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A Novel Traceless Solid-Phase Friedländer Synthesis

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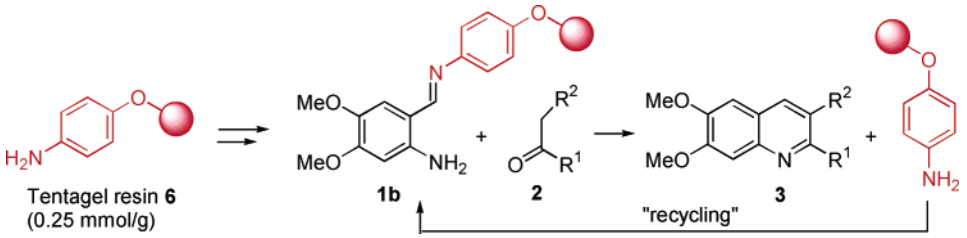
ABSTRACT

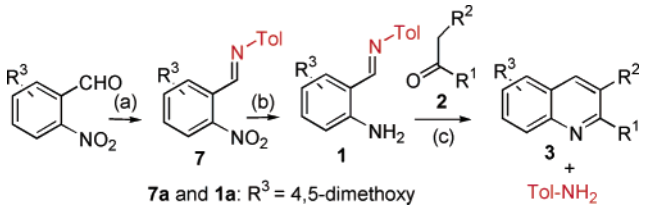


A new solid-phase synthesis of quinolines based on a Friedländer-type reaction between the resin-bound azomethine 1b and ketones 2 is described. This cyclative cleavage approach affords quinolines 3a–f in 50–81% yields. The polymer-bound aniline equivalent is easily recycled and may be reused with comparable performance.

Parallel solid-phase synthesis is widely used to produce libraries of small organic molecules. Of particular interest due to their broad range of biological activities, substituted heterocyclic compounds exhibit a high degree of structural diversity that makes them attractive candidates in the development of new processes for parallel solid-phase synthesis.[1] The Friedländer condensation is still considered, with the Skraup synthesis, as the most popular method, which provides rapid access to quinolines and related azaaromatic compounds.[2] This methodology makes a wide range of heterocycles easily available to chemists. However, despite being a very efficient method, one major limitation of Friedländer syntheses arises from the poor stability of the prerequisite *o*-aminobenzaldehydes, which may undergo self-condensation.[3]

A useful modification developed by Borsche allows these side reactions to be avoided by employing the more stable azomethines **1** of *o*-benzaldehydes.[4] The desired arylimines **1** are conveniently synthesized from the condensation of *p*-toluidine with an *o*-nitrobenzaldehyde followed by sodium sulfide reduction.[5] The resulting "masked" *o*-aminobenzaldehydes **1** react smoothly under basic conditions with a variety of active methylene compounds **2** to afford quinolines **3** in fairly good to excellent yields along with *p*-toluidine (Scheme 1).

Scheme 1. Borsche Modification of the Friedländer Synthesis[a]



[a] Conditions and reagents: (a) *p*-toluidine/EtOH; (b) Na_2S/EtOH/reflux; (c) piperidine or NaOH/EtOH/reflux.

We wish to report in this communication the preparation of resin-bound azomethine **1b** and its application in the development of a traceless solid-phase synthesis of quinoline

(1) Franzén, R. G. *J. Comb. Chem.* **2000**, *2*, 195.

(2) (a) Cheng, C. C.; Yan, S. J. *Organic Reactions*; John Wiley and Sons: New York, 1982; Vol. 28, p 37. (b) Dormer, P. G.; Eng, K. K.; Farr, R. N.; Humphrey, G. R.; McWilliams, J. C.; Reider, P. J.; Sager, J. W.; Volante, R. P. *J. Org. Chem.* **2003**, 467.

(3) (a) Friedländer, P.; Henriques, S. *Chem. Ber.* **1882**, *15*, 2572. (b) McGeachin, S. G. *Can. J. Chem.* **1966**, *44*, 2323. (c) Abert, A.; Yamamoto, H. *J. Chem. Soc B* **1966**, 956.

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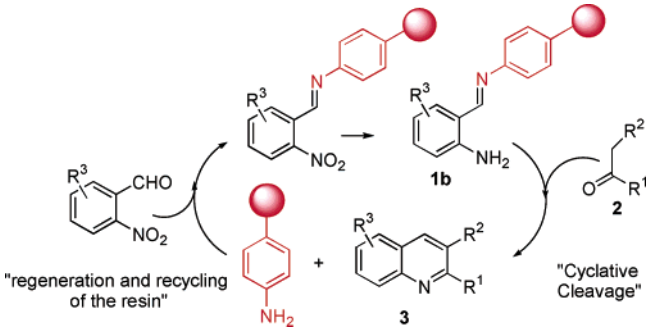
Scheme 2. Solid-Phase Synthesis Approach



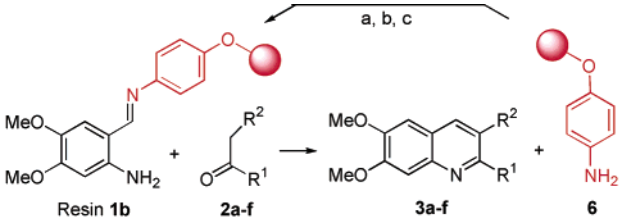
derivatives **3** (Scheme 2). This solid-phase approach combines two highly desirable characteristics in SPS: (a) a cyclative cleavage step[6] releasing the desired quinolines **3** from the polymer support and (b) the regeneration and recycling of the resin. Last, immobilization of azomethine **1** will minimize self-condensation reaction and facilitate the workup procedure (Scheme 2).

We first investigated the preparation of resin-bound azomethine **1** on TentaGel resin. This choice was mainly motivated by the good compatibility of this resin with ethanol, the solvent used in the overall process. Although a wide variety of resin-bound amines are commercially available, a polymer-bound equivalent of aniline was inaccessible until the recent work of Balasubramanian and co-workers.[7]

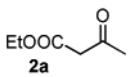
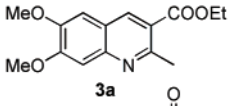
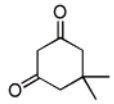
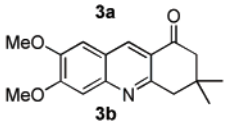
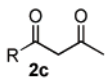
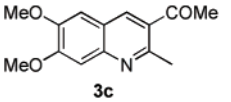
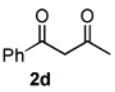
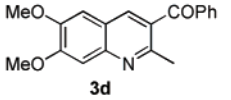
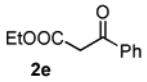
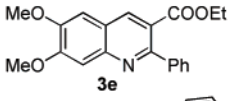
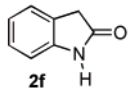
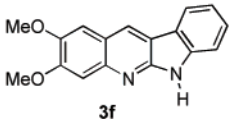
According to this work, the Boc-protected aminophenol **4** [7] was treated with commercial TentaGel-Br resin (loading 0.30 mmol/g) to furnish resin **5**, which was characterized by ^{13}C-gel-phase NMR and FT-IR. The yield was determined by nitrogen microanalysis (0.37% N; loading 0.25 mmol/g).

Subsequent cleavage of the Boc group under classical conditions (TFA/CH_2Cl_2) afforded resin **6** (0.39% N; loading 0.25 mmol/g). The removal of the Boc group was confirmed by the complete disappearance of the Boc carbonyl stretch (1715 cm^{-1}). The supported azomethine **1b** was prepared in two steps from resin **6** by treatment with 3,4-dimethoxy-6-nitrobenzaldehyde in refluxing ethanol, affording resin-bound *o*-nitroimine **7b** (0.76% N; loading 0.25 mmol/g). Subsequent reduction of the nitro group was accomplished in the presence of sodium sulfide in refluxing ethanol to furnish the desired resin-bond "masked" *o*-aminobenzaldehyde **1b** (0.79% N; loading 0.25 mmol/g). The FT-IR spectra of both resins **7b** and **1b** were compared with that of solution-phase models **7a** and **1a**, respectively, showing common bands. In particular, it is informative to note that the peak for nitro stretching at 1286 cm^{-1} of **7a** and **7b** has completely

Table 1. Parallel Solid-Phase Synthesis of Quinolines **3a**−**f**



Reagents and conditions: (a) HCl 2M/THF/water/12h/r.t., (b) EtOH/reflux/3h; (d) $Na_2S.9H_2O$/EtOH/ reflux/20 min.

Entry	Ketones **2**	Product **3**	Yield[a]
1	 **2a**	 **3a**	60% (58)[b]
2	 **2b**	 **3b**	79% (65)[b]
3	 **2c**	 **3c**	58% (60)[b]
4	 **2d**	 **3d**	60% (62)[b]
5	 **2e**	 **3e**	50% (55)[b]
6	 **2f**	 **3f**	81% (75)[b]

[a] Yield calculated from the loading of resin **1**. [b] Yield obtained by conventional solution-phase synthesis.

disappeared in **1a** and **1b** after the reduction step. In contrast, the imine stretch in the range 1630−1567 cm^{-1} present in the IR spectra of **7a**,**b** is still observed in **1a**,**b**, providing evidence for the chemoselective reduction of **7b** into **1b**. The resulting resin **1b** could be stored for several weeks without significant deterioration of chemical properties (Scheme 3).

The synthesis of quinoline derivatives **3a**−**f** was accomplished on a Quest 210 parallel synthesizer by treating resin **1b** with the various ketones **2a**−**f** under the typical Borsche conditions, i.e., in refluxing ethanol in the presence of piperidine. Quinoline derivatives **3a**−**f** were obtained in 50−81% yields (Table 1). In all cases, the Friedländer parallel solid-phase synthesis of quinolines **3a**−**f** led to similar yields when compared to those obtained under homogeneous conditions from azomethine **1a** and ketones **2** (piperidine/ethanol/reflux/12 h). Their purification is made easier by simple filtration of the polymer-bound aniline **6**. It should be noted that flash chromatography is, however, required to eliminate piperidine and ketones **2** having been used in excess to drive the reaction to completion. The regeneration of resin **1b** was also

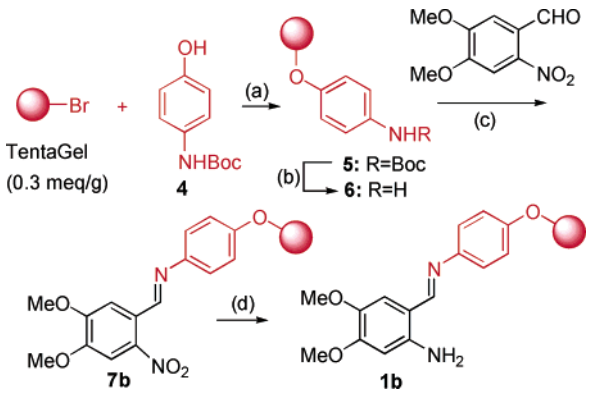
(4) (a) Borsche, W.; Ried, W. *Liebigs Ann. Chem.* **1943**, *554*, 269. (b) Borsche, W.; Barthenheier, J. *Liebigs Ann. Chem.* **1941**, *548*, 50.

(5) Porter, H. K. *Org. React.* **1973**, *20*, 455.

(6) For reviews on cyclative cleavage strategies, see: (a) van Maarseveen, J. H. *Comb. Chem. High Throughput Screening* **1998**, *1*, 185. (b) Tzschucke, C. C.; Market, C.; Bannwarth, W.; Roller, S.; Hebel, A.; Haag, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 3964. (c) Park, K. H.; Kurth, M. J. *Drug Future* **2000**, *25*, 1265. (d) Blaney, P.; Grigg, R.; Sridharan, V. *Chem. Rev.* **2002**, *102*, 2607.

(7) Gordon, K. H.; Balasubramanian S. *Org. Lett.* **2001**, *3*, 53.

Scheme 3. Preparation of the Supported Azomethine 1 on TentaGel Resin[a]



[a] Reagents and conditions: (a) NaH/DMF/12 h; (b) TFA/CH_2Cl_2/12 h; (c) EtOH/reflux/3 h; (d) $Na_2S{\cdot}9H_2O$/EtOH/reflux/20 min.

examined.[8] Resin **6** was then treated as above, i.e., with *o*-nitrobenzaldehyde followed by Na_2S, affording resin **1** (0.79% N; loading 0.25 mmol/g) in nearly quantitative yield. Comparison of the IR spectrum of recycled resin **1b** with that of freshly prepared resin **1b** did not show any significant changes. The resin thus recycled was reused, affording quinolines **3a**−**f** in comparable yields, demonstrating that the activity of the resin **1b** is preserved after the regeneration process.

In summary, the preparation of resin **1b** has been achieved in two steps from the known resin-bound aniline **6**. This polymer-bound equivalent of Borsche's reagent could be successfully used in the preparation of quinoline derivatives **3** in good yields. A simple isolation procedure of the product is made possible thanks to a cyclative cleavage approach. Resin **1b** may be stored for several weeks without loss of activity. Last, regeneration and recycling of the resin offer an additional benefit over a classical homogeneous process. This solid-phase approach, extended to the preparation of various resin-bound *o*-aminobenzaldehydes, should provide a useful tool for the construction of large quinoline and related azaheterocycle libraries.

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Supporting Information Available: Experimental procedures and full characterization for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) During the cyclative cleavage process, the resulting resin **6** may react with ketones **2** still present in solution to give the corresponding imines. To ensure the complete removal of ketones **2a**−**f**, which could have been scavenged, the recovered resin **6** was thus treated under acidic conditions (2 M HCl/THF/water) prior to regenerating resin **1b**.