Organic LETTERS

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# A Convenient Allenoate-Based Synthesis of 2-Quinolin-2-yl Malonates and β-Ketoesters

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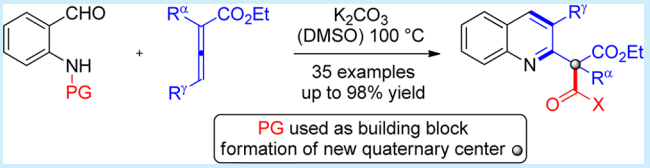
Supporting Information

**ABSTRACT:** *N*-Protected *o*-aminobenzaldehydes smoothly react with α,γ-dialkylallenoates under Brønsted basic conditions to yield 2,3-disubstituted quinolines. This three-step reaction cascade of Michael addition, aldol condensation, and 1,3-N → C rearrangement uses the complete protecting group as a building block in a highly efficient C,C-bond formation of a new all-carbon quaternary center. Carbamate protected substrates (*N*-Boc, *N*-Cbz, *N*-Alloc) thus give 2-quinolin-2-yl-malonates, while amide protected substrates (*N*-Ac, *N*-Bz) afford 2-quinolin-2-yl-β-ketoesters in high yields.




The quinoline ring system is an important heteroaromatic moiety which is present in a wide variety of bioactive and pharmaceutically useful substances,[1] such as the *Cinchona* alkaloids, the cytotoxic alkaloid camptothecin, quinoline antibiotics,[2] or the new antituberculosis drug Bedaquiline.[3] Of the many classical syntheses of quinolines, the Friedländer condensation between an aromatic 2-amino carbonyl and an active methylene compound is still the method of choice for the synthesis of quinolines substituted on the pyridine ring,[4] and improvements of this methodology continue to be developed up to this day.[5] While a number of related quinoline syntheses have been developed by variation of the amino component relatively early on (e.g., the Niementowski and Pfitzinger syntheses),[6] little work has been devoted to variation of the active methylene compound. Today, alkynes represent the only major alternative to enolizable carbonyls.[7]

Following up on our work on α,γ-dialkylallenoate esters as versatile building blocks in the synthesis of heterocycles,[8] we became interested in the possible application of allenoates for quinoline synthesis. Allenes, just like isomeric alkynes, can formally be considered as dehydrated carbonyl compounds.[9] α-Allenic esters exhibit strong electrophilicity on the central β-carbon and are latent nucleophiles at the α- and γ-position. A Friedländer-type quinoline synthesis with *o*-aminobenzaldehyde and allenoates would therefore proceed as an aza-Michael addition−aldol condensation sequence.[10] A related allenoate-based approach to the chromane skeleton with *o*-hydroxybenzaldehyde has in fact already been investigated in detail.[11]

We began our investigations with the reaction of free *o*-aminobenzaldehyde (**1**) and α,γ-dimethylallenoate **2**, but to our disappointment, no reaction could be observed under a variety of conditions.[12] *N*-Boc protected *o*-aminobenzaldehyde (**1a**), on the other hand, smoothly reacted with allenoate **2** under Brønsted basic conditions at rt to give two different quinoline products **3** and **4a** in various proportions (see Scheme 1). The formation of these two products can be rationalized as follows: *N*-Boc protection increases the acidity of the NH-proton sufficiently to allow for deprotonation by $K_2CO_3$ and formation of a highly nucleophilic amide anion. Aza-Michael addition of this anion to allenoate **2** results in intermediate **A**, which selectively cyclizes at the γ-position to give the bicyclic intermediate **B**. Intermediate **B** itself was too unstable to be isolated after aqueous workup and column chromatography. *N*-Boc deprotection and aromatization/tautomerization quickly result in the formation of 2-quinolin-2-yl-propanoate **3**. While the formation of **3** can thus be explained quite intuitively, the formation of malonic ester **4a** was much more surprising at first. Here, the former *N*-Boc protecting group has obviously been transferred to the adjacent nonaromatic position with the concomitant formation of a new all-carbon quaternary center. The *N*-Boc group thus not only activates the aminoaldehyde substrate for nucleophilic attack but also plays a rather unusual role as a building block in C,C-bond formation. This protecting group transfer can be explained easily; however, if intermediate **B** is considered in its mesomeric form **B′**. Aromatization converts the quinolinyl ring into a cationic leaving group, thus activating the Boc-group for nucleophilic attack, and simultaneously provides a stabilized anionic carbon center in direct proximity. Despite the usually unreactive nature of the *N*-Boc group, this special situation favors an efficient 1,3-N → C acyl transfer to product **4a**.[13]

The relative amounts of the two isolable products **3** and **4a** were strongly dependent on the reaction conditions. Heating of the reaction mixture both drastically reduced reaction times and increased the selectivity for the formation of rearranged product **4a**. After a short optimization (see Supporting Information), we identified DMSO as the optimal solvent, freshly ground $K_2CO_3$

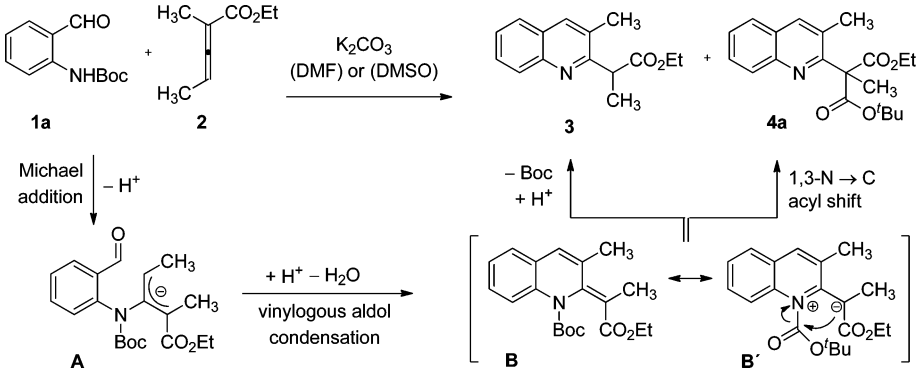
**Received:** August 29, 2014
**Published:** September 12, 2014





dx.doi.org/10.1021/ol502554e | *Org. Lett.* 2014, 16, 5192−5195

**Scheme 1. Overview of the Allenoate-Based Friedländer Quinoline Synthesis**




as a cheap and efficient Brønsted base, and 100 °C as the optimum temperature, which allowed for the isolation of **4a** in 72% yield (Table 1, entry 1).

We next investigated a number of readily available $\alpha,\gamma$-dialkylallenoates **5**–**10** in the reaction with **1a** and were pleased to find that all expected *tert*-butyl ethyl malonates **11a**–**16a** were formed in good yields without any further optimization (Table 1, entries 2–7). $\alpha$-Me, $\alpha$-$^n$Pr, $\alpha$-Bn, $\gamma$-Me, $\gamma$-$^n$Bu, $\gamma$-Bn, branched $\gamma$-$^i$Pr, and even $\gamma$-$^t$Bu substituents on the allenoate were all well tolerated. Branched substituents $^i$Pr and $^t$Bu increased the required reaction times from a few minutes to several hours, but even with the extremely bulky $^t$Bu-allenoate **10**, product **16a** bearing two directly adjacent quaternary centers on the quinoline ring, was still available in 69% yield.

*N*-Cbz and *N*-Alloc protected *o*-aminobenzaldehyde (**1b**, **1c**) reacted in the very same fashion and gave benzyl ethyl malonates **4b**, **11b**–**16b** (Table 1, entries 8–14) as well as allyl ethyl malonates **4c**, **11c**–**16c** (Table 1, entries 15–21) in good to excellent yields. The reactions were very clean, and only occasionally could small amounts of protecting group free quinolines (cf. **3**) be observed as side products. All three widely used carbamate protecting groups *N*-Boc, *N*-Cbz, and *N*-Alloc were thus readily employed as *O*-protected malonate building blocks.

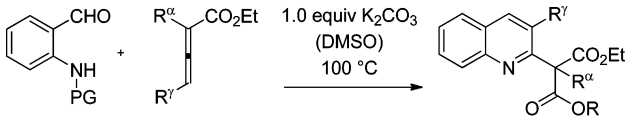
In light of these results, we became interested if other—noncarbamate—*N*-protecting groups were suitable for the 1,3-N → C rearrangement as well, and *N*-acetyl and *N*-benzoyl protected *o*-aminobenzaldehyde (**1d**, **1e**) were chosen as additional substrates (see Table 2). Again, the reactions proceeded very smoothly. Transfer of the *N*-Ac protecting group from **1d** gave rise to aliphatic $\beta$-ketoesters **4d**, **11d**–**16d** (Table 2, entries 1–7), while transfer of the *N*-Bz protecting group from **1e** afforded aromatic $\beta$-ketoesters **4e**, **11e**–**16e** (Table 2, entries 8–14) in high yields. Only the most unreactive $^t$Bu allenoate **10** gave comparably low yields of $\beta$-ketoesters **16d**/**e**. As amides **1d**/**e** are more labile to basic hydrolysis than carbamates **1a**–**c**, prolonged reaction times >1 h lead to *N*-deprotection and deactivation of the substrates.

The reactions were readily scalable under the same conditions to give excellent yields and gram-amounts of products **13b**/**e** (Tables 1 and 2, entry 11). Our newly found allenoate based quinoline synthesis thus offers a convenient alternative to the classical Friedländer methodology, especially for the formation of sterically congested products which are difficult to access with conventional synthetic methods, and often require special, prefunctionalized substrates or multistep syntheses.[14]

The structure of the rearranged products was unambiguously confirmed by X-ray crystal diffraction of crystalline $\beta$-ketoester **15e** (Figure 1).

The now easy availability of quinolinyl malonates and $\beta$-ketoesters prompted us to explore the potential for further functional group manipulations in these products (Figure 2). Benzyl malonates **13b** and **16b** were readily converted to their corresponding quinolinyl-2-propanoates **17** and **18** in excellent yields by hydrogenolysis and spontaneous decarboxylation. Despite this known disposition for decarboxylation,[14c] manip-

**Table 1. Synthesis of 2-Quinolin-2-yl-malonates from Carbamate Protected *o*-Aminobenzaldehydes**[a]



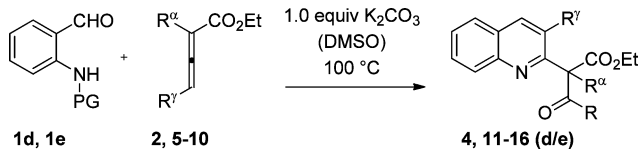

| entry | substrates | | PG | $R^\alpha$ | $R^\gamma$ | R | product | yield [%][b] |
|---|---|---|---|---|---|---|---|---|
| 1 | **1a** | **2** | Boc | Me | Me | $^t$Bu | **4a** | 72 |
| 2 | **1a** | **5** | Boc | $^n$Pr | Me | $^t$Bu | **11a** | 71 |
| 3 | **1a** | **6** | Boc | Bn | Me | $^t$Bu | **12a** | 68 |
| 4 | **1a** | **7** | Boc | Me | $^n$Bu | $^t$Bu | **13a** | 83 |
| 5 | **1a** | **8** | Boc | Me | Bn | $^t$Bu | **14a** | 79 |
| 6 | **1a** | **9** | Boc | Me | $^i$Pr | $^t$Bu | **15a** | 78 |
| 7 | **1a** | **10** | Boc | Me | $^t$Bu | $^t$Bu | **16a** | 69 |
| 8[c] | **1b** | **2** | Cbz | Me | Me | Bn | **4b** | 85 |
| 9 | **1b** | **5** | Cbz | $^n$Pr | Me | Bn | **11b** | 97 |
| 10 | **1b** | **6** | Cbz | Bn | Me | Bn | **12b** | 82 |
| 11 | **1b** | **7** | Cbz | Me | $^n$Bu | Bn | **13b** | 88[d] |
| 12 | **1b** | **8** | Cbz | Me | Bn | Bn | **14b** | 92 |
| 13 | **1b** | **9** | Cbz | Me | $^i$Pr | Bu | **15b** | 60 |
| 14 | **1b** | **10** | Cbz | Me | $^t$Bu | Bn | **16b** | 59 |
| 15 | **1c** | **2** | Alloc | Me | Me | allyl | **4c** | 88 |
| 16 | **1c** | **5** | Alloc | $^n$Pr | Me | allyl | **11c** | 92 |
| 17 | **1c** | **6** | Alloc | Bn | Me | allyl | **12c** | 92 |
| 18 | **1c** | **7** | Alloc | Me | $^n$Bu | allyl | **13c** | 87 |
| 19 | **1c** | **8** | Alloc | Me | Bn | allyl | **14c** | 94 |
| 20 | **1c** | **9** | Alloc | Me | $^i$Pr | allyl | **15c** | 61 |
| 21 | **1c** | **10** | Alloc | Me | $^t$Bu | allyl | **16c** | 68 |

[a]Reactions were carried out on a 1.0 mmol (**1a**) or 0.5 mmol (**1b**/**c**) scale, using 1.25 equiv of allenoate and 1.0 equiv of $K_2CO_3$. [b]Yields of isolated products. [c]Reaction with 0.36 mmol of **1b**. [d]94% (1.97 g) **13b** on a 5.0 mmol scale.



dx.doi.org/10.1021/ol502554e | *Org. Lett.* 2014, 16, 5192–5195

**Table 2. Synthesis of 2-Quinolin-2-yl-β-ketoesters from Acetyl and Benzoyl Protected *o*-Aminobenzaldehydes[a]**




1d, 1e 2, 5-10 4, 11-16 (d/e)

| entry | substrates | | PG | $R^\alpha$ | $R^\gamma$ | R | product | yield [%][b] |
|---|---|---|---|---|---|---|---|---|
| 1 | **1d** | **2** | Ac | Me | Me | Me | **4d** | 88 |
| 2 | **1d** | **5** | Ac | $^n$Pr | Me | Me | **11d** | 91 |
| 3 | **1d** | **6** | Ac | Bn | Me | Me | **12d** | 79 |
| 4 | **1d** | **7** | Ac | Me | $^n$Bu | Me | **13d** | 84 |
| 5 | **1d** | **8** | Ac | Me | Bn | Me | **14d** | 86 |
| 6 | **1d** | **9** | Ac | Me | $^i$Pr | Me | **15d** | 69 |
| 7 | **1d** | **10** | Ac | Me | $^t$Bu | Me | **16d** | 21 |
| 8 | **1e** | **2** | Bz | Me | Me | Ph | **4e** | 96 |
| 9 | **1e** | **5** | Bz | $^n$Pr | Me | Ph | **11e** | 97 |
| 10 | **1e** | **6** | Bz | Bn | Me | Ph | **12e** | 83 |
| 11 | **1e** | **7** | Bz | Me | $^n$Bu | Ph | **13e** | 90[c] |
| 12 | **1e** | **8** | Bz | Me | Bn | Ph | **14e** | 95 |
| 13 | **1e** | **9** | Bz | Me | $^i$Pr | Ph | **15e** | 90 |
| 14 | **1e** | **10** | Bz | Me | $^t$Bu | Ph | **16e** | 21 |

[a]Reactions were carried out on a 0.5 mmol scale, using 1.25 equiv of allenoate and 1.0 equiv of $K_2CO_3$. [b]Yields of isolated products. [c]97% (1.90 g) **13e** on a 5.0 mmol scale.

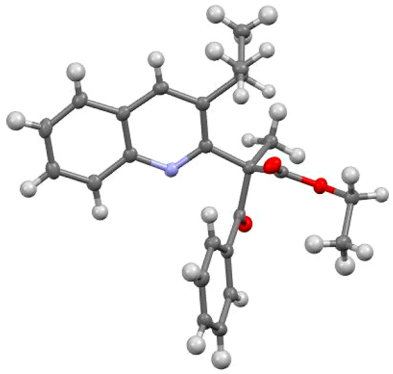


**Figure 1.** X-ray crystal structure of β-ketoester **15e**. Ellipsoids at 50% probability.[15]

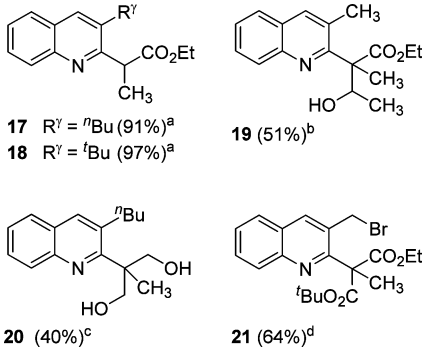



**Figure 2.** Derivatization of quinoline products: [a] From **13b**/**16b** with $H_2$, Pd/C; [b] From **4d** with $NaBH_4$; [c] From **13b** with $LiAlH_4$; [d] From **4a** with NBS, AIBN. All yields are of isolated products and are unoptimized.

ulations of the malonate or β-ketoester moiety which keep the quaternary center intact were also possible. Reduction of β-ketoester **4d** with $NaBH_4$ afforded 51% of diastereomerically pure alcohol **19**, and $LiAlH_4$ reduction of malonate **13b** gave the 1,3-diol **20** in 40% unoptimized yield. Finally, we could show that 3-Me substituted products such as **4a** were easily elaborated for further reactions on the benzylic position by straightforward radical bromination with NBS/AIBN.

In conclusion, we developed a quick and convenient method for the synthesis of densely substituted 2-quinolin-2-yl malonates and β-ketoesters from *N*-protected *o*-aminobenzaldehydes and α,γ-dialkylallenoates. The reaction features a highly effective, aromatization-initiated 1,3-N → C rearrangement of carbamate or amide protecting groups with the formation of a new quaternary carbon center. The reaction succeeds with high yields and under very simple conditions with Boc, Cbz, Alloc, Ac, and Bz protecting groups. Investigations regarding the functional group transfer of other *N*-protecting groups are currently ongoing in our laboratory.

## ■ ASSOCIATED CONTENT

### Supporting Information

Syntheses of starting materials, full synthetic procedures, optimization data, details on X-ray crystal analysis, full analytical data and copies of $^1H$ and $^{13}C$ NMR spectra of quinoline products and derivatives. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

We thank the Fonds der Chemischen Industrie (FCI) for financial support (Liebig-Scholarship to P.S.). Special thanks go to Prof. Dr. D. Enders, Institute of Organic Chemistry, RWTH Aachen University, for the generous provision of laboratory space and chemicals.

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