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Unexpected reactivity of annulated 3*H*-benzothiazol-2-ylideneamines as an acyl transfer catalyst

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Abstract—Catalytic ability of annulated 3*H*-benzothiazol-2-ylideneamines and 1*H*-pyridin-2-ylideneamines for acylation of alcohols was investigated and 3,4-dihydro-2*H*-9-thia-1,4a-diazafluorene (**2b**) was found to be an extremely effective catalyst, the reaction with which was faster than that with DMAP.

Acylation or esterification of alcohols is an important, basic transformation in organic and bioorganic chemistry. Non-peptide small organic molecules, such as pyridine and imidazole derivatives, are well known as an effective catalyst for the transformation. Recently, an enantioselective variant catalyzed by non-peptide compounds has been of great interest as a versatile means for acylative kinetic resolution and asymmetric desymmetrization.[1] Many of the effective catalysts developed so far have a 4-aminopyridine nucleus as a reactive core, achiral derivatives of which, such as 4-*N*,*N*-dimethylaminopyridine (DMAP), have been used in a wide range of organic reactions.[1] A new aspect has been shown by Birman et al. who introduced a new class of acyl transfer catalysts, 2,3-dihydroimidazo[1,2-*a*]pyridines, **1a** and its derivatives, and elegantly applied their optically active derivatives such as **1c** as a catalyst to kinetic resolution of racemic aryl alcohols (Fig. 1).[2] The results prompted us to investigate the possibility of annulated benzothiazol-2-ylideneamines **2** as a catalyst, expecting that they might have a more nucleophilic nitrogen atom than compounds of the type **1** and could exhibit good catalytic activity. In the course of the study we found that 3,4-dihydro-2*H*-9-thia-1,4a-diazafluorene (**2b**) was an unexpectedly effective catalyst for acyl transfer reaction, the efficiency of which was higher than that of the compounds illustrated in Figure 1, including 4-*N*,*N*-dimethylaminopyridine (DMAP, **4**). Herein we report the results of investigation on catalytic reactivity and the mechanism of annulated benzothiazol-2-ylideneamines **2** and pyridin-2-ylideneamines **1** as a reactive core of the catalyst. During these investigations, quite recently Birman et al. have reported that tetramisole (**3**) and its benzo derivative **2c** were efficient enantioslective acyl transfer catalysts, the latter of which exhibited a high selectivity factor in the 100–350 range in the kinetic resolution of secondary benzylic alcohols.[3]

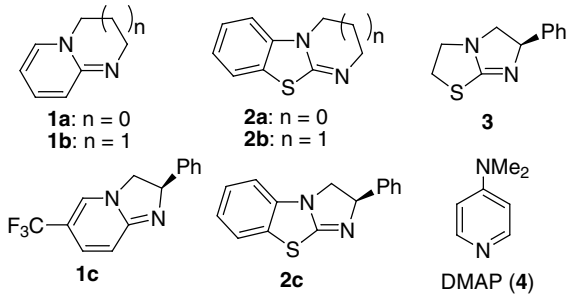

Figure 1. Structures of compounds **1**, **2**, **3**, and **4**.

Annulated benzothiazol-2-ylidenamines **2a** and **2b** were synthesized according to the procedure illustrated in Scheme 1.[4,5] Thus, 2-chlorobenzthiazoles were substituted with 1,2- or 1,3-aminoalcohols followed by chlorination of the resulting alcohols and cyclization under basic conditions. 2,3-Dihydroimidazo[1,2-*a*]pyridine **1a** and **1b** were prepared by the procedure reported with minor modification.[2]

First, we carried out the reaction of 1-phenylethylalcohol with acetic anhydride (Ac_2O) in the presence of **1a**,**b**, **2a**,**b** or DMAP under the identical reaction conditions

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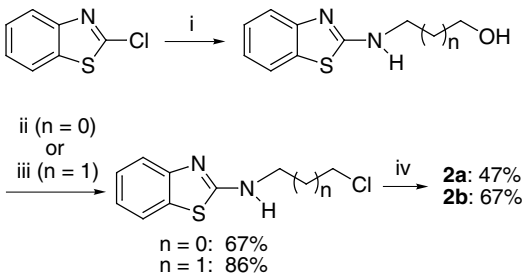
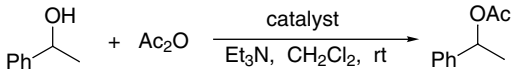


Scheme 1. Synthesis of **2**: (i) $HOCH_2(CH_2)_nCH_2NH_2$, neat, 130 °C; (ii) $SOCl_2$, DMF, reflux; (iii) $SOCl_2$, $CHCl_3$, reflux; (iv) K_2CO_3, $CHCl_3$.

(Eq. 1). Thus, to a solution of 1-phenylethylalcohol (1.0 mmol), Et_3N (1.5 mmol) and the catalyst (5 mol %) in CH_2Cl_2 (5 mL) was added Ac_2O (1.5 mmol) at 22–24 °C. The TLC analysis of the reaction showed the approximate reaction time for consumption of the substrate alcohol to be >40, >40, 15, <0.25, and <0.25 h, respectively, with **1a**,**b**, **2a**,**b**, and DMAP (**4**).



(1)

To confirm the relative efficiency of catalysts, the reaction with **1a**,**b** or **2a** was performed with 1-phenylethylalcohol (1.0 mmol), Ac_2O (1.0 mmol), Et_3N (1.5 mmol), and a catalyst (5 mol %) in 1 mL of CH_2Cl_2, while that with **2a** or DMAP was carried out with 1-phenylethylalcohol (1.0 mmol), Ac_2O (1.0 mmol), Et_3N (1.5 mmol), and a catalyst (1 mol %) in 10 mL of CH_2Cl_2. The time course of the reaction was traced by TLC analysis: thus, images of stained TLC were allowed to be imported as digital data to computer by image-scanning and analyzed by the image processing and analysis software (**NIH *image***)[6] and the amounts of the alcohol and the acetate were quantified to determine the conversion. The results are illustrated in Figure 2. As revealed in Figure 2a, pyridine derivatives **1a**,**b** and dihydroimidazo derivative of benzothiazole **2a** have similar catalytic activity and the reactions with them were much slower than that with DMAP and, surprisingly, a dihydropyrimido derivative of benzothiazole **2b** was found to be an extremely effective catalyst and the activity was higher than that of DMAP. These reactions could be treated as a pseudo-second order kinetics (Fig. 2b).[7] From the time versus 1/(1-x) plots (x = conversion, $0 \leqslant x \leqslant 1$) shown in Figure 2b, TOF_{50} [turnover factor at 50% conversion, h^{-1} (mol of product/(mol of catalyst × h))][8,9] was calculated for each catalyst: 3.04 for **1a**, 3.61 for **1b**, 3.57 for **2a**, 531 for **2b**, and 278 for DMAP. Although a similar trend that the dihydropyrimido derivative was more active than the dihydroimidazo derivative was observed for **1** and **2**, it was noteworthy that the difference between **2a** and **2b** was much larger than that between **1a** and **1b**.

With these results in hand, we next carried out the stoichiometric reaction of catalyst compounds in $CDCl_3$ which were analyzed by 500 MHz ^1H NMR. The reaction shown in Eq. 1 might consist of the following reactions shown in Eqs. 2–4, where the reactions of Eqs. 5 and 6 among catalyst compound, AcOH and Et_3N may be involved. Regarding Eqs. 5 and 6, in all cases, NMR spectra of the 1:1:1 mixture of the catalyst compound, AcOH and Et_3N in $CDCl_3$ showed peaks of a neutral catalyst compound and of an acetic acid salt of triethylamine quantitatively.

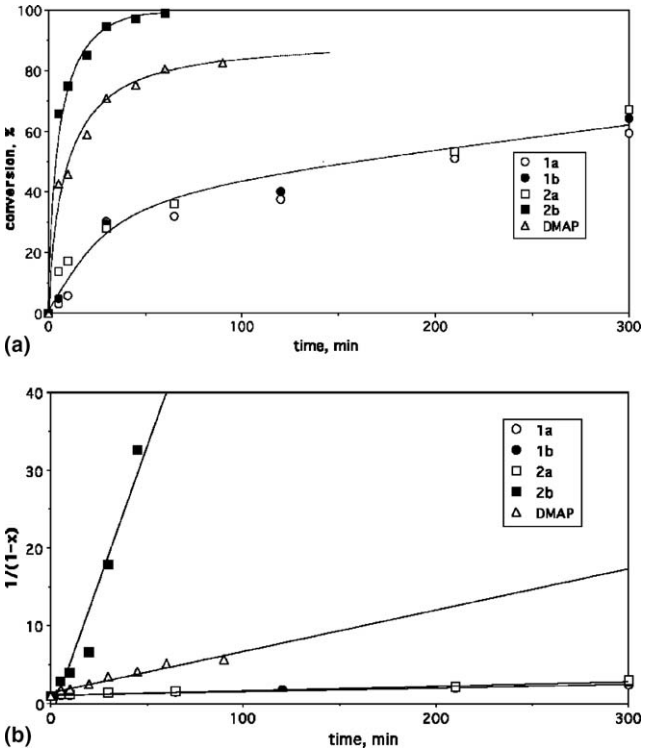


Figure 2. Kinetic study: The reaction was carried out with 5 mol % of **1a**,**b** or **2a** in a 1.0 M solution, or with 1 mol % of **2b** or DMAP in a 0.1 M solution (see text). (a) Time course of conversion, (b) time versus 1/(1 − conversion) plots.

$$\mathrm{Cat.} + \mathrm{Ac_2O} \rightleftharpoons [\mathrm{Cat.–Ac}]^{+}\,^{-}\mathrm{OAc} \quad (2)$$

$$[\mathrm{Cat.–Ac}]^{+}\,^{-}\mathrm{OAc} + \mathrm{ROH} \rightarrow \mathrm{ROAc} + \mathrm{Cat.} + \mathrm{HOAc} \quad (3)$$

$$\mathrm{HOAc} + \mathrm{Et_3N} \rightarrow [\mathrm{Et_3NH}]^{+}\,^{-}\mathrm{OAc} \quad (4)$$

$$\mathrm{Cat.} + \mathrm{HOAc} \rightleftharpoons [\mathrm{Cat.–H}]^{+}\,^{-}\mathrm{OAc} \quad (5)$$

$$[\mathrm{Cat.–H}]^{+}\,^{-}\mathrm{OAc} + \mathrm{Et_3N} \rightleftharpoons \mathrm{Cat.} + [\mathrm{Et_3NH}]^{+}\,^{-}\mathrm{OAc} \quad (6)$$

Next, NMR experiments of the reaction of catalyst compounds and Ac_2O were carried out. The addition of 1 equiv of Ac_2O to DMAP in $CDCl_3$ at room temperature gave no new peak other than DMAP and Ac_2O (data not shown), the results of which indicate that an acylated intermediate $[DMAP–Ac]^{+}$OAc becomes thermodynamically much less stable than DMAP, due to loss of aromaticity of the pyridine ring. Meanwhile, as shown in Figure 3, the mixture of benzothiazole derivatives **2** and 1 equiv of Ac_2O generated a considerable amount of the corresponding acylated compounds $[Cat.–Ac]^{+}$OAc. It can be explained by assuming that the acylated compounds of **2a** and **2b** may be stabilized by aromaticity of the newly formed thiazole structure and resonance effect of the nitrogen cation by the benz-

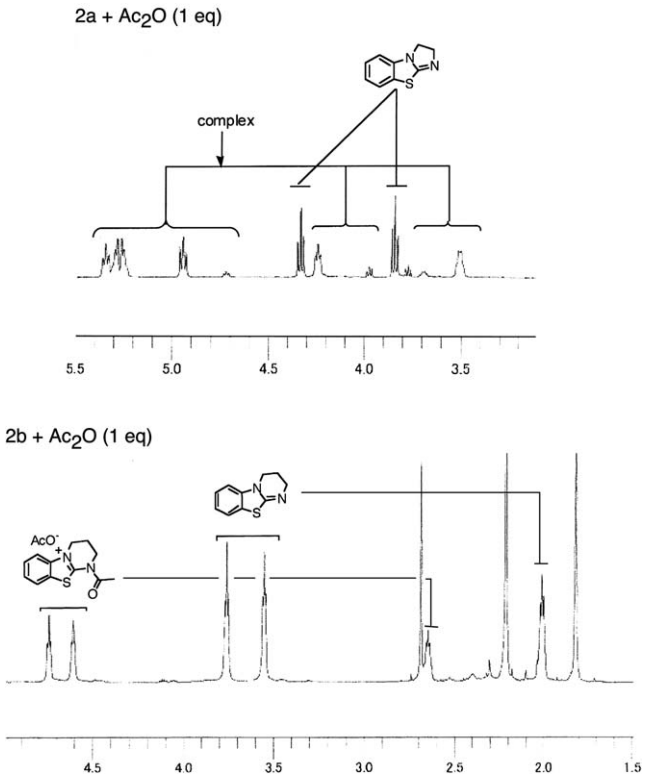


Figure 3. 500 MHz ^{1}H NMR spectra for a 1:1 mixture of **2a** and Ac_2O (the upper spectra) or for a 1:1 mixture of **2b** and Ac_2O (the lower spectra) in $CDCl_3$ at room temperature.

ene ring. Interestingly, although the spectra of a mixture of **2b** and Ac_2O involved one set of peaks corresponding to an acylated intermediate, those of a mixture of **2a** and Ac_2O were much more complicated. The different behaviors thus observed for **2a** and **2b** cannot be explained at this time but may reflect the difference of their relative catalytic activity.

To consider the large difference of catalytic reactivity between **2a** and **2b**, we tried to estimate energy differences among catalyst compounds and their acylated intermediates by calculation using molecular mechanics (MM2).[10] From the results shown in Figure 4, acylation of **2b** seems to be much easier than that of other compounds, and $[DMAP–Ac]^+$ may be expected to be relatively less stable. These assumptions are in good agreement with the results of NMR experiments for Eq. 2 mentioned above. Moreover, it may be considered that pyrimido derivatives **1b** and **2b** could be acylated easier than the corresponding imidazo derivatives **1a** and **2a**, respectively. Acylated **2b** is much more stable than acylated **2a**, presumably due to a larger ring strain of acylated **2a** than that of acylated **2b**. Although the confirmation of details of the mechanism must await further study, it may totally be assumed that easy generation of the acylated intermediate from **2b** due to a large energy gain by delocalizing stabilization of the generated positive charge might mainly affect the catalytic activity of **2b**.

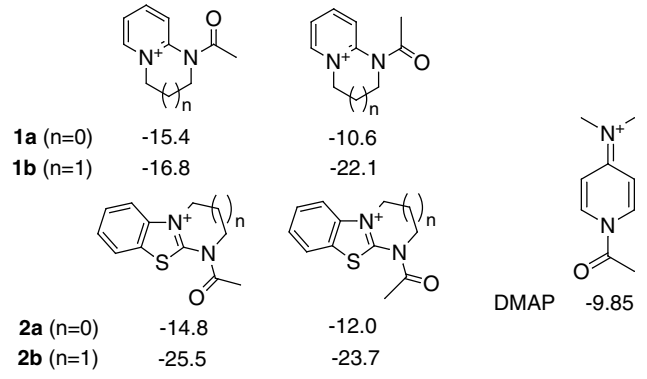


Figure 4. The preliminary results of calculation of energy differences between catalyst compound and the acylated derivative: Cat. to $[Cat.–Ac]^+$ (kcal/mol).

In summary, we have investigated the reactivity of annulated benzothiazol-2-ylidenamines **2** as an acyl transfer catalyst and found that the dihydropyrimido derivative of benzothiazole **2b** exhibited extremely high activity, which might be a good candidate as a reactive core for development of an asymmetric catalyst.

Acknowledgements

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5. Compound **2a**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.26 (d, $J = 7.6$ Hz, 1H), 7.19 (t, $J = 7.5$ Hz, 1H), 6.95 (t, $J = 7.6$ Hz, 1H), 6.67 (d, $J = 7.6$ Hz, 1H), 4.35 (t, $J = 8.9$ Hz, 2H), 3.85 (t, $J = 8.9$ Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.7, 138.2, 127.3, 124.7, 122.8, 122.5, 110.7, 42.6, 40.9. **2b**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27 (d, $J = 7.6$ Hz, 1H), 7.20 (dd, $J = 7.6$, 8.2 Hz, 1H), 7.00 (t, $J = 7.6$ Hz, 1H), 6.80 (d, $J = 8.2$ Hz, 1H), 3.79 (t, $J = 6.2$ Hz, 2H), 3.55 (t, $J = 5.7$ Hz, 2H), 2.01 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.2, 140.0, 126.2, 122.4 (2C), 121.9, 108.1, 44.1, 42.6, 19.3. Compound **1b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.85 (d, $J = 6.9$ Hz, 1H), 6.67 (t, $J = 6.3$ Hz, 1H), 6.04 (d, $J = 9.8$ Hz, 1H), 5.57 (t, $J = 6.9$ Hz, 1H), 3.74 (t, $J = 6.3$ Hz, 2H), 3.28 (t, $J = 6.3$ Hz, 2H), 1.77 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.0, 136.8, 132.9, 122.7, 103.2, 49.5, 43.3, 20.0.
6. Version 1.63 for Macintosh was used. This is available via the internet at http://rsb.info.nih.gov/nih-image/download.html.

7. $d[ROH]/dt = k[ROH][Ac_2O]$. When $[ROH]_0 = [Ac_2O]_0 = a$ and $x =$ conversion ($0 \leqslant x \leqslant 1$), $1/[a(1-x)] = kt + 1/a$. If $k' = ak$ (constant), $1/(1-x) = k't + 1$.
8. 0.50 mmol/[time (h) for 50% conversion][mmol of catalyst].
9. Line-fitting was performed using a graph software Cricket Graph 1.3.2 for Macintosh.
10. The MM2 calculations resulting in the data in Figure 4 were performed using CAChe software (Quantum 4.9 for Macintosh, Fujitsu Ltd.).