeniminium triflate. See: Falmagne, J.-B.; Escudero, J.; Taleb-Sahraoui, S.; Ghosez, L. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 879−880.

nolysis of the carbamate followed by reaction of the crude amine with an excess of acetic anhydride gave amide **20** which was purified by silica gel chromatography. Use of excess acetic anhyride prevented reaction of the amine with residual *p*-methoxybenzyl chloride which was formed in the dealkylation. Removal of the remaining *para*-methoxybenzyl group with neat trifluoroacetic acid provided intermediate **10a** following chromatography, which can be converted to **1** (Scheme 1).

In summary, we have developed two distinct strategies for the synthesis of compound **1**. The initial route utilized known methods to prepare 3-amino-1-benzyloxycyclobutane **4**, which was reacted with 1,4-DNI to yield intermdiate **6** as a 1:1 mixture of *cis*/*trans* isomers. The isomers were separated following tosylation and subsequently converted to **1**. In comparison, the second route incorporated a novel in situ generation/trapping of cyclobutenone to prepare the key intermediate **15**, was highly stereoselective, was four steps shorter than the first route (8 steps from commercially available material versus 12), and eliminated the potentially explosive 1,4-DNI.

Acknowledgment. We thank Dr. D. J. am Ende, P. Clifford, and N. Weston for determining the thermal and impact stability of 1,4-dinitroimidazole. We thank Dr. M. Sanner and Dr. C. O'Donnell for valuable suggestions during manuscript preparation.

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