The mammalian target of rapamycin complex (mTOR) is a key regulator of cell growth and proliferation by coordinating upstream signals from growth factors, cellular energy status and amino acid availability. As previously reported, we observed strong inhibition of the mTOR pathway in hypoxia, as detected by the markedly reduced phosphorylation of the mTOR complex 1 (mTORC1) target p70 S6 kinase. Interestingly, re-introduction of oxygen after hypoxic incubation resulted in a rapid reactivation of mTORC1 activity. Reoxygenation leads to an induction of cellular reactive oxygen species (ROS) and the reactivation of ATP synthesis via oxidative phosphorylation. However, our results suggest that these events do not contribute to the rapid mTOR reactivation upon reoxygenation. Moreover, mTOR reactivation is independent of the transcription factor Hypoxia-Inducible Factor-1α (HIF-1α) and its transcriptional target REDD1. Interestingly, reactivation of mTOR was completely blocked by dimethyloxalylglycine (DMOG), a 2-oxoglutarate analog and inhibitor of 2-oxoglutarate and oxygen dependent dioxygenase enzymes, including prolyl-hydroxylases (PHD) which regulate HIF-1α degradation. Treatment with other PHD inhibitors desferrioxamine and cobalt chloride did not produce such a pronounced effect. Hence, mTOR reactivation upon reoxygenation may be regulated by a DMOG sensitive enzyme that acts independently of the HIF-1α pathway.