# One-Step Regioselective Functionalization of *myo*-Inositol by Dissolution Strategy

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**Abstract:** Functionalizations of hydroxy groups of *myo*-inositol were usually nonselective due to its poor solubility. By dissolving *myo*-inositol in DMSO or LiCl–*N*,*N*-dimethylacetamide, we have achieved regioselective acylation, silylation, sulfonylation, phosphinylation to give the corresponding 1,3-di-*O*-substituted products in good yields.

**Key words:** acylation, regioselectivity, substitutions, inositol, DMA

Since the experimental disclosure of a significant role of inositol 1,4,5-trisphosphate as an intracellular secondary messenger in 1983,[1] the synthetic chemistry of inositol has remarkably developed,[2] and a variety of natural and related inositol derivatives such as inositol phosphates[3] and inositol phospholipids[4] were synthesized. *myo*-Inositol (**1**) has been derivatized to functional materials such as liquid crystals,[5] surfactants,[6] metal-complexing agents,[7] gelators,[8] chiral synthons for syntheses of various natural products[9] and analogues.[10] However, when *myo*-inositol is used as the starting material, some of its hydroxy groups need to be protected as monoketals, diketals, orthoesters or bis(disiloxane)[11] before further functionalization such as alkylation, acylation, sulfonylation or phosphorylation at required hydroxy groups. The direct regioselective introduction of acyl, alkyl, silyl or sulfonyl[12] group to *myo*-inositol has not so far been achieved, preventing efficient and economical derivatizations of the inositol for use in various applications. For instance, the reported procedure for the preparation of 1-*O*-tosyl-*myo*-inositol involve six steps starting from *myo*-inositol.[13] Similarly, 1,3-di-*O*-benzoyl-*myo*-inositol was prepared in four steps via orthoformate.[14] We report here a regioselective synthetic method for the preparation of 1,3-di-*O*-functionalized *myo*-inositol derivatives from *myo*-inositol in one step without protection, by the dissolution strategy.

## Solubility of *myo*-Inositol

On the basis of our consideration that dissolution of *myo*-inositol is essential to accomplish direct regioselective functionalization, we have screened several solvent systems, and found that dimethyl sulfoxide (DMSO) is suitable to make a solution of *myo*-inositol. Kuhn and Trischmann described that a DMSO solution was necessary to prepare permethylated *myo*-inositol.[15] Also, a DMSO solution of *myo*-inositol was used recently to improve the yield of camphor ketal during the optical resolution of inositol. This methodology gave better yield and diastereoselectivity than the previously reported procedure using a suspension of inositol.[16] The solution was prepared by heating or sonicating a mixture of *myo*-inositol and a relatively large volume of DMSO (1 g *myo*-inositol/20 mL DMSO). A combination of *N*,*N*-dimethylacetamide (DMA) and LiCl was also found to be suitable for solubilization of *myo*-inositol (1 g *myo*-inositol/10 mL 8% LiCl in DMA), although DMA alone was not enough. Such combinations are often used for dissolution of polysaccharides such as cellulose and starch. Furthermore, a combination of LiCl–*N*-methylpyrrolidone also solubilized *myo*-inositol, while LiCl–DMF did not.

## Regioselective Functionalization at the 1- and 3-Positions of *myo*-Inositol


1 2

**Equation 1**

Two chemically equivalent hydroxy groups at the 1 and 3 positions in mesomeric *myo*-inositol (Equation 1) are expected to have a higher reactivity than those at the remaining positions. This assumption is based on the fact that various kinds of regioselective functionalization at C1-OH of partially protected inositol derivatives have been achieved frequently.[17] When a suspension of *myo*-inositol in pyridine was treated with 2.3 equivalents of 1-naphthoyl chloride for 12 hours at room temperature, a complex mixture of di- tri-, tetra-, penta-, and peracylated products was obtained. The expected 1,3-di-*O*-naphthoyl-*myo*-inositol was formed only in 6% yield. In contrast, a homogeneous reaction medium has dramatically effected a highly regioselective functionalization of *myo*-inositol. Thus, when a solution of *myo*-inositol in a mixture of LiCl (8%) and DMA was treated with 1-naphthoyl chloride (3

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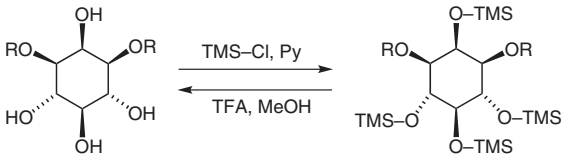
equiv) in the presence of triethylamine (7 equiv) at –20 °C for 20 hours the 1,3-diacylated product was selectively furnished in 83% yield. When the quantity of the base was decreased to five mole equivalents, the yield of the dinaphthoate decreased to 72%. The results can be explained by invoking the suppression of a Vielsmeyer-type side reaction[18] and the acceleration of the nucleophilic attack of *myo*-inositol hydroxy groups.[19] However, attempts to perform acylation with an acyl chloride in DMSO solution were met with failure, presumably because of a predominant Pummerer-type reaction.[20]

Dibenzoylation was similarly accomplished in high yield and regioselectively, but the product formed was extracted after silylation in situ with TMSCl owing to the high solubility of 1,3-di-*O*-benzoyl-*myo*-inositol in water (Equation 2). The silyl ether **3** was transformed back, without isolation, to the benzoate **2** (R = benzoyl) by TFA-assisted methanolysis. When a difunctionalized product of the general formula **2** is soluble in water, the silylation followed by aqueous workup procedure is convenient for the removal of LiCl and DMA, and the silylated product thus obtained can be desilylated to obtain the expected product. It has been observed that a fraction of the 1,3-dinaphthoate obtained was found to be dissolved in water layer during washing of the organic extract containing DMA.[21] The results of the 1,3-diacylation are collected in Table 1.



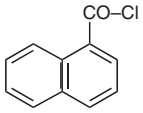
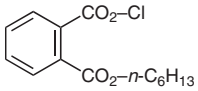

2 3

**Equation 2**

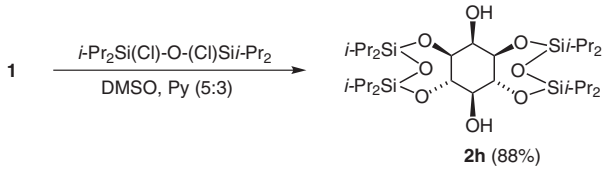
In order to explore the scope and generality of this regioselectivity enhancement by dissolution, we attempted functionalization with different electrophilic reagents. Silylation of *myo*-inositol with *tert*-butyldiphenylchlorosilane in a mixture of DMSO and pyridine (5:3) took place selectively at room temperature to give 1,3-di-*O*-silylated inositol in 89% yield. However, the silylation using *tert*-butyldimethylchlorosilane under similar conditions resulted in a mixture of products with poor selectivity. Silylation with vicinal diol protecting reagent tetraisopropyl-1,3-disiloxane dichloride gave bis(disiloxanyl) derivative **2h** in high yield (88%; Equation 3). It is worthy to note that the same reaction in pyridine (suspension) was reported to be sluggish, low yielding (**2h** only in 60% yield) and less selective (other by-products).[22]

Sulfonylation of *myo*-inositol with tosyl chloride in the 8% LiCl–DMA solvent system provided the 1,3-ditosylate in 79% yield. The ditosylate could be isolated without temporary derivatization to the TMS ether. The NMR of the reaction mixture obtained after the removal of DMA

**Table 1** Synthesis of 1,3-Di-*O*-substituted *myo*-Inositols **2**

| Compound **2** | RCl (equiv) | Base (equiv) | Solvent[a] | Temp. (°C) | Time (h) | Yield (%) |
|---|---|---|---|---|---|---|
| **a** | PhCOCl (3) | $Et_3N$ (7) | A | –10 | 4 | 95[b] |
| **b** |  (3) | $Et_3N$ (7) | A | –10 | 20 | 83 |
| **c** | *t*-BuCOCl (3) | $Et_3N$ (5) | A | 0 | 10 | 88[b] |
| **d** |  (2.5) | $Et_3N$ (7) | A | –10 | 9 | 85 |
| **e** | *t*-$BuPh_2SiCl$ (3) | Py (excess) | B | r.t. | 72 | 89 |
| **f** | *p*-$MeC_6H_4SO_2Cl$ (2.5) | $Et_3N$ (5) | A | 10 | 24 | 79 |
| **g** | $Ph_2P(O)Cl$ (3) | $Et_3N$ (7) | A | 0 | 20 | 86[b] |
| **h** | $[(i\text{-}Pr)_2SiCl]_2O$ (3) | Py (excess) | B | r.t. | 20 | 88[c] |

[a] A = 8% LiCl–DMA, B = DMSO–Py (5:3).
[b] Isolated via the TMS derivative.
[c] Bis(disiloxanyl) derivative **2h** was isolated.




**Equation 3**

and other volatile materials under reduced pressure, showed that the 1,3-disulfonate was almost exclusively formed, however the isolated yield was about 80%. This deviation could be due to the loss of the product during aqueous workup as mentioned above. Similarly, phosphinylation also proceeded in a highly regioselective manner to give 1,3-diphosphinate in good yield.

In summary, the dissolution strategy has allowed to achieve the regioselective functionalization of unprotected *myo*-inositol in high yield.[23] The procedure reported here provides a practical synthetic method for 1,3-difunctionalized inositol derivatives. The results presented here will be of interest not only to inositol chemists but also to a broad section of organic chemists given the application of inositol derivatives in a wide range of applications such as synthons for natural products, catalysts, supramolecular assemblies etc.

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distillation (1 and 20 mmHg). LiCl is so hygroscopic that it was weighed in a reaction vessel and dried by application of heat at about 300–400 °C under reduced pressure (0.5 mmHg).

**Typical Procedure for the Synthesis of 1,3-Di-*O*-benzoyl-*myo*-inositol (2a)**: To a reaction flask containing LiCl (400 mg, 9.44 mmol) were added inositol (100 mg, 0.55 mmol) and DMA (5 mL), and the mixture was heated at about 120 °C until the mixture became a clear solution (about 3 min). After addition of $Et_3N$ (391 mg, 3.89 mmol), the resulting solution was kept at –10 °C, and then benzoyl chloride (234 mg, 1.67 mmol) was added. The mixture was stirred at the same temperature for 4 h, and pyridine (2 mL) and TMSCl (1 mL, 7.82 mmol) were carefully added. The mixture was stirred at 0 °C for 5 h, and diluted with $H_2O$ and EtOAc. After partition to two layers, the aqueous layer was extracted with EtOAc (3 ×), and the organic layers combined with the initial organic one were washed successively with $H_2O$ (2 ×), 0.5 N HCl solution, $H_2O$, sat. $NaHCO_3$ solution, $H_2O$, and then brine. The organic layer was dried over $Na_2SO_4$, filtered and evaporated. The residue was dissolved in a small volume of $CHCl_3$ (1 mL), and MeOH (5 mL) and $CF_3CO_2H$ (74 mg, 0.64 mmol) were added. The solution was stirred for 4 h at r.t., and the volatile materials were all distilled off under reduced pressure (1.0 mmHg). The residue was subjected to a column chromatography on silica gel (MeOH–$CHCl_3$, 1:10) to give crystalline 1,3-di-*O*-benzoate (205 mg, 95% yield): $R_f$ 0.5 (MeOH–$CHCl_3$, 1:5); mp 174.5–175.0 °C (EtOAc–hexane). $^1$H NMR (400 MHz, $CD_3OD$): δ = 3.44 (1 H, t, $J$ = 9.8 Hz, $InsH_5$), 4.08 (2 H, t, $J$ = 9.8 Hz, $InsH_{4,6}$), 4.43 (1 H, t, $J$ = 2.6 Hz, $InsH_2$), 5.01 (2 H, dd, $J$ = 9.8, 2.6 Hz, $InsH_{1,3}$), 7.47 (4 H, t, $J$ = 8.0 Hz, $H_m$), 7.60 (2 H, t, $J$ = 8.0 Hz, $H_p$), 8.00 (4 H, d, $J$ = 8.0 Hz, $H_o$). $^{13}$C NMR (100 MHz, $CD_3OD$): δ = 69.29, 71.89, 75.90, 76.52 (6 × C, InsC), 129.42 (4 × C, $C_{ar3}$), 130.88 (4 × C, $C_{ar2}$), 131.50 (2 × C, $C_{ar1}$), 134.26 (2 × C, $C_{ar4}$), 167.69 (2 × C, CO). MS (FAB$^+$, *m*-nitrobenzyl alcohol): $m/z$ = 389 [M + H]$^+$. Anal. Calcd for $C_{20}H_{20}O_8 \cdot 1/2H_2O$: C, 60.45; H, 5.33. Found: C, 60.09; H, 5.13.

**1,3-Di-*O*-(1-naphthoyl)-*myo*-inositol (2b)**: As described above, a solution of inositol (100 mg, 0.55 mmol) and LiCl (400 mg, 9.44 mmol) in DMA (5 mL) was prepared. After addition of $Et_3N$ (391 mg, 3.89 mmol), the resulting solution was kept at –10 °C, and then 1-naphthoyl chloride (317 mg, 1.67 mmol) was added. The mixture was stirred at the same temperature for 20 h. $H_2O$ (about 0.1 mL) was added and the mixture was stirred for 10 min, and then partitioned to EtOAc and $H_2O$ layers. The aqueous solution was extracted with EtOAc (3 ×). The combined extract was washed with $H_2O$ (3 ×) and brine, dried over $Na_2SO_4$, filtered, and then evaporated. The residue was recrystallized from EtOAc–hexane to give crystals of **2b** (193 mg, 71%). The remaining dinaphthoate (32 mg, 12%) was isolated from the mother liquor by a flash column chromatography on silica gel (MeOH–$CHCl_3$, 1:14): $R_f$ 0.4 (MeOH–$CHCl_3$, 1:10); mp 195.5–196.0 °C (EtOAc–hexane). $^1$H NMR (270 MHz, $CD_3OD$): δ = 3.61 (1 H, t, $J$ = 9.6 Hz, $InsH_5$), 4.23 (2 H, t, $J$ = 9.6 Hz, $InsH_{4,6}$), 4.73 (1 H, t, $J$ = 2.4 Hz, $InsH_2$), 5.26 (2 H, dd, $J$ = 9.6, 2.4 Hz, $InsH_{1,3}$), 7.61 (6 H, complex, aromatic $H_{3,6,7}$), 7.96 (2 H, d, $J$ = 8.0 Hz, aromatic $H_5$), 8.11 (2 H, d, $J$ = 8.4 Hz, aromatic $H_4$), 8.41 (2 H, d, $J$ = 7.2 Hz, aromatic $H_2$), 9.00 (2 H, d, $J$ = 8.4 Hz, aromatic $H_8$). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 69.58 (C, $InsC_2$), 72.26 (2 × C, $InsC_{4,6}$), 76.30 (2 × C, $InsC_{1,3}$), 77.04 (C, $InsC_5$), 125.9, 127.2, 127.6, 128.8, 128.9, 129.9, 131.9, 132.9, 134.8, 135.5 (10 × C, aromatic), 169.0 (C=O). MS (FAB$^+$, *m*-nitrobenzyl alcohol): $m/z$ = 689 [M + H]$^+$. Anal. Calcd for $C_{28}H_{24}O_8$: C, 68.85; H, 4.95. Found: C, 68.56; H, 4.91.

The other compounds were identified similarly by spectroscopic data ($^1$H NMR and $^{13}$C NMR, FAB–MS) and elemental analysis.