

# SYNLETT Spotlight 277

## Isoureas: Versatile Alkylation Reagents in Organic Chemistry

Compiled by Yongwei Liu

This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

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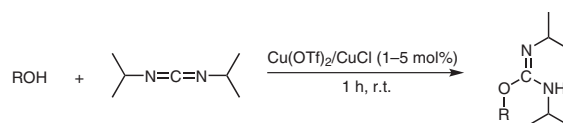
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### Introduction

The name of isoureas (alternatively named pseudoureas) derives from their isomeric relationship to ureas. However, their chemical reactivities are much different to that of ureas. Isoureas are important, sometimes commercial reagents in organic chemistry, mainly being used as alkylation reagents in esterification, etherification and in the synthesis of alkyl halides, etc. Isoureas can be conveniently prepared from alcohol and *N,N*-dialkyl carbodiimide. In most cases, the alkyl group is cyclohexyl or isopropyl. A typical procedure is as following: a mixture of alcohol,

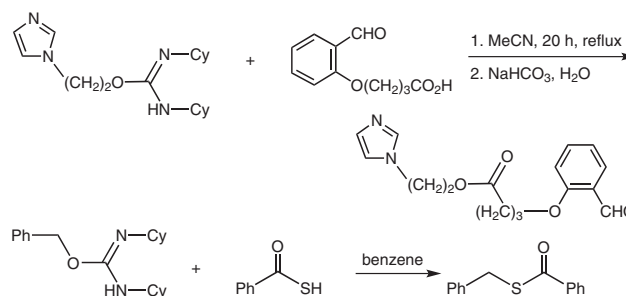
DIC and  $\text{Cu}(\text{OTf})_2/\text{CuCl}$  was stirred for 1 h at room temperature. The progress of the reaction can be monitored by IR spectroscopy by the disappearance of diimide absorption at  $2100\text{ cm}^{-1}$  and the appearance of isourea absorption at  $1660\text{ cm}^{-1}$ . Pure isoureas can be obtained after column chromatography or distillation.<sup>1</sup>



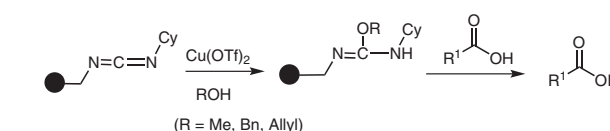
Scheme 1

### Abstracts

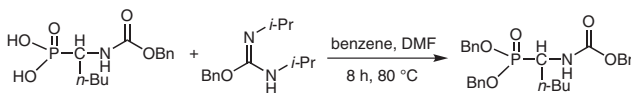
(A) The reaction of *O*-alkyl isoureas with carboxylic acids affords the corresponding esters.<sup>2</sup> Even though ester can be conveniently prepared by a one-pot reaction from carboxylic acid, alcohol and carbodiimide. The method via *O*-alkyl isourea provides an inversion of the alkyl configuration in case of a chiral one.<sup>3</sup> *S*-alkyl thioate can be obtained from thioic *S*-acid.<sup>4</sup>



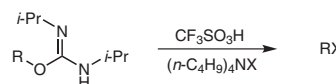
(B) The reaction of polymer-supported *O*-methyl, *O*-benzyl, and *O*-allyl isoureas with carboxylic acids provides the corresponding alkyl esters in high yields and purity. The reaction can be finished in 3 to 5 minutes with microwave heating, without compromising yield, purity, or chemoselectivity.<sup>5</sup>



(C) Phosphate esters could be obtained via the reaction of *O*-alkyl isoureas with phosphoric acid.<sup>6</sup>



(D) *O*-alkyl isoureas can be efficiently converted into alkyl bromides and iodides by treatment with one mol equivalent of trifluoromethanesulphonic acid in the presence of an excess of tetrabutylammonium bromide or iodide. The conversion can be performed either with the pure isolated *O*-alkyl isourea or with crude isourea without detriment to yield.<sup>7</sup>



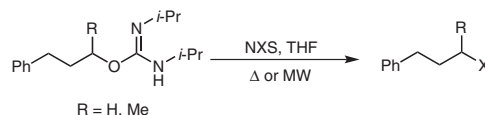
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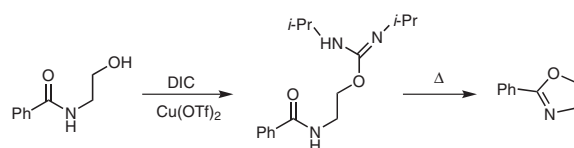
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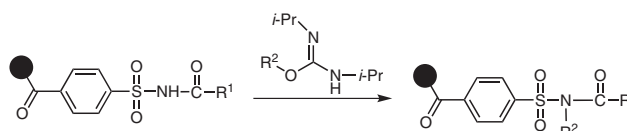
(E) Linclau and co-workers reported that primary and secondary alcohols were converted into the corresponding alkyl halide via the corresponding *O*-alkyl isoureas. High yields could be obtained in the case of chlorides and bromides. This method tolerates a range of functional groups and does not rely on the use of phosphines.<sup>8</sup>



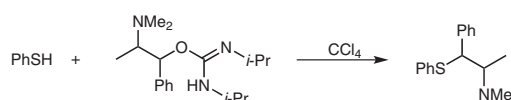
(F) Linclau also reported that *N*-( $\beta$ -hydroxy)amides could be cyclized with diisopropylcarbodiimide (DIC) to give the corresponding 2-oxazolines in high yields. The reaction requires only very mild Lewis acid catalysis [5mol% Cu(OTf)<sub>2</sub>] and can be accomplished with conventional heating or under microwave irradiation.<sup>9</sup>



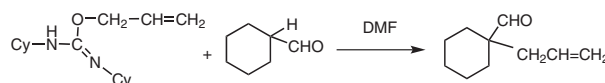
(G) The reaction of *O*-alkyl isoureas with *N*-acylsulfonamide gave the *N*-alkylated products. The reaction can be carried out with polymer-bound sulfonamide.<sup>10</sup>



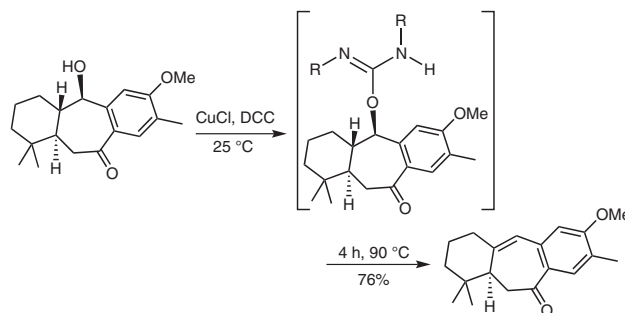
(H) Phenol ether and thiophenolether can be prepared via the reaction of *O*-alkyl isoureas with phenol and thiophenol, respectively.<sup>11,12</sup>



(I) *O*-alkyl isoureas were reported as allyl reagents in C–C bond formation reactions in the presence of a palladium catalyst.<sup>13</sup>



(J) The dehydration of secondary, tertiary and benzylic alcohols could be carried out in good yield in the presence of carbodiimide and catalytic amount of CuCl. It is believed that the reaction proceeds via *O*-alkyl isourea intermediates.<sup>14</sup>



(K) 2-Allyl isourea acts as a starting material for palladium-catalyzed Wittig-type allylidenation of aldehydes to give the corresponding conjugated olefins in moderate to good yields.<sup>15</sup>



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