Protein tyrosine phosphatase IB (PTP1B) has been pursued as a therapeutic target for type II diabetes for the past decade. During this time, many inhibitors and in-activators of the enzyme have been developed. A problem with these molecules, however, is their lack of selectivity toward PTP1B over other PTP’s. Recently, a novel approach emerged to increase selectivity for trapping PTP1B over other family members. The method utilized antibodies to “trap” the oxidized form of the enzyme that is generated during endogenous insulin signaling events. Inspired by this approach, our group set out to develop small molecules to “trap” oxidized PTP1B. Our approach involves capture of the oxidized enzyme with enolate carbon nucleophiles. This approach is advantageous in three ways. First, compared to large antibodies, this method utilizes small molecules that may have better bioavailability than an antibody. Secondly, the design of the carbon nucleophile allows us to synthesize a variety of different analogs with a wide range of pKa. Lastly, this new approach allows us to trap oxidized PTP1B covalently and irreversibly. Here we describe an efficient two-step synthesis to make a wide variety of ?-ketosulfones in reasonable yields. We reacted these carbon nucleophiles with a low molecular weight model of oxidized PTP1B. The results show that a variety of ?-ketosulfones can capture the electrophilic sulfur of oxidized PTP1B to form an adduct that is stable under physiologicall-relevant conditions.