Tetrahedron Letters 53 (2012) 5467–5470

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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

1,4-Addition of an aryllithium reagent to diethyl ketomalonate. Scalable synthesis of ethyl 1-(hydroxymethyl)-1,3-dihydroisobenzofuran-1-carboxylate

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ARTICLE INFO

Article history:
Received 23 November 2011
Revised 9 May 2012
Accepted 10 May 2012
Available online 17 May 2012

Keywords:
Directed *ortho* metalation
1,4-Addition
Annulation
Mono-reduction
Diethyl ketomalonate

ABSTRACT

While optimizing the synthesis of pharmaceutical building block **3** [ethyl 1-(hydroxymethyl)-1,3-dihydroisobenzofuran-1-carboxylate], we encountered an unusual addition of an aryllithium reagent to the ketone oxygen atom of diethyl ketomalonate. Compound **3** was ultimately prepared on a large scale by a two-step sequence involving (1) annulation of a functionalized Grignard reagent with diethyl ketomalonate and (2) selective mono-reduction of a geminal diester using lithium tri-*tert*-butoxyaluminum hydride.

Introduction

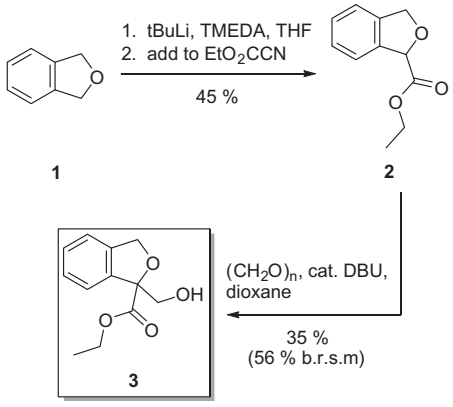
Drug discovery programs depend on the rapid synthesis of experimental medicines. To this end, research organizations maintain stores of small, multi-functional molecules that can be readily incorporated or transformed into novel structures of pharmaceutical interest. Naturally, robust synthetic procedures to access these building-block molecules are critical, as they allow rapid progression from milligram to multi-gram preparations.

Historically, organometallic methods have been limited due to incompatibility with pharmaceutically desirable polar functionality,[1] but recent developments have led to increased versatility. For instance, the use of in situ protecting groups[2] and, significantly, the development of a myriad of functionalized Grignard[3] and organozinc[4] reagents have produced highly attractive, scalable methods.

In the course of our medicinal chemical research program, we desired a preparative method for the chiral, conformationally restricted alcohol intermediate **3** to support advanced studies. The following account details our efforts culminating in a scalable synthetic route, as well as the observation of an unusual reaction defying the expected reactivity pattern of a ketone.

Results and discussion

Our milligram-scale synthesis of alcohol **3** is shown in Scheme 1. We selected phthalan (**1**) as our starting point, reasoning that use of a pre-constructed ring system would minimize the length of the synthetic route. Elaboration to alcohol **3** relied on the reactivity of a benzylic methylene group through iterative deprotonation and treatment with electrophilic reagents.[5,6] Whereas CO_2 was the only precedented electrophile giving a product in the desired (carboxylic acid) oxidation state, we were able to access the ethyl ester directly in higher yield via inverse addition to ethyl cyanoformate. Theoretically, addition of phthalan anion to a solution of excess electrophile should suppress subsequent reaction of the similarly electrophilic product. We found compound **2** to be sufficiently acidic to allow hydroxymethylation simply using paraformaldehyde



Scheme 1. Milligram-scale synthesis of pharmaceutical building block **3**.

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http://dx.doi.org/10.1016/j.tetlet.2012.05.052

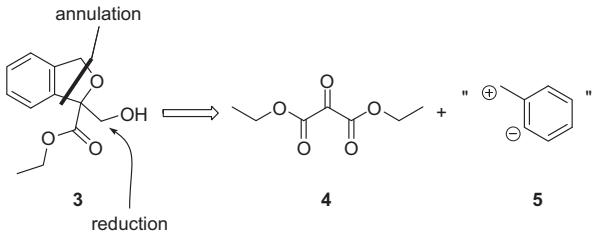


Figure 1. Annulation approach to compound **3**.

in the presence of a catalytic amount of DBU. Use of paraformaldehyde (vs gaseous or aqueous formaldehyde) provided a suitable balance between the need for anhydrous conditions and ease of handling. These conditions proved to be superior to traditional methods involving stoichiometric enolates,[7] which we found to be highly sensitive to both time and temperature.

Whereas this synthesis was succinct, and alcohol **3** was obtained in reasonable yield, two safety considerations precluded its use on larger scale: (1) *tert*-butyllithium solution is pyrophoric and (2) cyanide, a byproduct of addition to ethyl cyanoformate, is highly acutely toxic. Furthermore, chromatographic purification of ester **2** was difficult, and we observed it to undergo slow air oxidation.

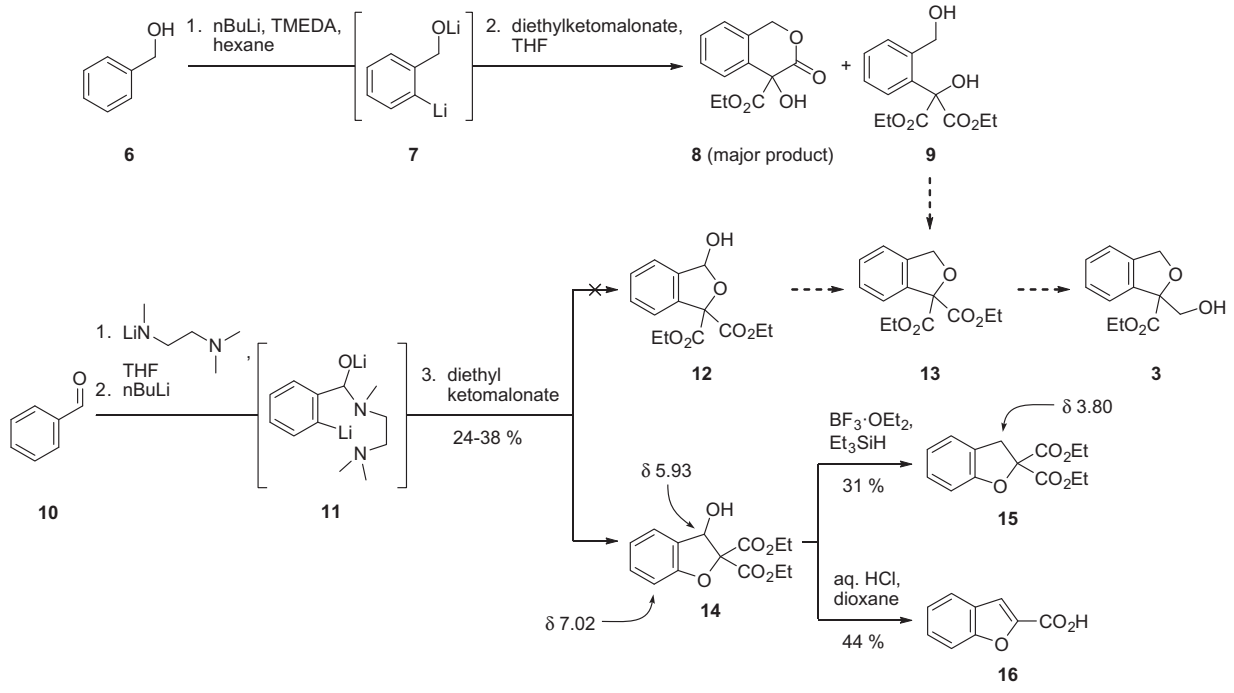
Changing strategies, we anticipated that the 1,3-dihydro-isobenzofuran ring system could be constructed via annulation of an appropriate toluene zwitterion synthon[8] (**5**) with diethyl ketomalonate (**4**) (Fig. 1). Inspired by a report from Ayers,[9] we expected that the resulting geminal diester could be selectively mono-reduced to install the desired β-hydroxy ester.

In our first attempt to reduce this strategy to practice, directed *ortho* lithiation of benzyl alcohol (**6**) was accomplished using *n*BuLi/TMEDA (Scheme 2).[10] Treatment of the resulting carbanion (**7**) with diethyl ketomalonate afforded predominately the undesired lactone **8** along with the desired diol **9**. Although we hypothesized that compound **9** could be converted into compound **3** in three steps (selective tosylation of the primary alcohol, intramolecular nucleophilic displacement, and selective mono-reduction of the geminal diester), we opted rather to explore methods that could circumvent formation of the lactone side product.

We reasoned that a suitable annulation precursor could be derived from benzaldehyde (**10**) by in situ protection using lithiated *N*,*N*,*N*′-trimethylethylenediamine[2a] and subsequent directed *ortho* lithiation. After treatment of this carbanion (**11**) with diethyl ketomalonate and an acidic workup, we isolated a product nearly consistent with structure **12** in terms of ^{1}H NMR and mass spectra. However, we were surprised to observe UV λ_{max} = 276 nm (MeCN/H_2O) for this compound having only an unconjugated benzene ring. Reduction of this intermediate using triethylsilane under the action of boron trifluoride[11] afforded a compound clearly inconsistent with structure **13** by ^{1}H NMR spectroscopy. Rather, the analytical data were consistent with the isomer **15**. *Apparently, 1,4-addition of the aryllithium reagent **11** to diethyl ketomalonate and subsequent intramolecular aldol reaction occurred, completely reversing the traditional reactivity of diethyl ketomalonate.* Instead of hemiacetal **12**, we obtained the similarly-behaved vinylogous hemiacetal **14**.[12]

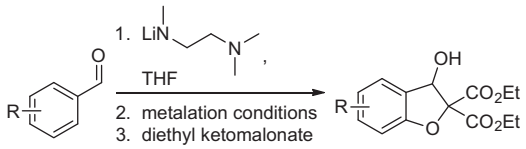
To further prove the structure of compound **14**, we treated it with hot aq HCl in dioxane. Ester saponification and decarboxylative elimination of the resulting β-hydroxy carboxylic acid afforded benzofuran-2-carboxylic acid (**16**), which was spectroscopically identical to an authentic sample.

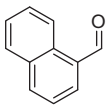
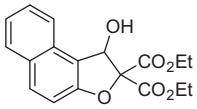
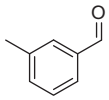
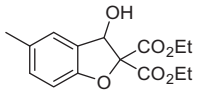
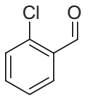
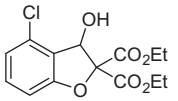
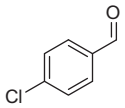
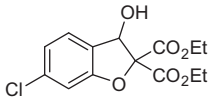
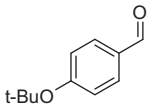
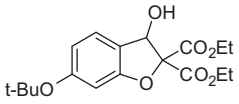
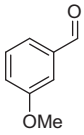
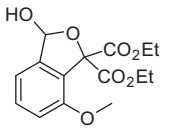
The unexpected reactivity of aryllithium reagent **11** toward diethyl ketomalonate can be rationalized in these terms: Whereas diethyl ketomalonate does not typically show nucleophilic susceptibility on the oxygen atom of its central carbonyl (1,2-addition is usually favored),[13,14] 1,4-addition is thermodynamically feasible when other factors intervene.[15,16] We postulate that in this case, the transition state leading to compound **12** or **14** is sterically encumbered due to the combined presence of the diamine directing group, the neighboring lithium alkoxide moiety, and coordinated solvent molecules. Kinetically, this would favor addition to the ketone oxygen atom, which is significantly more exposed than



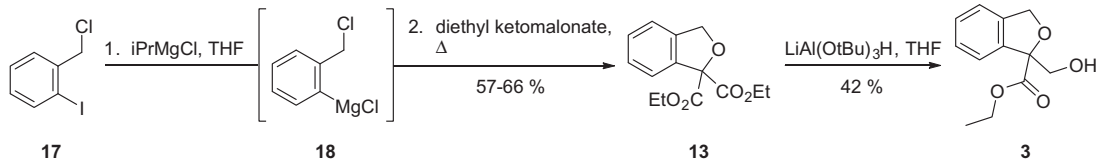
Scheme 2. Unexpected 1,4-addition of aryllithium reagent **11** to diethyl ketomalonate observed during our initial attempts to access compound **3** via an annulation.

Table 1
Reactivity of selected metalated benzaldehydes toward diethyl ketomalonate



Entry	Bezaldehyde	Metalation conditions	Product	Yield[a]/%
1		*n*BuLi (3 equiv), 24 h, −20 °C[2a]		29[c]
2		*n*BuLi (3 equiv), 48 h, −20 °C[2a]		33[b]
3		*n*BuLi (3 equiv), 2.5 h, −20 °C[2a]		11
4		*n*BuLi (3 equiv), 2.8 h, −20 °C[2a]		22
5		*n*BuLi (3 equiv), 24 h, −20 °C[2a]		53[b]
6		PhLi (3 equiv), 7 h, rt[19]		14[c]

[a] Refers to isolated yields. As noted, some products contained small amounts of impurities derived from diethyl ketomalonate and not containing aromatic rings.
[b] Product isolated in ca. 90% purity.
[c] Product isolated in ca. 85% purity.



Scheme 3. Scalable synthesis of compound **3**.

the fully-substituted carbon atom.[17] We also note precedence for the 1,4-addition of organomagnesium, -aluminum, and -zinc reagents to select iminomalonate diesters.[18]

To explore the generality of this result, we applied these conditions to a series of substituted benzaldehydes (Table 1). Accordingly, we found the reaction to tolerate simple substitution at any position (entries 2–5), as well as 2,3-ring fusion (entry 1). A particularly high yield in the reaction of 4-*tert*-butoxybenzaldehyde and lower yields in the case of 2- and 4-chlorobenzaldehyde suggest that electron donating substituents facilitate the reaction (entries 3–5). Interestingly, substrates bearing an *ortho* directing group in the 3-position either failed to produce product (3-fluorobenzaldehyde[20]) or afforded the initially expected 1,2-addition product in low yield (entry 6).

Still having not succeeded in our original goal, we focused our efforts on a transformation of the functionalized Grignard reagent **18**.[21] Using diethyl ketomalonate as the electrophile, this strategy quickly yielded positive results in the laboratory. Treatment of 2-iodobenzyl chloride (**17**) with *i*PrMgCl at −5 °C afforded the reagent **18**, which reacted smoothly with diethyl ketomalonate at temperatures below −50 °C. Finally, overnight heating of the reaction mixture induced cyclization, reliably affording compound **13** in acceptable yield (Scheme 3).

Reduction of compound **13** according to published procedure[9] afforded a surprisingly low yield of alcohol **3**, due to (1) incomplete conversion of compound **13** and (2) formation of significant quantities of compound **2** via retro-Claisen or retro-aldol side reactions. Optimization of these conditions (equiv of reducing agent, temperature, and time) led to a modified procedure whereby compound **13** is treated with only 2 equiv of lithium tri-*tert*-butoxyaluminum hydride for a short period at reflux. Reduction according to this procedure afforded compound **3** in 42% yield (Scheme 3).

Conclusion

We have developed a scalable synthesis of the pharmaceutical building block **3** [ethyl 1-(hydroxymethyl)-1,3-dihydroisobenzofuran-1-carboxylate] via annulation of a functionalized Grignard reagent with diethyl ketomalonate and subsequent selective mono-reduction of the intermediate geminal diester **13**. In the process, we encountered an unusual electrophilic oxygenation of protected and *ortho*-lithiated benzaldehydes. In the future, this reaction might provide orthogonal access to 2,2-disubstituted dihydrobenzofurans[22] and 2-carboxybenzofurans.[23] Significantly, it might also lead to a method for electrophilic oxygenation, currently a limited but important transformation.[24]

Acknowledgments

We thank Dr. Yong Tao for helpful discussions in the prosecution of this project. We are also grateful for help from Drs. David Piotrowski and Vincent Mascitti in the preparation of this manuscript.

Supplementary data

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.tetlet.2012.05.052.

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11. The low yield observed in this reaction was due to formation of oligomer side products, presumably through Friedel–Crafts alkylations.
12. LCMS and/or ^{1}H NMR data for the crude product and all chromatography peaks from the reaction **10** → **14** failed to detect isomeric products.
13. For recent examples of 1,2-additions to diethyl ketomalonate, see: (a) Sunazuka, T.; Handa, M.; Hirose, T.; Matsumaru, T.; Togashi, Y.; Nakamura, K.; Iwai, Y.; Ōmura, S. *Tetrahedron Lett.* **2007**, *48*, 5297–5300; (b) Okrasa, K.; Levy, C.; Wilding, M.; Goodall, M.; Baudendistel, N.; Hauer, B.; Leys, D.; Micklefield, J. *Angew. Chem., Int. Ed. Engl.* **2009**, *48*, 7691–7694; (c) Frings, M.; Atodiresei, I.; Wang, Y.; Runsink, J.; Raabe, G.; Bolm, C. *Chem. Eur. J.* **2010**, *16*, 4577–4587.
14. In our hands, lithium, magnesium, and zinc derivatives of benzene all reacted with diethyl ketomalonate in the typical 1,2-fashion. Furthermore, the adduct of lithiated 2-{[2-(dimethylamino)ethyl]methylamino}ethanol and phenyllithium also underwent 1,2-addition to diethyl ketomalonate.
15. The two electron-withdrawing groups on the central carbonyl of diethyl ketomalonate attenuate the polarity of the carbonyl, rendering its oxygen atom susceptible to nucleophilic attack. Atomic partial charge calculations according to extended Hückel theory (CambridgeSoft Chem 3D Pro 12.0) for the carbonyl in acetone are −0.52 (O) and +0.52 (C). In contrast, values for the central carbonyl in diethyl ketomalonate are −0.39 (O) and +0.35 (C).
16. In quantitative terms, the thermodynamic course of this reaction is a function of the pK_a's of the products obtained directly following addition. Accordingly, the pK_a of the observed 1,4-addition product (malonate diester, p$K_a \approx 12$) is expected to be similar to the pK_a of the desired 1,2-addition product (alcohol, p$K_a \approx 10$). (pK_a estimates were based on predictions by ACD Labs pK_a DB 12.01 software for diethyl 2-phenoxymalonate and diethyl 2-hydroxy-2-phenylmalonate.)
17. Use of 1.5 or 1.1 equiv of *n*BuLi in the metalation step (vs 3 as described in Refs. 2a and 19) resulted in a corresponding decreases in the yield of compound **14**; no effect on the qualitative outcome of the reaction was observed.
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24. Electrophilic oxygenation of organometallic reagents is currently accessed via MoOPH[a] or *N*-sulfonyl oxaziridines,[b] or indirectly via oxidation of a boronate ester.[c] See: (a) Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188–196; (b) Davis, F. A.; Chem, B.-C. *Chem. Rev.* **1992**, *92*, 919–934; (c) Fujikawa, N.; Ohta, T.; Yamaguchi, T.; Fukuda, T.; Ishibashi, F.; Iwao, M. *Tetrahedron* **2006**, *62*, 594–604.