Thermolysis of geminal diazido malonamides:

Access to tetrazoles and urea derivatives

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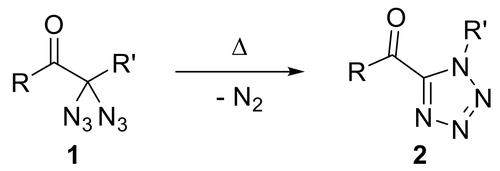
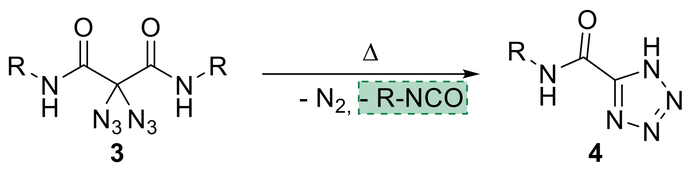
Summary

Geminal diazides have been known for decades.[1] Even though they show unique properties and reactivities, especially in terms of syntheses generating heterocycles, they were somehow overlooked over the years. In 1971 Moriarty and co-workers reported the thermolytic decomposition of diazido malonamide towards its tetrazole.[2] Additionally, we have shown with previous studies that the structural motif of geminal diazides and the thermolysis of them is an easy and versatile method to access heterocyclic compounds, such as tetrazoles.[3] Building on the early findings by Moriarty and inspired by our prior studies, we present studies on tetrazole formation through thermolysis of geminal diazido malonamides.

Earlier example of tetrazole formation through thermolysis of geminal diazides:



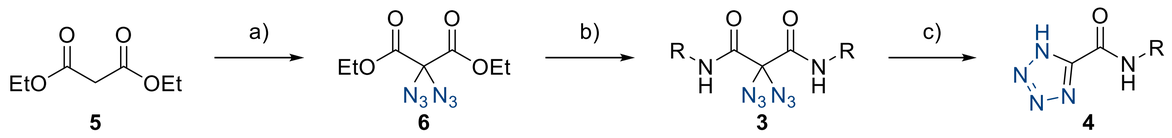
This work:



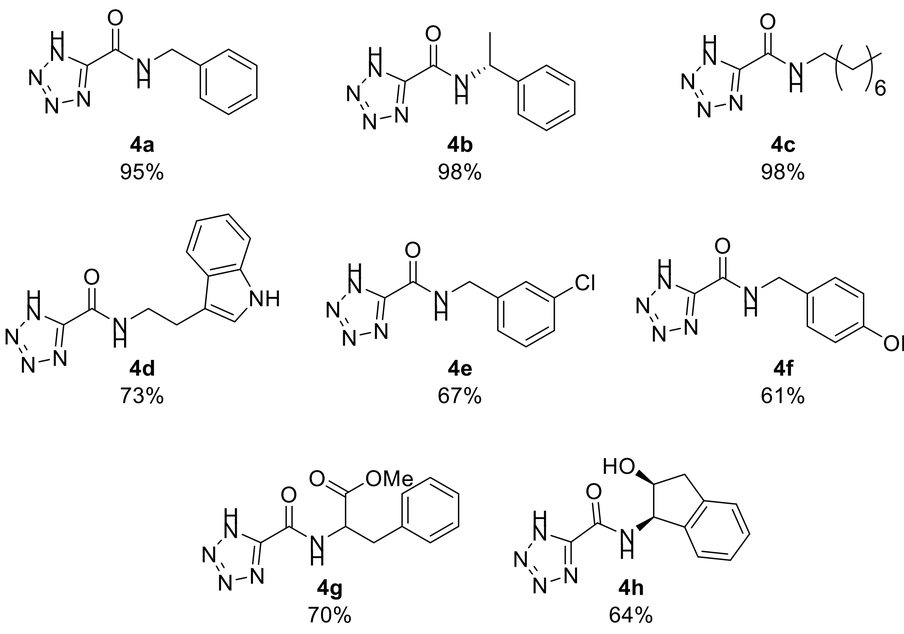
Throughout our studies various tetrazoles, starting from diethyl malonate by diazidation, amidation and thermolysis, could be synthesized in moderate to excellent yields. Mechanistically, the loss of one equivalent molecular nitrogen and isocyanate as an unconventional leaving group was hypothesised.
In situ formation of mentioned isocyanates was studied as well. Trapping of referred isocyanates with amines as nucleophiles afforded corresponding urea derivatives. This mechanistically proves the isocyanates as a leaving group, but also transformation from by-product to a product of value was transacted.

Investigation of tetrazole formation and selected scope

The formation of tetrazoles could be achieved in three steps starting from diethyl malonate, which is readily accessible and affordable. Optimised conditions, regarding safety, purification and yield, were used to obtain tetrazoles in partially excellent yields. Thermolysis was here used as a key step to introduce the tetrazole moiety. Further modification of 1*H*-position could be possible afterwards.



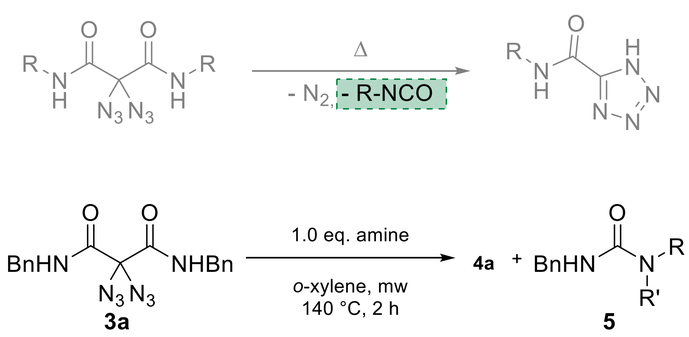
a) 2.2 equiv. I_2, 6.0 equiv. NaN_3, DMSO/H_2O, r.t., 2 h, 84%; b) 2.5 equiv. NH_2R, THF, r.t., 16 h or 2.5 equiv. NH_2R, 3.0 equiv. NEt_3, THF, r.t., 16 h; c) *o*-xylene (0,05 M), mw, 140 °C, 2 h



Trapping of *in situ* formed isocyanates

Since the proposed mechanism suggests isocyanate as a leaving group, it was investigated whether it could be trapped by addition of a nucleophile. Starting from the already established reaction conditions, addition of one equivalent of amine as nucleophiles was tested. Using *N*-benzyl diazido malonamide as a standard system, various urea derivatives could be synthesised using this method. The reaction showed a good functional group tolerance, leading to urea derivatives in good to excellent yields.

Using a substrate **3b** already bearing a nucleophilic group such as an alcohol, resulted in an intramolecular reaction of nucleophile and isocyanate and therefore formation of a cyclic carbamate.



Caution! Diazidated compounds are potentially explosive and hazardous substances and should be handled with care.

[1] Forster, M. O.; Fierz, H. E.; Joshua, W. P. *J. Chem. Soc. Trans.* **1908**, *93*.
[2] a) Moriarty, R. M.; Serridge, P. *J. Am. Chem. Soc.* **1971**, *93*. b) Moriarty, R. M.; Bailey, B. R.; Prakash, I. *J. Org. Chem.* **1985**, *50*.
[3] a) Holzschneider, K.; Tong, M. L.; Mohr, F.; Kirsch, S. F. *Chem. Eur. J.* **2019**, *25*. b) Erhardt, H.; Kunz, K. A.; Kirsch, S. F. *Org. Lett.* **2017**, *19*.