Tetrahedron Letters 53 (2012) 2543–2547

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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

Complementary α-alkylation approaches for a sterically hindered spiro[pyrazolopyranpiperidine]ketone

Chris Limberakis *, Jianke Li, Gayatri Balan, David A. Griffith, Daniel W. Kung, Colin Rose, Derek Vrieze

CVMED Chemistry, Pfizer Worldwide Research and Development, Eastern Point Road, Groton, CT 06340, USA

ARTICLE INFO

Article history:
Received 18 February 2012
Revised 6 March 2012
Accepted 8 March 2012
Available online 15 March 2012

Keywords:
Spiro[pyrazolopyranpiperidine]ketone
Enolate alkylation
DMPU
Aldol condensation
1,4-Addition

ABSTRACT

Complementary α-alkylation methods are used to derivatize a sterically hindered spiro[pyrazolopyranpiperidine]ketone. More specifically, enolate alkylations in the presence of DMPU and aldol condensations are employed to deliver these compounds.

According to the World Health Organization (WHO), 346 million people globally have diabetes with numbers projected to steadily increase over the coming decades.[1] Of these diabetics, 90% suffer from type II diabetes (T2DB) where patients do not effectively use insulin. In recent years, acetyl CoA carboxylase (ACC) inhibitors have emerged as novel targets for the treatment of type II diabetes mellitus (T2DM) since ACC is a key metabolic switch which regulates lipogenesis and fatty acid oxidation.[2] To this end, our research program has identified a series of ACC inhibitors including the novel spiro[pyrazolopyranpiperidine]ketone **1**[3] which was synthesized using intermediate **2**[3a,c,4] (Fig. 1). We were interested in exploring the impact of substitution adjacent to the ketone on ACC inhibition and metabolic clearance, so we embarked to synthesize α-mono and α,α-disubstituted derivatives of **2** to deliver building blocks **3** and **4**. During our synthetic efforts, we discovered that direct α-alkylation of the ketone was challenging due to the sterically congested environment of the keto α-center and the propensity for β-elimination under basic conditions. Hence, a multi-strategy approach was devised which involved enolate alkylations and aldol condensations.

It is well established that the related 4-chromanones can be directly α-alkylated with electrophiles via their respective enolates,[5] but there are examples where the resulting enolates also undergo preferential β-elimination to afford chalcones.[5b,d] Based on this literature precedent, we recognized that our spiro[pyrazolopyranpiperidine]ketone could suffer the same fate. Nonetheless, the necessary experiments were performed to test the viability of the enolate alkylation method. In a typical experiment, ketone **2** was treated with either LDA or LiHMDS at −78 °C to afford the enolate, then a variety of alkylating agents and aldehydes were added. To our disappointment, none of the desired products were isolated. Instead, the major product was the α,β-unsaturated ketone (**7**) which arose from a β-elimination pathway (Scheme 1).

Given these ungratifying results, we sought to enhance the rate of alkylation relative to β-elimination by focusing our efforts on increasing the enolate nucleophilicity and/or stabilizing the enolate. Like other organolithium species,[6] lithium enolates have complex aggregation states and exist in dimeric, trimeric, and other

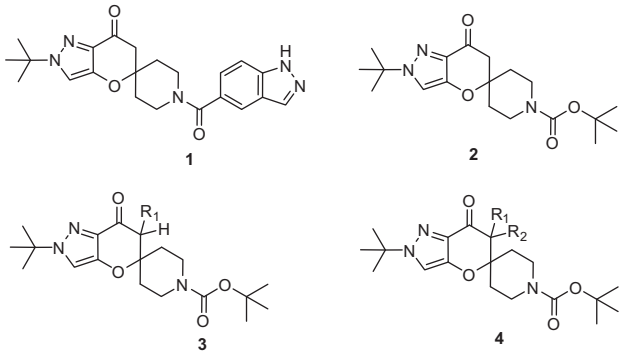

Figure 1. Key compounds.

* Corresponding author. Tel.: +1 860 686 9168.
E-mail address: chris.limberakis@pfizer.com (C. Limberakis).

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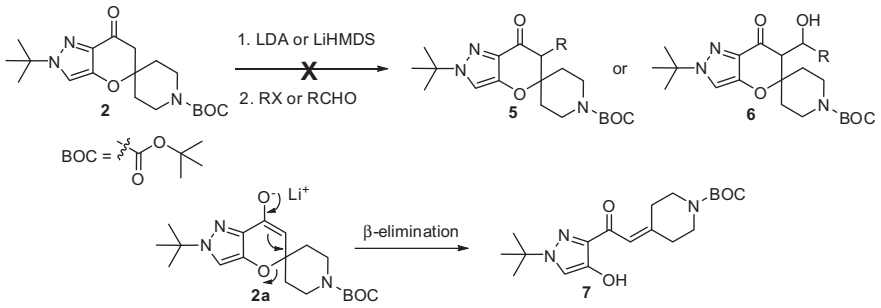
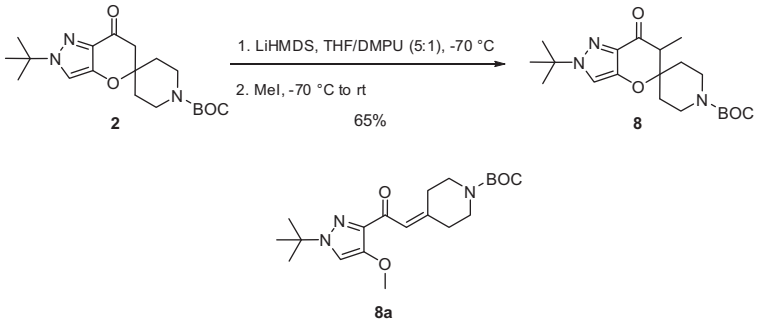
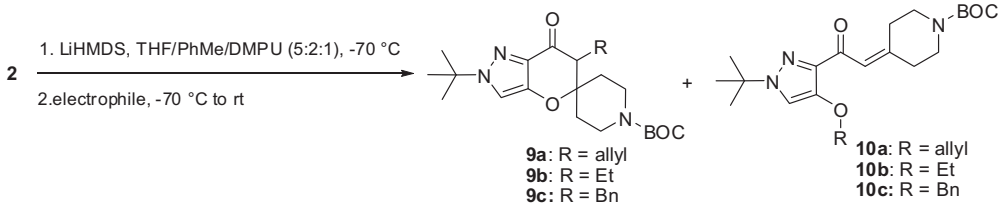
http://dx.doi.org/10.1016/j.tetlet.2012.03.030



Scheme 1. Initial alkylation experiments and β-elimination.



Scheme 2. Alkylation with methyl iodide in the presence of DMPU.



R-X	spiroketone	β-elimination product
	**9a** (39%)	**10a** (19%)
EtI	**9b** (0%)	**10b** (58%)
	**9c** (0%)	**10c** (63%)

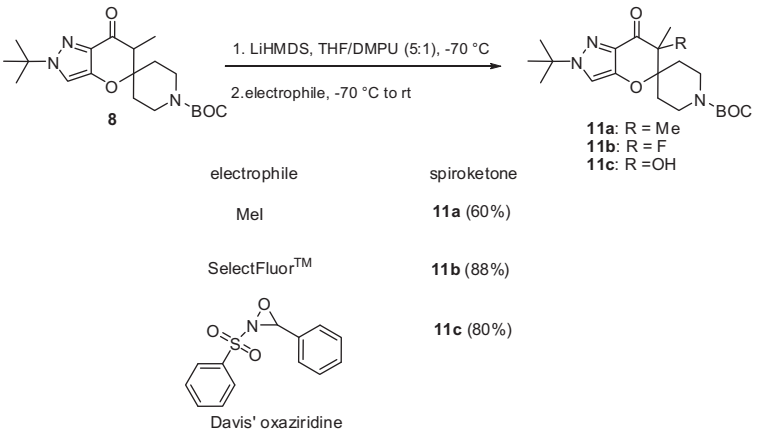
Scheme 3. Expanding alkylation with other electrophiles.

oligomeric forms depending on the solvent.[6,7] In addition, mixed aggregates may also form between the enolate and the base (i.e., LDA, LiHMDS, LiTMP, etc).[7] It is well known that polar aprotic solvents such as hexamethylphosphoramide (HMPA)[8] and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU)[9] enhance the basicity and nucleophilicity of reagents by forming cation–ligand complexes and thus alter the aggregation state and possibly lead to increased reactivity. Unlike its carcinogenic counterpart HMPA, DMPU has no apparent mutagenic properties, but exhibits similar solvent effects to HMPA.[9] Moreover, Seebach and coworkers demonstrated that DMPU can 'stabilize' enolates which are prone to β-elimination.[9,10] These DMPU effects are well documented and demonstrated with a wide variety of reactions.[11]

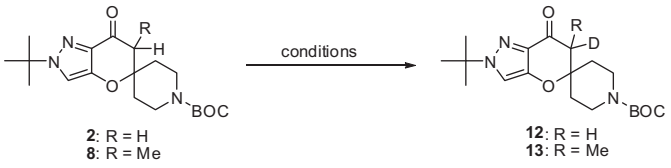
Our preliminary experiments were run in the binary mixture of THF/DMPU (5:1). In the event, ketone **2** was treated with LiHMDS in THF at −70 °C. After 30 min, DMPU was added, and stirring was continued at this temperature for an additional 10 min. Methyl iodide (5 equiv) was added, and the reaction mixture was then slowly warmed to room temperature over 3 h. To our delight, α-methylketone **8** was afforded in 65% yield with less than 10% yield of **8a** (Scheme 2).[12] Although we examined higher ratios of THF/DMPU (i.e., 10:1 and 20:1), the yield of **8** was significantly decreased to 30–35%. We also discovered that the alkylation worked equally as well in the ternary mixture of THF:toluene:DMPU (5:2:1).[13]

Armed with these results, the reaction conditions were applied to other electrophiles. Unfortunately, the results were mixed as shown in Scheme 3. Of the three additional electrophiles examined, only allyl iodide gave the corresponding α-alkylated ketone **9a**; however, the β-elimination product **10a** was also isolated (Scheme 3). Treatment of the enolate with ethyl iodide or benzyl bromide afforded only β-elimination products.[14]

Undaunted by the limited range of viable electrophiles using the enolate alkylation chemistry to make α-monosubstituted ketones, we studied the reaction of methylketone **8** to prepare



Scheme 4. Alkylations with DMPU to deliver α,α-disubstituted spiroketones.



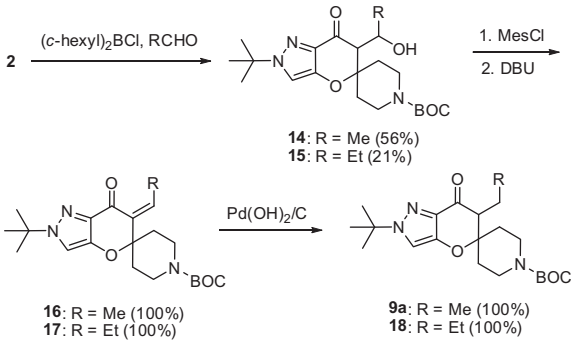
Conditions	Deuterium incorporation at the α-center[1] 2 → 12	8 → 13
a. LiHMDS, THF/PhMe (2.5:1), -70 °C, 30 min b. CD_3COOD	88%	17%
a. LiHMDS, THF/PhMe (2.5:1), -70 °C, 30 min b. DMPU, -70 C, 10 min[2] c. CD_3COOD	>95%	55%

[1]based on ^1H NMR integration of the α-H
[2]THF/PhMe/DMPU (5:2:1)

Scheme 5. Deuterium experiments and the role of DMPU.

α-methyl-α-substituted ketones. Like the enolate of spiroketone **2**, the enolate of spiroketone **8** also underwent β-elimination in the absence of DMPU. However, upon applying the identical DMPU conditions, methyl ketone **8** was converted to gem-dimethylketone **11a** in 60% yield. It is notable that a quaternary center was formed in the process resulting in two adjacent quaternary centers in the molecule (Scheme 4). Seeking to expand the scope of electrophiles, we treated the enolate with SelectFluor™ and Davis' oxaziridine[15] to afford racemic α-methyl-α-fluoro ketone **11b** and α-methyl-α-hydroxy spiroketone **11c** in high yield.

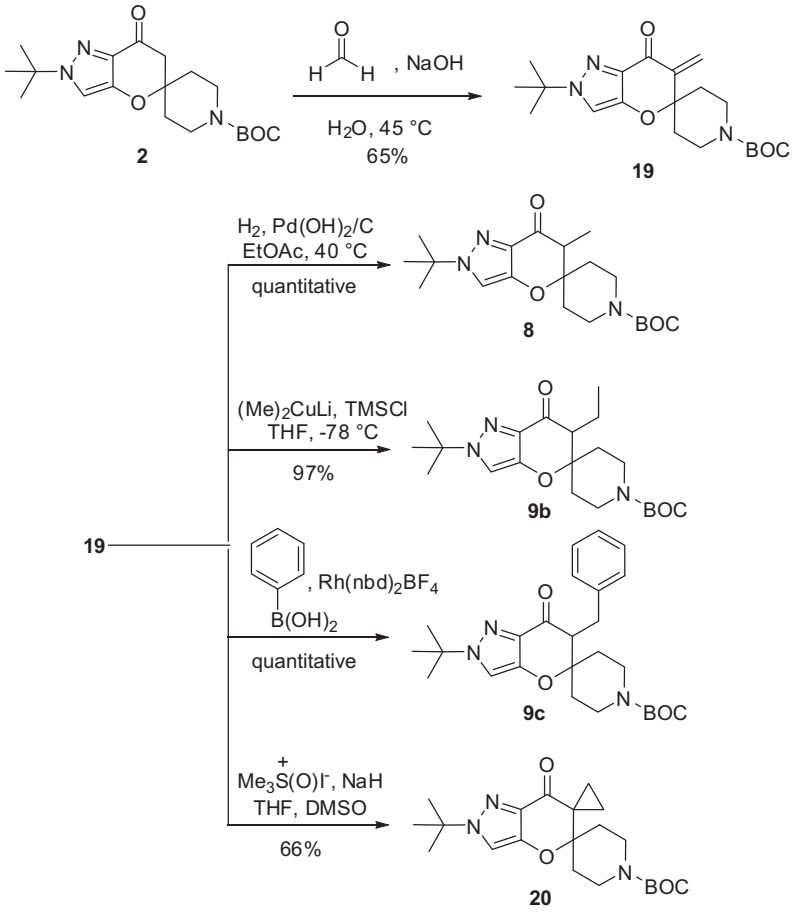
After these gratifying results, there was a desire to examine the reason for DMPU's effectiveness with some of the examples. While DMPU likely created a more reactive enolate, did it affect the deprotonation of the ketone to form the enolate? To probe this question, deuterium experiments were conducted with and without DMPU in the formation of the enolates derived from **2** and **8**. First, the enolate of **2** was generated with LiHMDS at −70 °C, and then quenched with acetic acid-d_4 to give 88% deuterium incorporation based on ^1H NMR (Scheme 5). In the presence of DMPU, deuterium incorporation increased to greater than 95%. In both instances, the enolate of **2** did not undergo β-elimination at −70 °C since the only products observed were α-D and α-H. Hence, it is logical to conclude that β-elimination occurred upon warming the enolate and that DMPU did not play a dominant role in the enolate formation. Since the desired α-alkylated products were isolated using methyl iodide and allyl iodide, DMPU did enhance the reactivity of the enolate. The identical deuterium experiments were then conducted with the enolate derived from the more



Scheme 6. Aldol approach.

sterically hindered α-methylketone **8** (Scheme 5). Interestingly, formation of the enolate from this substrate was greatly affected by DMPU's presence. Without DMPU, deuterium incorporation was only 17%; however, with DMPU, deuterium incorporation more than tripled to 55%. Once again, only α-D and α-H products were observed by ^1H NMR, so the enolate remained stable at −70 °C. Since alkylation products were only seen in the presence of the additive, DMPU also increased the enolate reactivity. So, in the case of the enolate of **8**, DMPU played a dual purpose: enhancement of enolate formation and enolate reactivity.

Although some success was achieved in the direct alkylation approach to make α-substituted ketones, we required a more



Scheme 7. Derivatives using α,β-unsaturated ketone **19**.

diverse set of derivatives to explore SAR, so our attention then turned to an aldol condensation. After surveying various aldol conditions, we were pleased to discover that treatment of the dicyclohexylboron enolate of ketone **2**, generated using dicyclohexylboron chloride,[16] with acetaldehyde afforded aldol product **14** in 56% yield (Scheme 6). The alcohol was then converted to the mesylate and treatment of the mesylate with DBU delivered α,β-unsaturated ketone **16** in quantitative yield. Finally, hydrogenation using Pearlman's catalyst gave the previously elusive α-ethylketone in 56% yield over four steps. Extension of this methodology proved difficult. With propionaldehyde, the desired alcohol was isolated in only 21% yield. The more sterically demanding isobutyraldehyde, benzaldehyde, and 2-phenylacetaldehyde gave no desired products.

We reasoned that the scope of α-functionalization was limited by steric hinderance from the adjacent quaternary center. A two-step approach was thus considered to introduce a wider range of alkyl groups utilizing α,β-unsaturated ketone **19**. Despite the limitations of the aldol approach, we discovered after some experimentation that treatment of ketone **2** with formaldehyde in the presence of sodium hydroxide gave an intermediate aldol product which readily dehydrated to α,β-unsaturated ketone **19** in 65% yield.[17] With this versatile intermediate in hand, we envisaged a scenario where a diverse set of derivatives were accessible by taking advantage of this conjugated system (Scheme 7). To this end, α,β-unsaturated ketone **19** was quantitatively hydrogenated in the presence of Pearlman's catalyst to yield **8**. Also, we were pleased to obtain α-ethyl ketone **9b** in 97% yield with a conjugate addition reaction using dimethylcuprate/TMSCl.[18] Moreover, the previously unattainable α-benzyl ketone **9c** was smoothly formed in quantitative yield using a Rh-catalyzed 1,4-addition with bis-(norbornadiene)rhodium(I) tetrafluoroborate and phenylboronic acid.[19] Finally, cyclopropyl derivative **20** was afforded in 66% yield via a Corey–Chaykovsky cyclopropanation using trimethylsulfoxonium ylide which was generated with trimethylsulfoxonium iodide and NaH in DMSO.[20]

In conclusion, we accessed a number of α-substituted and α,α-disubstituted spiro[pyrazolopyranpiperidine]ketones using two complementary approaches: enolate alkylations and aldol condensations. Although the enolate alkylations were not a panacea, we demonstrated that the additive DMPU was critical in delivering some of the alkylated products in a direct fashion. Finally, the aldol condensations produced useful intermediates to afford products unattainable with the former route.

Acknowledgments

We are grateful for the NMR support and mass spectroscopy assistance provided by Dennis P. Anderson, Kathleen A. Farley and Jason Ramsay. We would also like to thank David Edmonds, David Piotrowski, and Aaron Smith for their insightful discussions.

Supplementary data

Supplementary data (characterization data for compounds **7**, **8a**, **9a–c**, **10a–c**, **11a–c**, **16**, **19**, and **20** and a detailed experimental procedure for the synthesis of **19**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.03.030.

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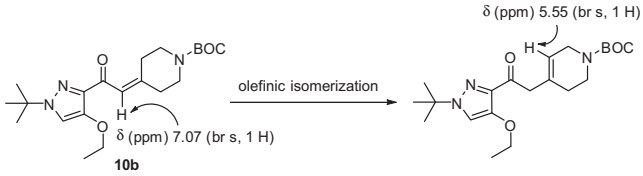
12. Representative procedure using DMPU as an additive: *tert-Butyl-2-tert-butyl-6′methyl-7′-oxo-6′,7′-dihydro-2′H-spiro[piperidine-4,5′-pyrano[3,2-c]pyrazole]-1-carboxylate* (**8**). Ketone **2** (50 mg, 0.14 mmol) in THF (0.5 mL) was cooled to −70 °C, then treated with LiHMDS (1 M in toluene, 0.207 mL, 0.207 mmol) over 10 min. The resulting yellow solution was stirred at −70 °C for 30 min, then DMPU (0.1 mL) was added and stirring continued at this temperature for an additional 10 min. Methyl iodide (0.043 mL, 0.690 mmol) was added, and the reaction mixture was stirred at −70 °C for 10 min, then allowed to warm to room temperature over 3 h. The reaction mixture was quenched with saturated aqueous sodium bicarbonate (0.5 mL) and partitioned between EtOAc (10 mL) and water (2 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting crude product was purified using medium pressure flash chromatography (silica gel, 12 g) eluting with a gradient of heptanes:EtOAc (90:10 to 60:40) to deliver 34 mg (65%) of α-methylketone **8**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (s, 1H), 3.94–3.81 (m, 2H), 3.16–3.04 (m, 2H), 2.49 (q, J = 7.3 Hz, 1H), 2.06–1.97 (m, 2H), 1.60 (s, 9H), 1.59–1.50 (m, 2H), 1.46 (s, 9H), 1.22 (d, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 190.4, 154.7, 146.3, 133.7, 112.0, 82.9, 79.7, 60.7, 51.1, 39.2, 39.0, 32.6, 30.2, 29.7, 29.6, 28.4, 10.8; IR (thin film, neat) 3152, 3121, 2968, 2924, 2854, 1690, 1574, 1421, 1366, 1240, 1152 cm^{-1}; LRMS m/z 378.3 (M+1). HRMS (ESI) 378.2395 [$C_{20}H_{32}N_3O_4$ (M+1) requires 378.2387].
13. 1 M LiHMDS in tetrahydrofuran or toluene was purchased from Sigma–Aldrich.
14. It was serendipitously determined that the α,β-unsaturated ketone products **10a–c** readily isomerized to the endo-olefins upon sitting in $CDCl_3$ for several hours. For a related β-elimination see Bagley, S. W.; Southers, J. A.; Cabral, S.; Rose, C. R.; Bernhardson, D. J.; Edmonds, D. J.; Polivkova, J.; Yang, X.; Kung, D. W.; Griffith, D. A.; Bader, S. J. *J. Org. Chem.* **2012**, *77*, 1497–1506.



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