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ANODICALLY INDUCED 1-3 CYCLOADDITION OF ACETONITRILE TO 3,6-DIISOBUTYLPIPERAZINE-2,5-DIONE

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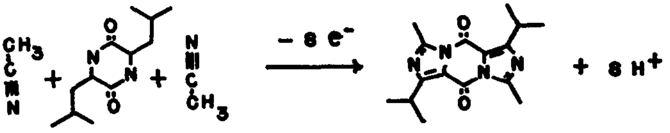
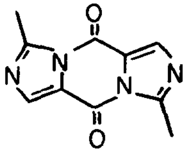
We have undertaken an examination of the anodic behavior of diketopiperazines because of their nominal similarity to dipeptides. 3,6-Di-*i*-butylpiperazine-2,5-dione (I) was taken as the model compound and the reaction was carried out in 0.5 *M* NaClO$_4$-MeCN in a divided cell. The anode potential was controlled by an electronic potentiostat at +2.2 V vs. Ag/AgNO$_3$ (0.5 *M*)-MeCN. Based upon the known behavior of amides[1], C-N scission at the 1-6 or 3-4 positions is the only expected reaction. However, one of the products is a higher molecular weight compound which we believe to be 1,6-di-*i*-propyl-3,8-dimethyl-5*H*,10*H*-diimidazo[1,5-*a*:1',5'-*d*]pyrazine-5,10-dione (II), which is formed as a result of reaction of two molecules of solvent with the reactive product of the initial electron transfer steps. The overall reaction is indicated in equation 1.



(I) (II) (Eq.1)

Structures similar to (II) have been reported.[2] We have prepared 3,8-dimethyl-5*H*,10*H*-diimidazo[1,5-*a*:1',5'-*d*]pyrazine-5,10-dione (III) by the method of Godefroi, *et al*, and have compared it with (II).



(III)

High resolution mass spectroscopy and elementary analysis indicate that (II) is $C_{16}H_{20}N_4O_2$, Mass: calc. 300.1586, obs, 300.1617; composition: % calc.(obs) *C*-64.00 (63.89); *H*-6.66 (6.73); *N*-18.66 (18.54). The proton magnetic resonance spectrum of (II) has a singlet at δ2.86*, a doublet centered at δ1.32 (J=7.0Hz) and heptet centered at δ3.74 (J=7.0Hz). Integration gives a 3:6:1 ratio, respectively, which indicates an isolated methyl and an isolated isopropyl group attached to an unsaturated system. The methyl absorption in the NMR of (III) occurs at δ2.85, in agreement with the assigned methyl peak of (II). The carbonyl absorption in the infrared (KBr pellet) occurs at 2.85 μ for both (II) and (III). The ultraviolet spectra in acetonitrile of (II) and (III) are very similar.

λnM(logε): 316(4.08); 244s(4.08); 236(4.15) (II)
306(4.10); 242s(4.11); 233(4.15) (III)

Incorporation of two molecules of acetonitrile can be inferred from the data given above. To substantiate this, the reaction of (I) was carried out in 14 mole percent deuteroacetonitrile and a mass spectrum was made of the product. Peak intensities at P+3 and P+6, normalized to the molecular ion at m/e 300 were: m/e; relative intensity (calc.) *obs.* 303(0.32)*0.30*; 306(0.028)*0.030*. Based upon reaction 1, these results show statistically correct peak intensities and therefore do indicate that acetonitrile is incorporated into the product.

The basicity of (I) causes a large amount of it to be inactivated by protonation as is generally true for electrochemical oxidation of amines and amides[1]; accordingly the overall yield of (II) is 5%. However, based upon the amount of (I) that undergoes electrochemical reaction, the yield is about 50%. Other reaction products have not been identified, but there is no evidence, based on T.L.C. results, that any substantial amount of monocycloaddition products is formed. We are investigating methods of improving the yield and are considering the preparation of analogous compounds by using different diketopiperazines and different nitriles.

*measured in ppm downfield from TMS.

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References

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2. E. F. Godefroi, C. A. Van der Eycken, and C. Van De Westeringh, *J. Org. Chem.*, **29**, 3707 (1964).