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Efficient dehydrogenation of 1,2,3,4-tetrahydroquinolines mediated by dialkyl azodicarboxylates

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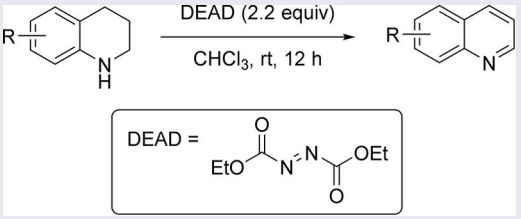
ABSTRACT

Various dialkyl azodicarboxylates were investigated for the dehydrogenation of 1,2,3,4-tetrahydroquinolines to quinolines. The dehydrogenation rates varied according to the electronic and steric nature of the used dialkyl azodicarboxylates. Among solvents screened with diethyl azodicarboxylate, chloroform exhibited superior results to others. A variety of 1,2,3,4-tetrahydroquinolines underwent the present dehydrogenation to produce the corresponding quinolines. Diethyl hydrazodicarboxylate, which is a reduced species of diethyl azodicarboxylate, was easily separated for recycle.

GRAPHICAL ABSTRACT



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Introduction

Dialkyl azodicarboxylates including diethyl azodicarboxylate (DEAD), diisopropyl azodicarboxylate (DIAD), and di-*tert*-butyl azodicarboxylate (DBAD) are of importance in organic synthesis due to their interesting reactivity.[1] The most representative utilization of dialkyl azodicarboxylates, especially DEAD, is Mitsunobu reaction.[2] The Mitsunobu reaction has been widely used in the preparation of chiral alcohol due to clean inversion of the stereogenic center.[3] In addition to Mitsunobu reaction, dialkyl azodicarboxylates were used in electrophilic amination,[4] [4+2] cycloaddition,[5] hydroacylation,[6] alcohol oxidation,[7] amine oxidation,[8] and oxidative coupling of tertiary amines.[9]

Quinolines are common pharmacophores in numerous pharmaceuticals and bioactive compounds.[10] For the synthesis of quinolines, Friedländer reaction is a traditional method using a condensation of 2-amino benzaldehydes with carbonyl derivatives containing α -methylene group.[11] Similarly, various quinolines synthesis using aniline derivatives have been developed by virtue of appropriate coupling partners and catalysts.[12] Recently,

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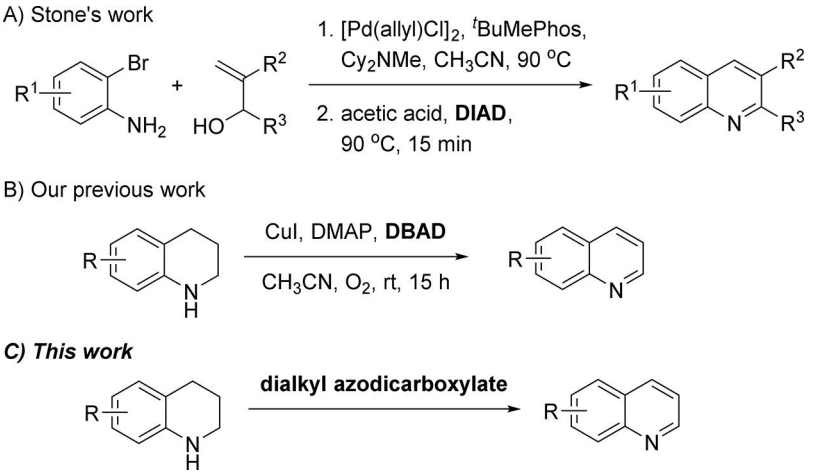


Scheme 1. Previously reported dehydrogenation of 1,2,3,4-tetrahydroquinolines using dialkyl azodicarboxylates.

dehydrogenative approaches from 1,2,3,4-tetrahydroquinoline have received much attention from organic chemists.[13] However, the reported dehydrogenation of 1,2,3,4-tetrahydroquinolines usually required transition metals and harsh conditions.

In 2011, Stone revealed that DIAD increased the yield of quinoline products in the Pd-catalyzed Heck reaction between 2-bromoanilines and allylic alcohols through the DIAD-mediated dehydrogenation of 1,2,3,4-tetrahydroquinolines (Scheme 1A).[14] Recently, our group developed CuI/DBAD-catalyzed aerobic dehydrogenation of 1,2,3,4-tetrahydroquinolines under mild conditions.[15] The developed method consisted of DBAD-mediated dehydrogenation of 1,2,3,4-tetrahydroquinolines and CuI-catalyzed aerobic regeneration of DBAD from di-*tert*-butyl hydrazodicarboxylate (DBAD-H_2) (Scheme 1B). Although it was already reported that dialkyl azodicarboxylates could be used in the dehydrogenation of 1,2,3,4-tetrahydroquinolines, the reaction parameter and the substrate scope for the dehydrogenation of 1,2,3,4-tetrahydroquinolines were not investigated sufficiently. Herein, we describe our efforts and findings for dialkyl azodicarboxylate-mediated dehydrogenation of 1,2,3,4-tetrahydroquinolines (Scheme 1C).

Results and discussion

Initially, we measured reaction rates of the dehydrogenation of 6-methyl-1,2,3,4-tetrahydroquinoline **1a** in $CDCl_3$ at room temperature using aliquot method with various dialkyl azodicarboxylates (Fig. 1). It was observed that bis(2,2,2-trichloroethyl) azodicarboxylate (BTAD), which has electron-withdrawing trichloroethyl groups, showed the fastest dehydrogenation rate. In addition, the significant reaction rate drop with DBAD was observed compare to other dialkyl azodicarboxylates. These observations indicated that electron-deficient as well as less sterically hindered dialkyl azodicarboxylates were required for the successful dehydrogenation of 1,2,3,4-tetrahydroquinolines. We also examined the dehydrogenation of **1a** with other azo compounds such as 1,1′-(azodicarbonyl)dipiperidine (ADDP), *N,N,N′,N′*-tetramethylazodicarboxamide, azobenzene, and ethyl 2-phenylazocarboxylate, however, these azo compounds showed no reactivity. Although BTAD displayed

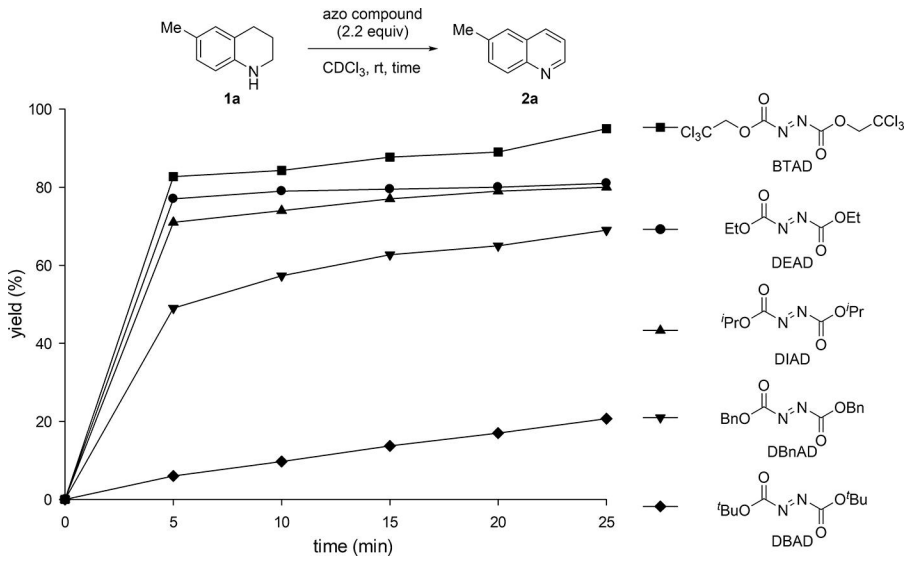


Figure 1. Reaction rates of the dehydrogenation of **1a** with various dialkyl azodicarboxylates.

slightly better performance than DEAD, the lower cost of DEAD relative to BTAD prompted us to proceed with DEAD.

Next, we tried to investigate the effect of solvent on the dehydrogenation of **1a** (Fig. 2) with DEAD. The dehydrogenation of **1a** in $CDCl_3$ showed a superior reaction rate to other deuterated solvents such as CD_3CN, THF-d_8, DMSO-d_6, and toluene-d_8. Gratifyingly, no decrease of reaction rate was observed in the dehydrogenation of **1a**, when we used commercially available DEAD solution in toluene (40 wt%). For safety issue, we decided to use

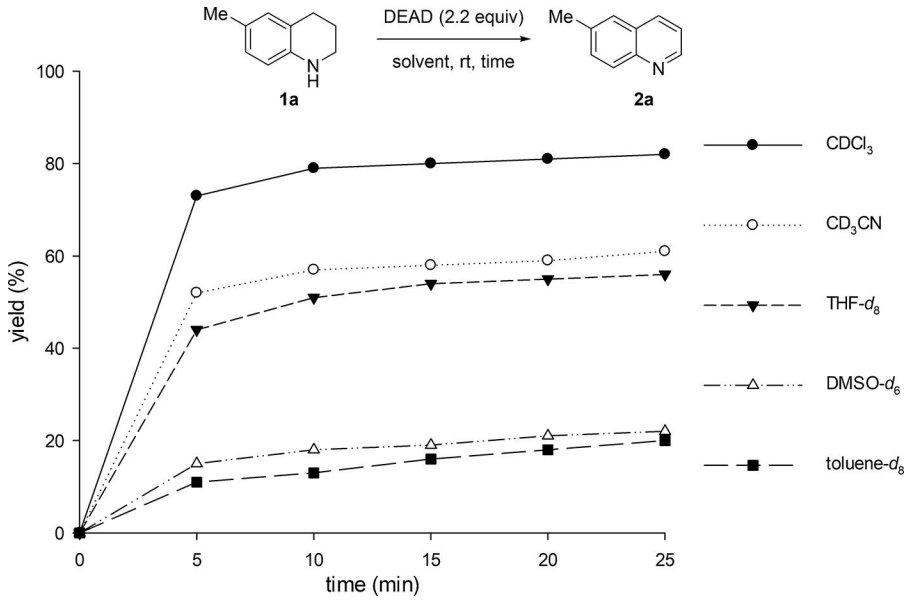
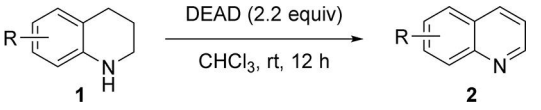


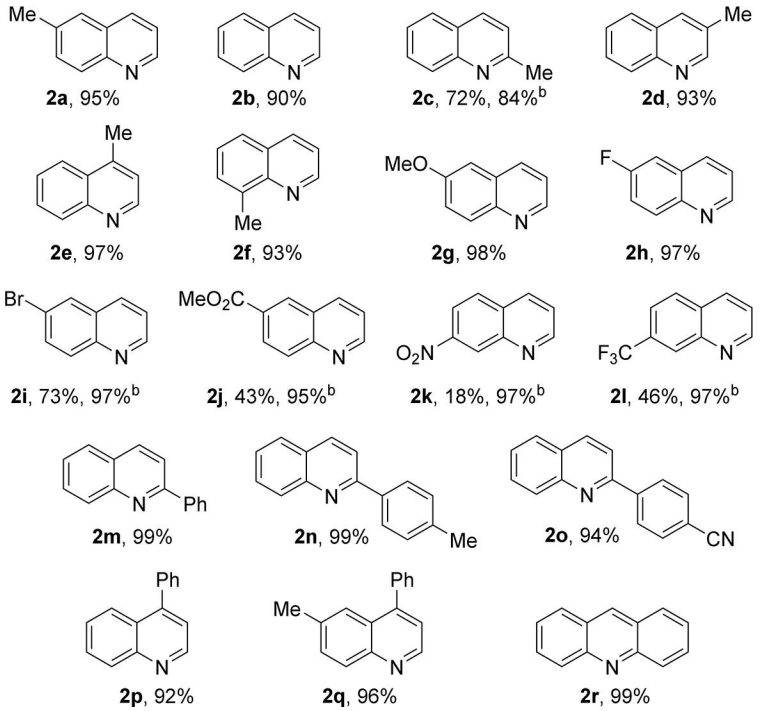
Figure 2. Reaction rates of the dehydrogenation of **1a** in various solvents.

DEAD solution in toluene for further study. Although the dehydrogenation of **1a** in $CHCl_3$ with DEAD solution showed an acceptable result in 3 h, prolonged reaction time (12 h) was required for full conversion of **1a**.

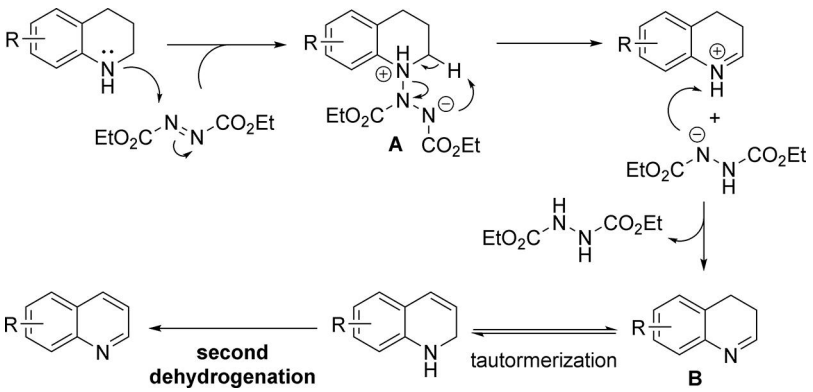
With the optimized conditions in hand (2.2eq DEAD, $CHCl_3$, and 12 h), we investigated the substrate scope of 1,2,3,4-tetrahydroquinolines (Table 1). In general, the developed dehydrogenation protocol produced various quinolines in high to excellent yields. Simple 1,2,3,4-tetrahydroquinolines underwent dehydrogenation to produce quinoline in 90% yield (**2b**). Although a variety of methyl substituted quinolines were efficiently synthesized in high yields from the corresponding tetrahydroquinolines (**2c**–**2f**), the dehydrogenation of 2-methyl 1,2,3,4-tetrahydroquinoline **1c** showed a lower yield in the optimized conditions presumably due to steric effect. When the dehydrogenation of **1c** was performed at reflux, however, we could obtain 2-methyl quinoline **2c** in 84% yield. Several 1,2,3,4-tetrahydroquinolines having other substituents were also tested in the developed protocol. While electron rich 1,2,3,4-tetrahydroquinolines such as 6-methoxy 1,2,3,4-tetrahydroquinoline underwent the present dehydrogenation efficiently (**2g**), the dehydrogenation of 1,2,3,4-tetrahydroquinolines having electron withdrawing substituents gave poor yields (**2i**–**2l**). Similar to the dehydrogenation of **1c**, these substrates required the increase of

Table 1. Substrate scope of DEAD-mediated dehydrogenation of 1,2,3,4-tetrahydroquinolines.[a,b]

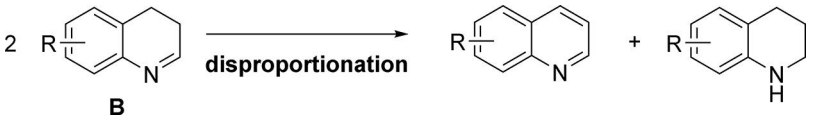




[a]Reaction conditions: 1 (0.5 mmol) and DEAD solution 40 wt% in toluene (2.2 eq, 1.1 mmol, 0.5 mL) in $CHCl_3$ (1.0 mL) at room temperature for 12 h.
[b]At reflux.



Scheme 2. Proposed mechanism.



Scheme 3. Disproportionation of intermediate **B**.

temperature to obtain acceptable yields (**2i**–**2l**).[1] This may be attributed to the facilitation of nucleophilic attack of electron poor 1,2,3,4-tetrahydroquinolines to DEAD for the formation of triazane at higher temperature (*vide infra*). The dehydrogenation of 2-phenyl 1,2,3,4-tetrahydroquinolines, which could be synthesized Suzuki coupling of 2-chloroquinoline with the corresponding phenyl boronic acid followed by reduction with $NaBH_3CN$,[13h] gave 2-phenylquinolines in quantitative product yields, regardless of electronic environments in phenyl groups (**2m**–**2o**). In addition to 2-phenylquinolines, 4-phenylquinolines were produced in high yields by dehydrogenation of 4-phenyl 1,2,3,4-tetrahydroquinolines synthesized from anilines and cinnamaldehyde (**2p** and **2q**).[16] The use of 9,10-dihydroacridine in the present dehydrogenation conditions produced the acridine in quantitative yield (**2r**).

On the basis of previous references and our observations, a possible mechanism for DEAD-mediated dehydrogenation of 1,2,3,4-tetrahydroquinolines is illustrated in Scheme 2. We propose that the present dehydrogenation is initiated by the formation of a triazane intermediate **A** which is generated by a Micheal-type addition of 1,2,3,4-tetrahydroquinolines to DEAD.[8a,17] The generated triazane **A** then undergoes an elimination and a proton transfer to produce an imine intermediate **B** as well as diethyl hydrazodicarboxylate (DEAD-H_2), which is the reduced form of DEAD. The tautomerization of the resulting imine **B** and the following second dehydrogenation give the desired quinolines,[13e] however, the disproportionation of **B** cannot be ruled out at this stage (Scheme 3).[14]

[1]Instead of $CHCl_3$, the use of other solvents such as CH_3CN and dichloroethane (DCE) at 70 °C also gave high product yields. For example, the yields of **2i** were 97% in CH_3CN and 96% in DCE at 70 °C.

The used oxidant, DEAD, was able to be recycled by the simple process.[8b] After the present protocol, DEAD-H_2 was generated as a byproduct. Because DEAD-H_2 has poor solubility in nonpolar organic solvents, we could simply isolate the generated DEAD-H_2 from the reaction mixture through the recrystallization with hexane (87%). The isolated DEAD-H_2 could be transformed to DEAD by the known oxidation process.[18]

Conclusion

In summary, we have developed dehydrogenation of 1,2,3,4-tetrahydroquinolines mediated by dialkyl azodicarboxylate. The measurement of reaction rates revealed that electronic and steric nature of dialkyl azodicarboxylates affected on the developed dehydrogenation. A variety of quinolines could be synthesized by the DEAD-mediated dehydrogenation of the corresponding 1,2,3,4-tetrahydroquinolines. Although several 1,2,3,4-tetrahydroquinolines showed poor yields in the optimized conditions, slightly modified conditions including temperature increase produced quinolines in acceptable yields. The generated DEAD-H_2, which was the byproduct in the present protocol, could be isolated by simple recrystallization after the reaction and used for the recycle of DEAD.

Experimental details

All commercially available compounds and solvents were purchased and used as received, unless otherwise noted. Analytical thin layer chromatography (TLC) was performed on precoated silica gel 60 F254 plates. Visualization on TLC was achieved by the use of UV light (254 nm) and treatment with phosphomolybdic acid stain followed by heating. Flash chromatography was performed using silica gel (particle size 40–63 μm, 230–400 mesh). ^{1}H and ^{13}C NMR spectra were recorded on 400 MHz NMR (400 MHz for ^{1}H, 101 MHz for ^{13}C). Chemical shift values are given in parts per million relative to internal TMS (0.00 ppm for ^{1}H) or $CDCl_3$ (77.06 ppm for ^{13}C). The following abbreviations were used to describe peak splitting patterns when appropriate: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, dd = double of doublet, dt = double of triplet, td = triple of doublet. Coupling constants, *J*, were reported in hertz unit (Hz).

General procedure of the DEAD-mediated dehydrogenation of 1,2,3,4-tetrahydroquinolines

To a 10 mL round bottom flask equipped with a magnetic stir bar, 1,2,3,4-tetrahydroquinoline (0.5 mmol), DEAD solution 40 wt% in toluene (2.2 eq, 1.1 mmol, 0.5 mL), and $CHCl_3$ (1.0 mL) was added. The reaction mixture was stirred at room temperature for 12 h. The mixture was concentrated on rotary evaporator. The residue was purified by column chromatography with EtOAc:hexane (1:5) to give quinolines.

In case of **2f** and **2m**, the product spot was close to the spot of the remained DEAD. To eliminate the remained DEAD, 1 equivalent of PPh_3 was added after the reaction and the reaction mixture was stirred.[19] After 10 min, the reaction mixture was concentrated on rotary evaporator. The residue was purified by column chromatography with $CHCl_3$: hexane (1:1) to give quinolines.

Selected product

6-Methylquinoline (**2a**)[13h]; 95% (68 mg), yellow oil, EtOAc/hexane = 1:5, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (d, J = 4.0 Hz, 1H), 8.14–7.75 (m, 2H), 7.55–7.49 (m, 2H), 7.35–7.27 (m, 1H), 2.50 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.5, 146.8, 136.3, 135.3, 131.7, 129.0, 128.2, 126.5, 121.0, 21.5.

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