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Electrostatically Enhanced Thioureas

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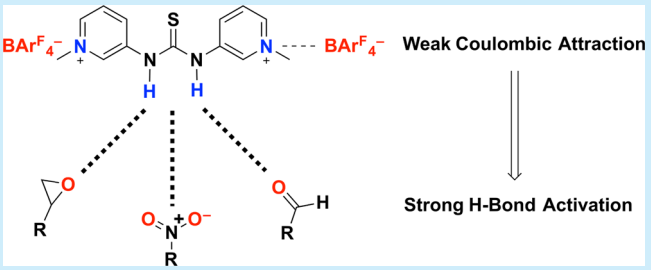
Supporting Information

ABSTRACT: A new class of readily prepared thiourea catalysts with one or more positively charged centers and no new hydrogen-bonding sites are exploited in several bond-forming reactions and are orders of magnitude more reactive than Schreiner's thiourea. These findings provide the basis for a new strategy for activating hydrogen-bond catalysts.



Small molecule metal-free hydrogen-bond catalysis has become an active and vibrant research area over the past two decades.[1] Numerous classes of compounds have been explored including binols,[2] silane diols,[3] squaramides,[1e,4] and $\alpha,\alpha,\alpha,\alpha$-tetraaryl-1,3-dioxolane-4,5-dimethanols (TADDOLs)[5] among others, but no species have received more attention than thioureas.[6] Of these, *N*,*N*′-bis(3,5-bis(trifluoromethyl)-phenyl)thiourea [$(3,5\text{-}(CF_3)_2C_6H_3NH)_2CS$], also known as Schreiner's thiourea,[7] occupies a privileged position because it is an especially effective catalyst leading to relatively rapid transformations. This has been attributed to its enhanced acidity due to the four electron-withdrawing trifluoromethyl groups[8] and weak C−H···S hydrogen bonds that are thought to play a factor in stabilizing the reactive *Z*,*Z*-conformer.[7b,c]

Cationic hydrogen bond donors such as amidinium,[9] ammonium,[10] guanidinium,[11] pyridinium,[12] and quinolinium[13] ions also have been extensively explored.[14] These species correspond to protonated neutral bases and consequently are more acidic than their corresponding conjugate bases. This may account for their enhanced reactivities, but conformational rigidity, changes in the binding site, and the potential use of an additional hydrogen bond are also important contributing effects. A different strategy for increasing the reactivity of neutral hydrogen bond catalysts, especially in nonpolar solvents where organic transformations of this sort are typically carried out, is to incorporate a charged center without introducing a new hydrogen bond site. A recent report by Berkessel et al. exploiting this novel approach to develop Coulombic anion-binding catalysts[15] and our observation that the catalytic ability of a phenol can be enhanced by orders of magnitude by the presence of a charged site[16] suggests that electrostatic enhancement of hydrogen-bond catalysts is a new general design strategy.[17]

To explore this hypothesis, thioureas with one and two *N*-methylpyridinium ion centers were prepared, and their reactivities in several different types of transformations were examined. These new catalysts were compared to *N*,*N*′-diphenylthiourea (**1**) and Schreiner's thiourea (**2**) (Figure 1) and are found to be orders of magnitude more reactive in nonpolar solvents.[18]

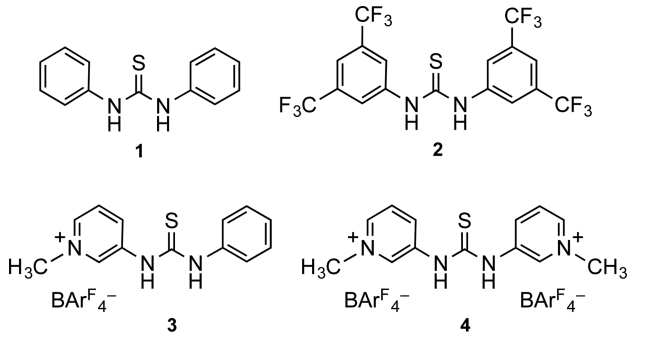


Figure 1. Thiourea catalysts employed in this work.

Mono- and di-*N*-methylpyridinium ions **3** and **4** were readily synthesized starting with commercially available 3-amino-pyridine (**5**) as illustrated in Figure 2. Thiophosgene was used to convert this amine into its isothiocyanate,[19] and this product was subsequently alkylated with methyl iodide to afford the corresponding pyridinium ion **7**. This key intermediate was reacted with aniline to afford the iodide salt of **3** (**3I**).

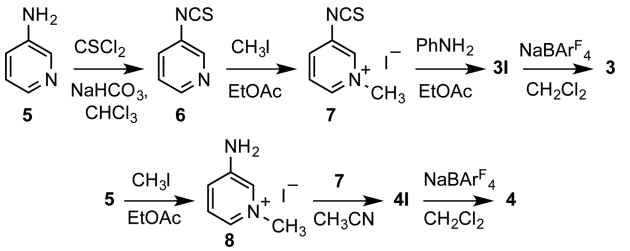


Figure 2. Synthetic routes for thioureas **3** and **4**.

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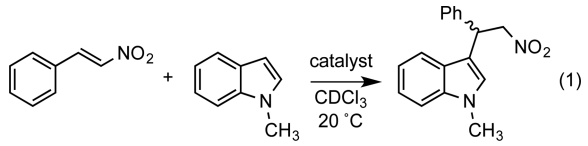
Org. Lett. XXXX, XXX, XXX−XXX

Alternatively, methylation of 3-aminopyridine occurs at the more nucleophilic ring nitrogen atom,[20] and the resulting pyridinium iodide **8** was reacted with **7** to yield the doubly charged thiourea derivative of **4** (**4I**). Both iodide salts have limited solubilities in weakly polar solvents and presumably form deactivating NH···I^- hydrogen bonds so they were converted to their tetrakis(3,5-bis(trifluoromethyl)phenyl)-borate (BAr^F_4) salts **3** and **4**. These metathesis reactions were readily accomplished by stirring **3I** or **4I** with $NaBAr^F_4$ in CH_2Cl_2.

To evaluate the catalytic activity of electrostatically enhanced thioureas **3** and **4**, the Friedel–Crafts alkylation of *trans*-*β*-nitrostyrene with *N*-methylindole was examined in $CDCl_3$ at room temperature (eq 1). This transformation was chosen



(1)

because the reaction rate has been observed to correlate with the acidity of hydrogen bond catalysts, whereas acetic acid does not promote this process.[21,22] Second-order rate constants were determined by monitoring the reaction via ^{1}H NMR spectroscopy, and the data are summarized in Table 1. Diphenylthiourea **1** is a poor catalyst in that it only speeds up the uncatalyzed process by a factor of 1.4, and more than a month is needed for half of the starting material to be converted to product. Schreiner's thiourea is 28 times more effective than **1**, but this transformation is still slow and has a half-life of 29 h. *N*-Methylpyridinium ion containing thioureas **3** and **4** are much more active than **2** and have half-lives of 5 h and 4 min, respectively. An acidic impurity in **3** or **4** acting as the active catalyst was discounted since 1 mol % of *p*-toluenesulfonic acid (*p*-TsOH) did not afford any observable product by ^{1}H NMR over 20 h. These results indicate that the one charged center in **3** is more effective than the four CF_3 groups in **2** by a factor of 7, and that the presence of two cationic sites affords an even more active catalyst that is 400 times more reactive.

Table 1. Kinetic Data for the Room-Temperature Friedel–Crafts Reaction of *trans*-*β*-Nitrostyrene with *N*-Methylindole

entry	cat.	mol %	solvent	k (M^{-1} h^{-1})	$t_{1/2}$ (h)	k_{rel}
1			$CDCl_3$	2.8×10^{-3}	1100	
2	**1**	10	$CDCl_3$	3.9×10^{-3}	820	0.035
3	**2**	10	$CDCl_3$	1.1×10^{-1}	29	1.0
4	**3**	10	$CDCl_3$	7.1×10^{-1}	4.5	6.5
5	**4**	10	$CDCl_3$	45	0.071 (4.3 m)	410
6	**4**	5	$CDCl_3$	11	0.29 (17 m)	
7	**4**	2.5	$CDCl_3$	9.1×10^{-1}	3.5	
8	**4**	1	$CDCl_3$	1.6×10^{-2}	200	
9	**4**	5	$C_6D_5CD_3$	14	0.23 (14 m)	
10	**4**	5	CD_2Cl_2	55	0.058 (3.5 m)	

Catalyst loading was explored for **4** (Table 1, entries 5–8), and as expected the Friedel–Crafts reaction rate increases with the amount of added catalyst. A linear dependence was not observed, but a straight line was obtained from a plot of the second-order rate constants versus the square of the catalyst concentrations (Figure 3). This suggests that the dimer of **4** is the active catalyst in this transformation, which is consistent with a previous report on thiourea catalysts.[23]

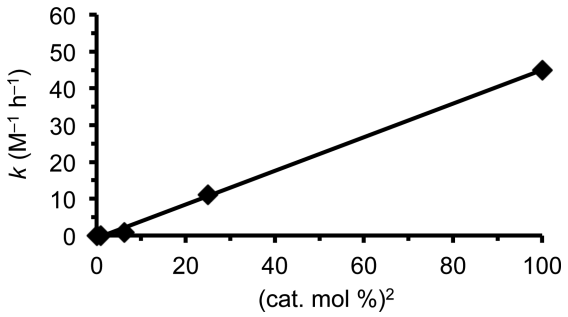


Figure 3. Linear least-squares fit of the second-order Friedel–Crafts rate constants vs (cat. %)^2; $k = 0.46$(cat. %)$^2 - 0.70$, $r^2 = 0.999$; Table 1, entries 5–8.

Carrying out the Friedel–Crafts alkylation in a few different solvents was also examined. Little impact was noted by switching from $CDCl_3$ to toluene-d_8, but a 5-fold increase was observed when the reaction was carried out in CD_2Cl_2. All three of these solvents have dielectric constants of less than 10, but the most polar one of these leads to the fastest transformation. This may be a reflection of the aggregation state of **4** in these solvents. In any case, the doubly charged thiourea salt is soluble in nonpolar media and displays excellent performance characteristics.

We next turned our attention to the Diels–Alder reaction between cyclopentadiene and methyl vinyl ketone (eq 2), in

(2)

part because Schreiner's thiourea previously has been reported to catalyze this transformation.[7b] At room temperature in $CDCl_3$ with 1 mol % of the catalyst, **2** accelerates this cycloaddition by less than a factor of 1.5 relative to the uncatalyzed process (Table 2). In contrast, the charge

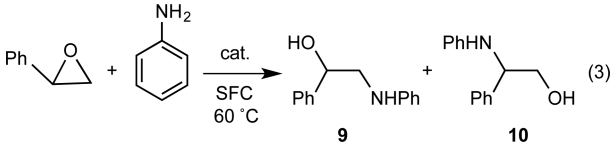
Table 2. Diels–Alder Kinetic Data

entry	cat.	k (M^{-1} h^{-1})	$t_{1/2}$	k_{rel}[a]	*endo*/*exo*
1		0.72	2.2 h		71:29
2	**2**	1.0	1.6 h	1.0	81:19
3	**3**	7.3	13 m	24	88:12
4	**4**	28	3.5 m	97	88:12

[a]Corrected for the rate of the uncatalyzed reaction.

containing thioureas **3** and **4** enhance the background-corrected rates by one and 2 orders of magnitude, respectively. The half-life for the latter transformation is also under 4 min. As for the selectivity, the major product is the *endo* isomer in each instance as expected. Its relative contribution, however, increases from 71% for the uncatalyzed process to 81% with Schreiner's thiourea and 88% when either **3** or **4** is used.

Lastly, the ring-opening aminolysis of styrene oxide with aniline was explored under solvent free conditions (SFC, eq 3).



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Org. Lett. XXXX, XXX, XXX–XXX

Product formation was monitored for each transformation and zero and first-order processes were found to fit the data depending upon which catalyst, if any, was used. Consequently, qualitative results are reported (Table 3), but it is apparent that

Table 3. Catalytic Results for the Solvent Free Aminolysis of Styrene Oxide with Aniline

entry	cat.	mol %	t (h)	% conv	9/10
1			2.33	5.8	38:62
2	**2**	1	2.33	39	35:65
3	**3**	1	2.33	55	13:87
4	**4**	1	0.5	93	10:90
5	**4**	0.1	0.5	53	10:90

3 and **4** are much more effective catalysts than **2**. That is, significantly higher selectivities and greater conversions are observed (e.g., **4** gives a 93% conversion in 0.5 h whereas only 39% of the starting material has reacted in 2.33 h with **2**). The dicharged thiourea was also found to outperform **2** even when 10 times less was used (i.e., 0.1 mol % of **4** led to a 53% conversion in 0.5 h whereas 39% of the reactant went on to product in 2.33 h with 1 mol % of **2**).[24]

Charged substituents are not especially effective in enhancing acidities and lowering pK_a values in polar solvents.[16,25] Based upon the 2.4 and 1.3 pK_a unit acidifying effect of a *m*-CF_3 group on phenol and *N*,*N*′-diphenylthiourea,[8,26] respectively, and the recently measured 5.5 pK_a difference between phenol and 3-hydroxy-*N*-octylpyrinium ion[16] all in dimethyl sulfoxide (DMSO), one can estimate that pK_a(**3**) = 10.4.[27] This value is essentially the same as incorporating two meta trifluoromethyl groups into **1** and consequently **3** is ∼2 pK_a units less acidic than Schreiner's thiourea.[8] In nonpolar solvents, a reversal in their relative acidities undoubtedly takes place. As a result, incorporation of a single positively charged center into a thiourea without adding a new hydrogen bond site was found to be catalytically more effective than the four electron-withdrawing trifluoromethyl groups in Schreiner's thiourea.[28] Addition of a second ionic center presumably enhances the DMSO acidity of **4** so that it is similar to **2** but leads to rate accelerations of $\sim 10^2$–10^3. These results represent a new strategy for activating hydrogen bond catalysts, and a potential means for improving stereoselectivities since lower temperatures typically can be employed when transformations occur more rapidly at room temperature.[29]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03213.

Experimental procedures, NMR spectra, and reaction data (PDF)

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Notes

The authors declare no competing financial interest.

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(27) This value was obtained by solving the following equation: $1.3/2.4 = x/5.5$ and subtracting the result from the acidity of **2** (i.e., 13.4 as given in ref 8).
(28) Given the differences in activity between **3** and **4**, it seems unlikely that their methyl groups are serving as activating hydrogen bond donors in the reactions that were examined. Carbon−hydrogen bond donors acting as catalysts, however, recently were reported in a noteworthy contribution. See: Shirakawa, S.; Liu, S.; Kaneko, S.; Kumatabara, Y.; Fukuda, A.; Omagari, Y.; Maruoka, K. *Angew. Chem., Int. Ed.* **2015**, *54*, 15767.
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