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# SODIUM BOROHYDRIDE–MEDIATED TRANSESTERIFICATION

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***In the presence of sodium borohydride, esters react with alcohols with formation of the corresponding esters. The reaction is sensitive to the solvent, structure of the ester, and is often concurrent with reduction. Thioesters containing an ester group can be selectively cleaved by the reagent. Both esters and thioesters attached to solid support are resistant toward sodium borohydride. The* in situ *prepared sodium tetraalkoxyborate is introduced as an efficient reagent and catalyst for transesterification.***

***Keywords***: Esterification; reduction; selectivity; synthesis; thioesters



## INTRODUCTION

Synthesis of esters by transesterification is of significant interest for organic synthesis[1] and is usually performed in the presence of a wide variety of catalysts.[2] These procedures often require rather harsh conditions and therefore are not applicable to acid- or base-sensitive substrates. Here we report that alcoholic sodium borohydride, touted as unreactive toward esters, may substitute for the alcoholic fragment in esters with a solvent-originated alkoxide group. This reaction has been often overlooked because ethanolic sodium borohydride is a common reagent for selective reduction of polyfunctional compounds with both the ethyl ester and the oxo-groups. Alcoholic solutions of sodium borohydride are neither strongly acidic nor basic, which makes the reagent convenient for transesterification of acid- and base-labile esters.

## RESULTS AND DISCUSSION

The reagent provides practical yields when reacted with methyl esters in ethanol. Thus, methyl benzoate **1** was converted by 0.5 equiv. of sodium borohydride to ethyl benzoate **2** (73%) along with a small amount of benzyl alcohol **3** (11%) when reacted for 24 h at room temperature (Table 1, entry 1; Scheme 1). Progress of the reaction was monitored by NMR (singlet at 4.7 ppm, $CH_2$-group of benzyl alcohol

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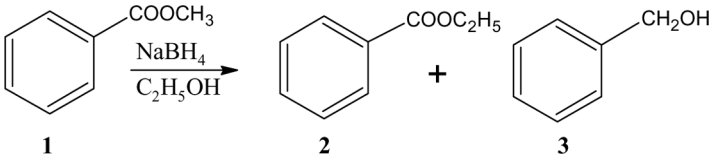
**Table 1.** Reaction of sodium borohydride with esters (reaction time 24 h)

| Entry | Ester | Solvent | Ester/$NaBH_4$ ratio | Starting material (%) | Product of reesterification (%) | Product of reduction (%) |
|---|---|---|---|---|---|---|
| **1** | $PhCO_2Me$, **1** | 95% EtOH | 2:1 | 7 | 73 | 11 |
| **2** | $PhCO_2Me$, **1** | 95% EtOH | 1:1 | 0 | 57 | 29 |
| **3** | $PhCO_2Me$, **1** | abs. EtOH | 2:1 | 23 | 67 | 10 |
| **4** | 4-$H_2NPhCO_2Me$, **4** | 95% EtOH | 2:1 | 90 | 0 | 0 |
| **5** | 2-$H_2NPhCO_2Me$, **5** | 95% EtOH | 2:1 | 64 | 16 | 0 |
| **6** | 4-$O_2NPhCO_2Me$, **7** | 95% EtOH | 2:1 | 0.7 | 74 | 12 |
| **7** | $PhCO_2C_4H_9$-n, **10** | 95% EtOH | 2:1 | 93 | 0 | 0 |
| **8** | $PhCO_2Me$, **1** | *i*-PrOH | 2:1 | 92 | 7 | 1 |
| **9** | $PhCO_2Me$, **1** | DMF | 2:1 | 94 | 0 | 0 |
| **10** | n-$C_7H_{15}CO_2Me$, **12** | abs. EtOH | 2:1 | 10 | 64 | 7 |
| **11** | n-$C_7H_{15}CO_2Me$, **12** | *i*-PrOH | 2:1 | 94 | 0 | 0 |
| **12** | Diester **13** | 95% EtOH | 2:1 | 90 | 0 | 0 |

**3**[5], and quadruplet at 4.35 ppm, $CH_2$-group of ethyl benzoate **2**[6]). Increasing the ratio of sodium borohydride/ester to 1:1 favors reduction and thus lowers the yield of transesterification to 57% (Table 1, entry 2). The reaction is moderately sensitive to the presence of water in the solvent. In 95% ethanol, the reaction product contained only 9–14% of benzoic acid, due to hydrolysis. In absolute ethanol, the reaction was not accompanied with hydrolysis but proceeded more slowly and with less selectivity of transesterification vs. reduction (Table 1, entry 3).

Both reduction and reesterification are completely suppressed by the electron-donating 4-amino group in the benzene ring (Table 1, entry 4), probably because of increased conjugation with the carbonyl group, stabilizing the starting material. The 2-amino isomer **5** is also significantly less reactive than methyl benzoate **1**, but the reaction does take place and produces exclusively the product of transesterification (ethyl 2-aminobenzoate **6**[7]) at 16% yield. In the latter case, the reaction was not completely suppressed, probably because of coordination of the reagent with the amino group, which increases the entropy of the step of nucleophilic attack. Interestingly, both reactivity and selectivity of methyl 4-nitrobenzoate **7** (Table 1, entry 6) are similar to those of the unsubstituted ester **1**. No product of reduction of the nitro-group was detected along with the products of transesterification **8**[8] and ester reduction **9**.[9]

As opposed to methyl esters, butyl benzoate **10** was not reactive (Table 1, entry 7), probably due to the steric hindrance at the alkoxy-leaving group.



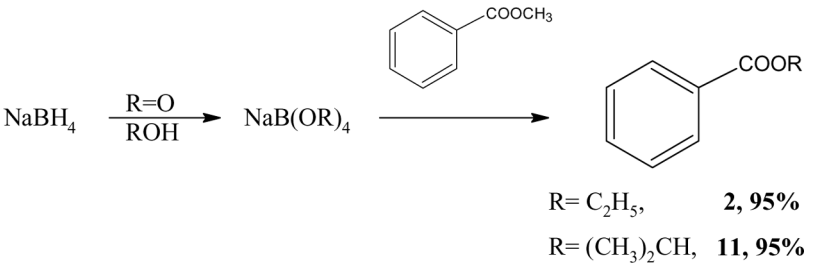

**Scheme 1.** Reaction of methyl benzoate with $NaBH_4$ in ethanol.

Both reduction and borohydride-mediated alcoholysis are strongly affected by the solvent. Thus, methyl benzoate **1** undergoes alcoholysis (producing *iso*-propyl benzoate **11**[8]) and reduction in *iso*-propanol very slowly (Table 1, entry 8). It remains unchanged in dimethylformamide (DMF; Table 1, entry 9). It is not surprising, considering the possibility of the hydride-to-alkoxy-ligand exchange in the borohydride anion as a key step of transesterification. Methanol rapidly decomposes sodium borohydride and thus proved to be an ineffective solvent.

We believe that the ligand exchange mechanism does not create significant concentrations of free alkoxide anions, which makes the reaction significantly different from the known fast (30-min) transesterification by the in situ–generated secondary alkoxides.[9] It is known that tetraalkoxyborohydrides can be prepared by the reaction of alkoxides with trialkoxyboranes, heavily shifted to the product,[10] and the alkoxide exchange rate at boron in alcoholic solutions of alkoxyborohydrides is extremely slow.[11] However, we cannot completely rule out the intermediacy of the alkoxide anions in the observed transesterification. The products of the ligand exchange (full or partial) at boron can potentially act as transesterification reagents. The synthetic potential of one of these complexes (tetraalkoxyborates) was further explored in this study.

We found that in situ–prepared primary and secondary tetraalkoxyborates[12] are efficient reagents for transesterification. Thus, a solution prepared by stirring 57 mg (1.5 mmol) of sodium borohydride, 2 ml of *iso*-propanol, and 0.5 ml (6.8 mmol) of acetone for 30 min at room temperature quantitatively converted 0.1 ml (0.75 mmol) of methyl benzoate **1** to *iso*-propyl benzoate **11** for 24 h (Scheme 2). Substitution of *iso*-propanol with ethanol and acetone with acetaldehyde produced ethyl benzoate **2**.

We found that the in situ–prepared tetraalkoxyborate reacts with methyl benzoate in the absence of the alcohol solvent; however, the reaction rate decreases. Although the transesterification performed in *iso*-propanol produced the ester **11** (95%) in 24 h, replacing the solvent with dimethylformamide (DMF) decreased the conversion to 63%. Besides the influence on the reaction rate, the alcohol solvent seems to rapidly exchange alkoxy- groups with the borate complex under the reaction conditions. We took advantage of this fact to increase the synthetic value of tetraalkoxyborates as transesterification reagents. First, tetra(*iso*-propoxy)borate in ethanol converted methyl benzoate **1** to ethyl benzoate **2** at an excellent yield (95%), which eliminated the need for the aldehyde, corresponding to the alkoxide to be introduced into the ester molecule.




**Scheme 2.** Transesterification with tetraalkoxyborates.

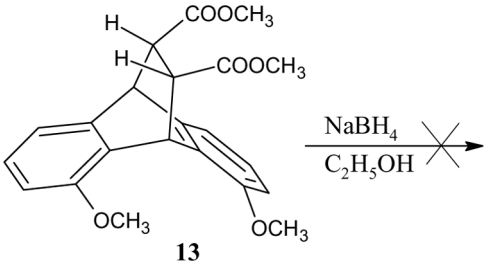
Further, in situ–prepared tetra(*iso*-propoxy)borate from acetone in ethanol still afforded the target ethyl ester **2** at 92%, which simplified the procedure even more. The treatment of methyl benzoate **1** with sodium tetraethoxyborate in *iso*-propanol predominantly led to *iso*-propyl benzoate **11** along with ethyl benzoate **2** and starting methyl benzoate **1** (molar ratio 1:0.15:0.03), which lends additional support to the active participation of the solvent in the reaction course.

Because of the exchange of alkoxy-groups between the borate complex and the solvent, tetraalkoxyborates can be used as mild transesterification catalysts rather than stoichiometric reagents. Thus, reaction of the in situ–prepared sodium tetra(*iso*-propoxy) borate with 11-fold molar excess of methyl benzoate **1** in ethanol led to its 85% conversion to ethyl benzoate **2** in 24 h, which increased up to 93% after another 24 h.

The optimal time for transesterification with tetraalkoxyborates was found to be 24 h, with a half-conversion time of 4 h. Importantly, applicability of this reaction is not limited to methyl esters. Thus, an equimolar mixture of ethyl benzoate **2** and methyl benzoate **1** was completely converted to *iso*-propyl benzoate **11** by the in situ–generated sodium tetra(*iso*-propoxy)borate.

The suggested sodium borohydride–mediated transesterification is also applicable to aliphatic esters, which would have undergone Claisen condensation in the presence of alkoxides. Reactivity and selectivity of methyl octanoate **12** (Table 1, entry 10) was found to be similar to methyl benzoate **1**. The major product of the reaction was ethyl octanoate **13**[13] along with a small amount (7%) of 1-octanol **14**.[14] However, as opposed to methyl benzoate **1**, neither transesterification nor reduction of **12** took place in *iso*-propanol (Table 1, entry 11). Similar to the bulkiness of the alkoxy-group, steric hindrance in the acidic fragment of esters strongly affected their reactivity with sodium borohydride. Thus, both carbomethoxy-groups of the significantly hindered bicyclic diester **13**[15] (Scheme 3) were inert toward sodium borohydride in ethanol (Table 1, entry 12). Possible coordination of the reagent with the ether methoxy-group proved to be insufficient to activate the substitution.

It is known that reduction of aliphatic S-thioesters (S-thioesters of aliphatic acids) by sodium borohydride in ethanol is not accompanied by alcoholysis.[16,17] The hydride ligand at the atom of boron is expected to be "softer" than its alkoxide counterpart, which explains its greater affinity for the more polarizable thioester group. Although reactivity of the ester group toward sodium borohydride is significantly diminished in bulky *iso*-propanol and completely suppressed in *tert*-butanol, we found that thioesters are efficiently reduced under these conditions. Thus, the




**13**

**Scheme 3.** Structure of bicyclic ester **13**.

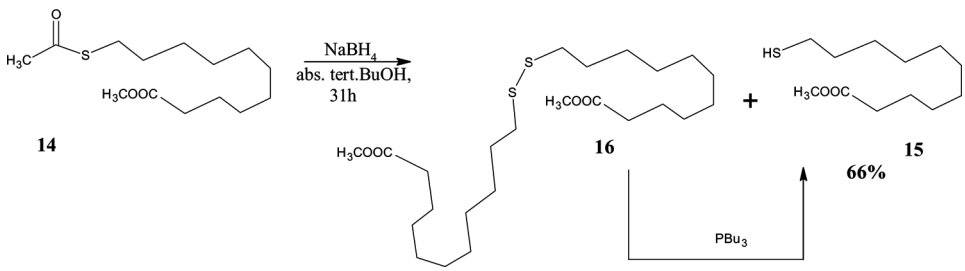
thioester group of methyl 11-acetylthioundecanoate **14**[18] was selectively reduced (78% of the product of reduction and 22% of the starting material; no alcoholysis took place) by 8 equiv. of sodium borohydride in *tert*-butanol for 31 h. However, reduction of **14** on air was accompanied by partial oxidation of the produced mercaptoester **15**[18] to the corresponding disulfide by air. The disulfide **16**[19] was converted back to the mercaptane **15** by the subsequent treatment with 1 equiv. of tributylphosphine (a known reagent for cleavage of disulfides[20]) in 3 ml of chloroform and one drop of water for 10 min. The overall conversion of **14** to **15** was 66% (Scheme 4). The progress of these transformations was monitored by $^1$H NMR (δ 2.86 for $CH_2$, connected to the acetylthio- group,[18] δ 2.53 for $CH_2$, connected to the mecrapto-group,[18] and δ 2.68 for $CH_2$, connected to the disulfide group[21]). Utilization of either abs. *iso*-propanol or abs. ethanol solvent instead of *tert*-butanol led to significant ester hydrolysis (17–50%).

Sodium borohydride in DMF did not react with the thioester or the ester group of **14**, probably because of the strong solvation of the borohydride anion. Attempts to cleave the compound **14** with the in situ–generated sodium tetra(*iso*-propoxy) borate led to a mixture of unidentified products.

As opposed to its methyl ester, 11-acetylthioundecanoic acid **17**[22] did not undergo noticeable reduction by 8 equiv. of sodium borohydride either in *tert*-butanol or in *iso*-propanol for up to 27 h. However, reduction in ethanol for 4 h quantitatively led to 11-mercaptoundecanoic acid **18**.[23] Therefore, formation of a boronic carboxy-derivative completely suppressed the reaction in branched solvents.

Although aliphatic and aromatic esters have similar reactivity toward sodium borohydride, reduction of aromatic thioesters seems to proceed slower than their aliphatic counterparts. Thus, reduction of methyl 11-benzoylthioundecanoate **19** [prepared by dicyclohexylcarbodiimide (DCC) esterification of 11-benzoylthioundecanoic acid **20**[24]] by 8 equiv. of sodium borohydride in *tert*-butanol led to 45% of thioester cleavage (versus 78% for methyl 11-acetylthioundecanoate **14**). This behavior supports an increased contribution of the first reaction step (addition to the carbonyl group, breaking its conjugation with the benzene ring) to the reduction of thioesters.

Interestingly, neither thioester reduction nor transesterification took place for 11-acetylthioundecanoic acid **17**, covalently immobilized on filter paper[25] or Wang resin via the ester linkage. No mercapto-groups on the surface were detected by the Ellman's reagent. To ensure appropriate swelling of the Wang resin conjugate, a 1:1 mixture of DMF and ethanol was selected as solvent for the attempted cleavage. However, deprotection of the Wang resin conjugate by sodium borohydride in




**Scheme 4.** Selective reduction of the thioester group in compound **14**.

ethanol did not take place either. Cleavage of the immobilized material from the solid support by 50% trifluoroacetic acid in dichloromethane (DCM) produced only the starting acid **17**. We attribute the lack of reactivity to the steric hindrance at the surface of a solid support. Therefore, sodium borohydride can be safely used for solid-supported syntheses, leaving the ester and thioester fragments intact.

## CONCLUSION

We introduced sodium borohydride in ethanol as a mild reagent for transesterification of methyl esters. Sodium borohydride in *tert*-butanol selectively cleaves thioesters, leaving the ester functionality intact. Both reesterification of esters and reduction of thioesters are highly sensitive to the solvent and steric hindrance at the reaction center. Tetraalkoxyborates generated in situ proved to be less selective but significantly more efficient reagents and catalysts for transesterification.



## EXPERIMENTAL

Reagents and solvents were purchased from Aldrich and Acros Organics. Wang resin was purchased from Chem Impex. NMR spectra were recorded on a Mercury-200 spectrometer with tetramethylsilane (TMS) as an internal reference. Thin-layer chromatography (TLC) was run on Silufol plates with an ultraviolet (UV) indicator.

### Reaction of Esters with Sodium Borohydride in Alcohols

Sodium borohydride (19 mg, 0.5 mmol) and the corresponding ester were stirred in 1 ml of solvent in a closed vial at rt, treated with 5 ml of water, acidified with 1 M HCl, and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, evaporated in vacuum, and analyzed by $^1$H NMR.

### *iso*-Propyl Benzoate 11

A solution, prepared by stirring 57 mg (1.5 mmol) of sodium borohydride, 3 ml of *iso*-propanol, and 0.5 ml (6.8 mmol) of acetone for 30 min at room temperature in a closed vial, was stirred with 0.1 ml (0.79 mmol) of methyl benzoate **1** for 24 h at room temperature, poured into 20 ml of 1 M HCl, and extracted with ether. The organic layer was dried over $MgSO_4$, filtered, and evaporated to yield 123 mg (95%) of *iso*-propyl benzoate **11** as a colorless liquid, identical to the known[8] compound by $^1$H-NMR.

### Ethylbenzoate 2

A solution, prepared by stirring 57 mg (1.5 mmol) of sodium borohydride, 3 ml of ethanol, and 0.5 ml (0.90 mmol) of acetaldehyde (added dropwise at cooling with ice) for 30 min at rt in a closed vial, was stirred with 0.1 ml (0.79 mmol) of methyl benzoate **1** for 24 h at rt, poured into 20 ml of 1 M HCl, and extracted with ether. The organic layer was dried over $MgSO_4$, filtered, and evaporated to yield 113 mg (95%) of ethyl benzoate **2** as a colorless liquid, identical to the known[6] compound by $^1$H NMR.

### Transesterification of Methyl Benzoate 1 in DMF

A solution, prepared by stirring 57 mg (1.5 mmol) sodium borohydride, 3 ml of *iso*-propanol, and 0.5 ml (6.8 mmol) of acetone for 30 min at room temperature in a closed vial, was evaporated in vacuum to dryness. The residue was stirred with 3 ml of DMF and 0.13 ml (1.03 mmol) of methyl benzoate **1** for 24 h at rt, poured into 20 ml of 1 M HCl, and extracted with ether. The organic layer was dried over $MgSO_4$, filtered, and evaporated to yield 151 mg of a colorless liquid, which consisted (by $^1$H NMR) of *iso*-propyl benzoate **11** (63% yield) and starting **1** (32% yield).

### Synthesis of Ethyl Benzoate 2 Without the Use of Acetaldehyde

A solution, prepared by stirring 57 mg (1.5 mmol) sodium borohydride, 3 ml of *iso*-propanol, and 0.5 ml (6.8 mmol) of acetone for 30 min at rt in a closed vial, was evaporated in vacuum to dryness. The residue was stirred with 3 ml of abs. ethanol and 0.1 ml (0.79 mmol) of methyl benzoate **1** for 24 h at rt, poured into 20 ml of 1 M HCl, and extracted with ether. The organic layer was dried over $MgSO_4$, filtered, and evaporated to yield 113 mg (95%) of ethyl benzoate **2** as a colorless liquid.

### Synthesis of Ethyl Benzoate 2 by the In Situ–Prepared Sodium Tetra(*iso*-propoxy)borate

A solution, prepared by stirring 57 mg (1.5 mmol) of sodium borohydride, 3 ml of ethanol, and 0.5 ml (6.8 mmol) of acetone for 30 min at rt in a closed vial, was stirred with 0.1 ml (0.79 mmol) of methyl benzoate **1** for 24 h at rt, poured into 20 ml of 1 M HCl, and extracted with ether. The organic layer was dried over $MgSO_4$, filtered, and evaporated to yield 110 mg (92%) of ethyl benzoate **2** as a colorless liquid.

### Synthesis of *iso*-Propyl Benzoate 11 with Sodium Tetraethoxyborate in *iso*-Propanol

A solution, prepared by stirring 57 mg (1.5 mmol) sodium borohydride, 3 ml of ethanol, and 0.5 ml (0.90 mmol) of acetaldehyde (was added dropwise at cooling with ice) for 30 min at rt in a closed vial, was evaporated in vacuum to dryness. The residue was stirred with 3 ml of *iso*-propanol and 0.1 ml (0.79 mmol) of methyl benzoate **1** for 24 h at rt, poured into 20 ml of 1 M HCl, and extracted with ether. The organic layer was dried over $MgSO_4$, filtered, and evaporated to yield 132 mg of a colorless liquid, which consisted (by $^1$H NMR) of *iso*-propyl benzoate **11**, ethyl benzoate **2**, and starting methyl benzoate **1** in the molar ratio of 1:0.15:0.03.

### Tetraalkoxyborate-Catalyzed Transesterification of Methyl Benzoate 1

A solution, prepared by stirring 57 mg (1.5 mmol) of sodium borohydride, 30 ml of ethanol, and 0.5 ml (6.8 mmol) of acetone for 30 min at rt in a closed flask, was stirred with 2 ml (16 mmol) of methyl benzoate **1** for 24 h at rt. A 3-ml sample of

the reaction mixture was poured into 20 ml of 1 M HCl and extracted with ether. The organic layer was dried over $MgSO_4$, filtered, and evaporated to yield 195 mg of a colorless liquid, which consisted (by $^1$H NMR) of ethyl benzoate **2** and starting methyl benzoate **1** in the molar ratio of 1:0.18 (85% conversion). NMR analysis of a sample taken after another 24 h showed 93% conversion.

### Full Transesterification of a 1:1 Mixture of Ethyl Benzoate 2 and Methyl Benzoate 1

A solution, prepared by stirring 57 mg (1.5 mmol) of sodium borohydride, 3 ml of *iso*-propanol, and 0.5 ml (6.8 mmol) of acetone for 30 min at rt in a closed vial, was stirred with 123 mg of a 1:1 mixture of ethyl benzoate **2** and methyl benzoate **1** for 24 h at rt, poured into 20 ml of 1 M HCl, and extracted with ether. The organic layer was dried over $MgSO_4$, filtered, and evaporated to yield 120 mg (81%) of *iso*-propyl benzoate **11** as a colorless liquid.

### Partial Transesterification of Methyl Benzoate 1

A solution, prepared by stirring 57 mg (1.5 mmol) of sodium borohydride, 3 ml of ethanol, and 0.5 ml (6.8 mmol) of acetone for 30 min at rt in a closed vial, was stirred with 0.1 ml (0.79 mmol) of methyl benzoate **1** for 4 h at rt, poured into 20 ml of 1 M HCl, and extracted with ether. The organic layer was dried over $MgSO_4$, filtered, and evaporated to yield 123 mg of a colorless liquid, which consisted (by $^1$H NMR) of ethyl benzoate **2** and starting methyl benzoate **1** in the molar ratio of 1:1 (50% conversion).

### Selective Reduction of Methyl 11-Acetylthioundecanoate 14

A mixture of methyl 11-acetylthioundecanoate **14** (23 mg, 0.08 mmol), sodium borohydride (24 mg, 0.64 mmol), and *tert*-butanol (1 ml) was stirred for 31 h at room temperature, acidified with 1 M HCl, and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, filtered, and evaporated to give 16 mg of viscous oil, which consisted (by $^1$H NMR) of methyl 11-mercaptoundecanoate **15** and the disulfide **16** in the molar ratio of 1.5:1. This material was stirred with one drop of tributylphosphine, 3 ml of chloroform, and one drop of water for 10 min and evaporated in vacuum. $^1$H NMR analysis ($\delta$ 2.86 for $CH_2$, connected to the acetylthio-group, $\delta$ 2.53 for $CH_2$, connected to the mecrapto-group, and $\delta$ 2.68 for $CH_2$, connected to the disulfide group) of the residue showed complete reduction of the disulfide to the mercapto-group.

### Reduction of 11-Acetylthioundecanoic Acid 17 in Ethanol

A mixture of 11-acetylthioundecanoic acid **17** (25 mg, 0.096 mmol), sodium borohydride (30 mg, 0.79 mmol), and ethanol (2 ml) was stirred for 4 h at rt, acidified with 1 M HCl, and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, filtered, and evaporated to give 19 mg (90%) of 11-mercaptoundecanoic acid **18**.

### Attempted Reduction of 11-Acetylthioundecanoic Acid 17 in *iso*-Propanol

A mixture of 11-acetylthioundecanoic acid **17** (25 mg, 0.096 mmol), sodium borohydride (30 mg, 0.79 mmol), and ethanol (2 ml) was stirred for 4 h at rt, acidified with 1 M HCl, and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, filtered, and evaporated to give 25 mg (100%) of the starting acid **17**.

### Methyl 11-Benzoylthioundecanoate 19

A mixture of 11-benzoylthioundecanoic acid **20** (58 mg, 0.18 mmol), DCC (41 mg, 0.20 mmol), and 4-dimethylaminopyridine (DMAP; 5 mg) was stirred in 3 ml of methanol at room temperature for 4 h, evaporated in vacuum, dissolved in 2 ml of ether, filtered, and evaporated to give 63 mg of impure methyl 11-benzoylthioundecanoate **19**. The crude material was chromatographed on a silica-gel column eluted by 5% ethyl acetate in hexane to yield a pure sample of **19** as colorless oil. $^1$H NMR ($CHCl_3$) δ 1.2–1.8 (m., 16H), 2.30 (t., 2H), 3.05 (t., 2H), 3.65 (s., 3H), 7.4–7.6 (m., 3H), 7.95 (d., 2H). Anal. $C_{19}H_{28}SO_3$ calc. (%): C, 67.82; H, 8.39. Found: C, 67.88; H, 8.58.

### Covalent Attachment of 11-Acetylthioundecanoic Acid 17[22] to Wang Resin

A mixture of Wang resin (935 mg, 1.6 mmol/g, 1.5 mmol), DCC (225 mg, 1.1 mmol), DMAP (25 mg), 11-acetylthioundecanoic acid **17** (260 mg, 1 mmol), and 9 ml of DMF was shaken for 16 h, filtered, washed with DMF (3 × 7 ml), DCM (3 × 7 ml), and methanol (2 × 7 ml), and dried in air at rt for 16 h.

## ACKNOWLEDGMENTS

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