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Selective Monoacylation of a Diamine Using Intramolecular Delivery by a DMAP Unit

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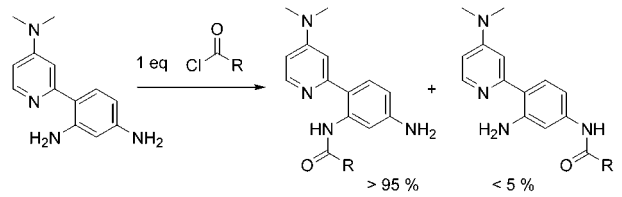
ABSTRACT



Regioselective monoacylation of a diamine is achieved by including a suitably positioned 4-(dimethylamino)pyridine (DMAP) group within the molecule.

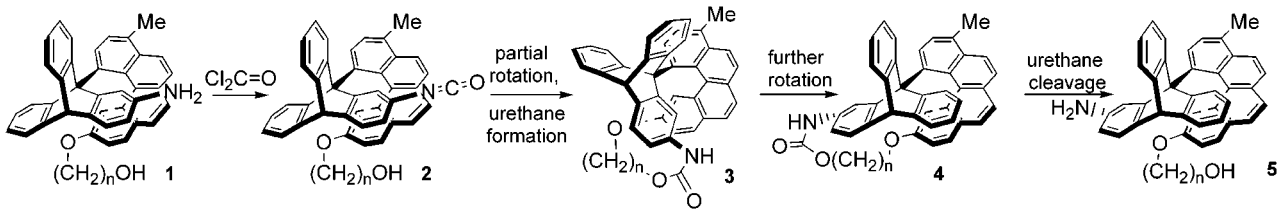
We recently reported a prototype of the first rationally designed, chemically powered molecular motor.[1] The operation of the prototype is summarized in Scheme 1. Addition of the fuel (phosgene) to **1** initiates a cascade of events resulting, after cleavage of the urethane (carbamate) in **4**, in the unidirectional 120° rotation of **1** to **5**.

With a functioning prototype in hand, the task turned to extending the original system so that the sequence of events in Scheme 1 could be achieved repeatedly. A continually rotating molecular motor would be the result.

To accomplish that aim, it is necessary to realize three subgoals (Figure 1): (i) **1** must be modified so that each blade of the triptycene is ready to be selectively armed at the appropriate time, and there must also be included within the system units that, with the appropriate spatial positioning and timing, (ii) can capture and deliver $Cl_2C{=}O$ and (iii) can cleave the urethane. Efforts in all three directions are underway; we recently described a partial solution to the third objective: cleavage of the urethane under reaction conditions compatible with the operation and analysis of the system as a whole.[2] Here we report the results of model studies directed toward the solution of the second problem: selective delivery of phosgene to only the amino group in the "firing position" (Figure 1).

4-(Dimethylamino)pyridine (DMAP) and other dialkyl aminopyridines are frequently used as catalysts for the acylation of sterically hindered alcohols and phenols.[3,4] The process usually takes place via the reaction of DMAP with

Scheme 1. Operation of a Prototype of the First Rationally Designed, Chemically Powered Molecular Motor



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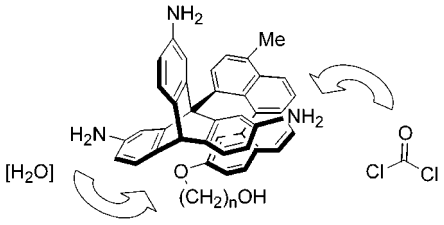


Figure 1. Schematic representation of the concepts underlying the design of a continually rotating motor (see text).

the acylating agent (usually an acid chloride or anhydride), followed by attack of the nucleophile on the resulting *N*-acylpyridinium salt. The acylation of amines with acid chlorides is usually so fast that it does not require the addition of any catalyst.[3] However, it has been documented that the DMAP-catalyzed reaction of *m*-chloroaniline with benzoyl chloride is about 10^6 times faster than the noncatalyzed reaction,[5] suggesting a decidedly higher reactivity of acid chlorides toward DMAP than toward anilines. We thus envisioned that inclusion of a suitably positioned DMAP group in our design for the molecular motor would allow for selective intramolecular delivery of phosgene to only the amino group situated proximate to the DMAP moiety (Figure 2, curved arrow). To our knowledge, no examples have been

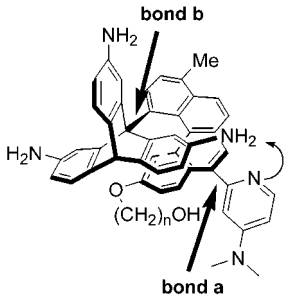


Figure 2. Specific molecular embodiment of the concept for site-selective delivery of phosgene in a motor molecule (see text).

reported of the use of DMAP as a selective intramolecular acylation catalyst for amines in a similar setting.[6] Therefore, to ascertain whether the design in Figure 2 had merit, we set out to test the concept in a simpler system.[7]

As a model, compound **6** (Figure 3) possesses the desired characteristics: (i) it contains two aniline groups in the same

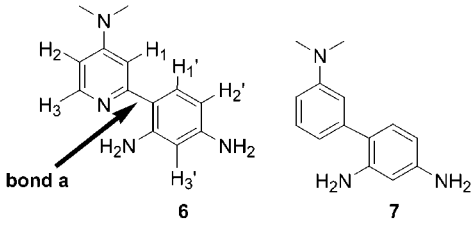


Figure 3. Model compounds studied.

molecule and (ii) only one of them is situated close enough to an internal DMAP group for the latter to be involved in the acylation reaction. To ensure that selective acylation of **6** was due only to the presence of the DMAP moiety and not to steric or electronic effects, compound **7** was chosen as a control.

Assuming[7] a nucleophilic catalysis mechanism, molecular modeling (Figure 4, Spartan pBP/DN**//AM1) of compound

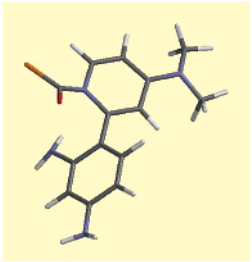


Figure 4. Acylpyridinium intermediate in its lowest energy conformation.

6 shows that once the DMAP unit has reacted with phosgene, the carbonyl carbon of the resulting acylating species (acylpyridinium ion) is in very close proximity to the reacting amine for conformations which are close in energy to the ground state conformation (by rotation around bond **a** in Figure 3). Similar calculations applied to the motor system in Figure 2 predict that the carbonyl carbon of the acylated pyridinium moiety is close to only the aniline in the firing position, by rotation around bond **a** and/or low energy[8] rotation around bond **b**.

(1) (a) Kelly, T. R.; de Silva, H.; Silva, R. A. *Nature* **1999**, *400*, 150. (b) Kelly, T. R.; Silva, R. A.; de Silva, H.; Jasmin, S.; Zhao, Y. *J. Am. Chem. Soc*. **2000**, *122*, 6935. (c) Kelly, T. R. *Acc. Chem. Res*. **2001**, *34*, 514.

(2) Kelly, T. R.; Cavero, M.; Zhao, Y. *Org. Lett*. **2001**, *3*, 3895.

(3) For reviews see: (a) Hassner, A.; Krespki, L. R.; Alexanian, V. *Tetrahedron* **1978**, *34*, 2069. (b) Höfle, G.; Steglich, W.; Vorbrüggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569. (c) Ragnarsson, U.; Grehn, L. *Acc. Chem. Res*. **1998**, *31*, 494. (d) Spivey, A.; Maddaford, A.; Redgrave, A. J. *Org. Prep. Proced. Int.* **2000**, *32*, 333. (e) Sheinkman, A. K.; Suminov, S. I.; Kost, A. N. *Russ. Chem. Rev.* **1973**, *42*, 642.

(4) For some recent publications involving DMAP derivatives see, inter alia: (a) Vedejs, E.; Chen, X. *J. Am. Chem. Soc*. **1996**, *118*, 1809. (b) Kawabata, T.; Nagato, M.; Takasu, K.; Fuji, K. *J. Am. Chem. Soc*. **1997**, *119*, 3169. (c) Sammakia, T.; Hurley, T. B. *J. Org. Chem*. **1999**, *64*, 4652. (d) Fu, G. C. *Acc. Chem. Res*. **2000**, *33*, 412. (e) Spivey, A. C.; Charboneau, P.; Fekner, T.; Hochmuth, D. H.; Maddaford, A.; Madalier-Jugroot, C.; Redgrave, A.; Whitehead, M. A. *J. Org. Chem*. **2001**, *66*, 7394. (f) Cupperly, D.; Gros, P.; Fort, Y. *J. Org. Chem*. **2002**, *67*, 238.

(5) Litvinenko, L. M.; Kirichenko, A. I. *Dokl. Akad. Nauk. SSSR* **1967**, *176*, 97 (*Dokl. Chem. Engl. Transl*. **1967**, 763).

(6) There are a large number of examples in the literature of the use of DMAP or imidazole units as acylation or phosphorylation catalysts in enzyme-mimetic (and enzyme) settings which could be considered intramolecular, since the substrate and the catalyst are usually bound during catalysis. However, most of these examples deal with alcohols (see, for instance: Sculimbrene, B. R.; Miller, S. J. *J. Am. Chem. Soc*. **2001**, *123*, 10125. Faber, K.; Riva, S. *Synthesis* **1992**, 895 and references cited therein);

To ensure that **6** was not some kind of electronic special case, the electrostatic potential of **6** and **7** was mapped onto their electronic surfaces (Spartan, pBP/DN**//AM1; Figure 5) demonstrating that in each molecule, the two amino groups

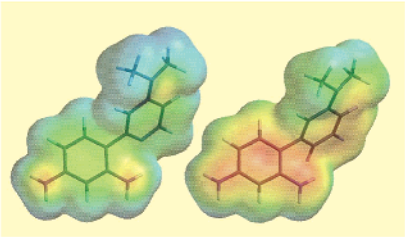


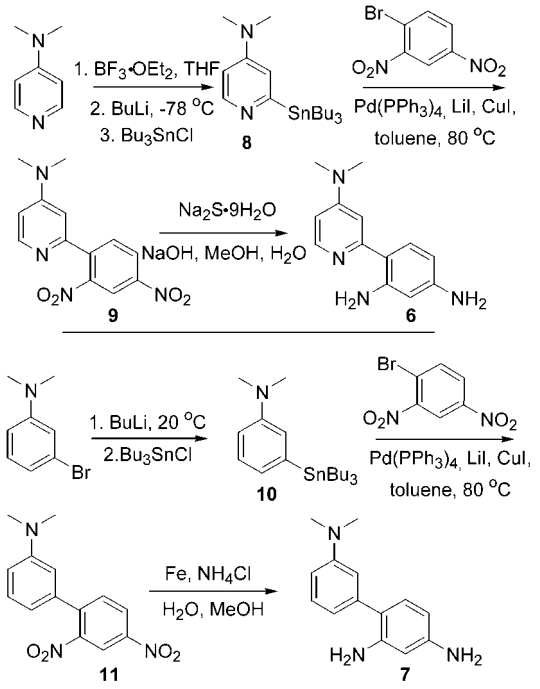
Figure 5. Electrostatic potential mapping: red, most electronegative; blue, least electronegative.

exhibit virtually identical values for the potential (ca. −45 kcal/mol). This indicates that in the absence of any better nucleophile[7] in the molecule (such as the DMAP in **6**) both anilines should react with an electrophile similarly and no selectivity should be observed. Therefore, it was expected that **6** would acylate selectively due to the presence of the DMAP, whereas **7** would give a mixture of acylated species under identical conditions.

Drawing from the earlier work of others,[9,10] model compounds **6** and **7** were prepared as described in Scheme 2.

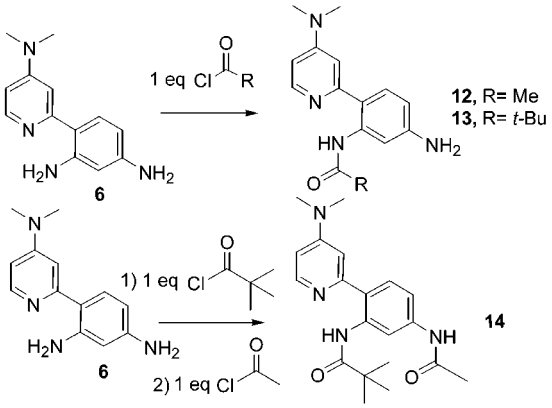
Gratifyingly, all of our predictions were borne out by experiment. When diamine **6** was treated with 1 equiv of pivaloyl or acetyl chloride in anhydrous $CHCl_3$ at room temperature, only the amino group adjacent to the DMAP unit was acylated (→**12**/**13**, Scheme 3).[11,12] Similarly, when **6** was treated sequentially with 1 equiv of pivaloyl chloride

Scheme 2. Synthesis of Diamines **6** and **7**



followed by 1 equiv of acetyl chloride, a single product that contained the two clearly differentiated amide groups was obtained in >95% yield (**14**).[13]

Scheme 3. Selective Acylation Experiments



Since it was not possible to unequivocally assign the structure of the formed regioisomer by simple analysis of 1D ^1H NMR and ^{13}C NMR spectra,[14] we carried out a series of 2D-COSY and NOESY experiments. Unfortunately, no NOEs could be observed between the acetyl or pivaloyl

we have found no examples dealing with the selective acylation of anilines.

(7) (a) For the several reasons given in this paragraph, the design of **6** was based on the premise that the acylation would proceed by a nucleophilic catalysis mechanism. Nonetheless, some referees suggest that in this specific instance the pyridine nitrogen is operating by intramolecular general base rather than nucleophilic catalysis, citing refs 4c and 7b. While we still believe that nucleophilic catalysis is operative here [molecular modeling of low-energy conformations of **6** (Figure 3) shows no hydrogen bond between the pyridine nitrogen and the proximate amino hydrogens: such a hydrogen bond would be necessary, at least in the transition state, if general base catalysis is operative] we agree with those referees that the verdict is not yet in. Since the objective of our study was to establish function (selective acylation), not necessarily prove mechanism, and since we were successful, more detailed mechanistic studies will be deferred until after the concepts in Figures 2 and 1 have been reduced to practice. (b) Anderson, H.; Su, C.-W.; Watson, J. W. *J. Am. Chem. Soc.* **1969**, *91*, 482.

(8) The barrier to full rotation around bond **b** is 20−25 kcal/mol.

(9) (a) Preparation of **8**: see ref 4c. For reactions related to the conversion of DMAP to **8** see ref 4a and: Kessar, S. V.; Singh, P.; Singh, K. N.; Dutt, M. *J. Chem. Soc., Chem. Commun.* **1991**, 570. (b) Reduction of **9** to **6**: Perry, P. J.; Reszka, A. P.; Wood, A. A.; Read, M. A.; Gowan, S. M.; Dosanjh, H. S.; Trent, J. O.; Jenkins, T. C.; Kelland, L. R.; Neidle, S. *J. Med. Chem.* **1998**, *41*, 4873. (c) Reduction of **11** to **7**: Krishnamurthy, R.; Natarajan, S. *Synth. Commun.* **1992**, *22*, 3189.

(10) All products were fully characterized by ^1H and ^{13}C NMRs and HRMS. COSY and NOESY 2D spectra are also provided for compounds **6** and **7**. See Supporting Information for details.

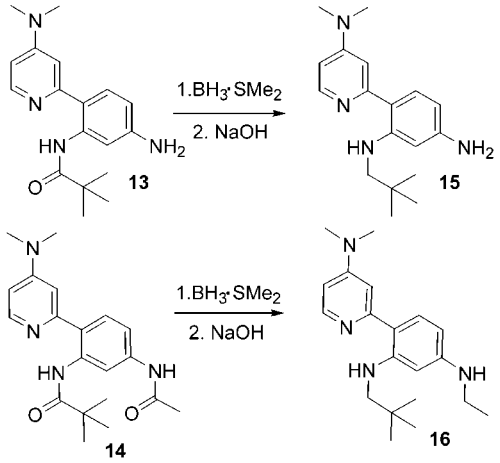
(11) Reaction was finished after <1 min (TLC). The product was isolated after a simple workup involving washing with base. The products obtained by reaction with both pivaloyl and acetyl chloride were >95% pure.

(12) No starting material or bisacylated product peaks could be observed in the ^1H NMR spectra. Bisacylated products (**22**/**23**, not shown) were prepared by treatment of **6** with 2 equiv of pivaloyl or acetyl chloride and were fully characterized (see Supporting Information) for comparison purposes.

(13) For additional details on experimental procedures and characterization of acylation products see the Supporting Information.

hydrogens and any ring hydrogen. This is easily explained if the amide adopts the more stable and quite rigid trans conformation in solution.[15] Therefore, to render the substituents more freely rotating and to introduce CH_2 groups in closer proximity to the ring hydrogens, the amide groups in **13** and **14** were reduced to the corresponding amines (Scheme 4).[16] Compounds **15** and **16** thus obtained displayed

Scheme 4



the NOEs summarized in Figure 6, thereby confirming the structures of **12**/**13**.

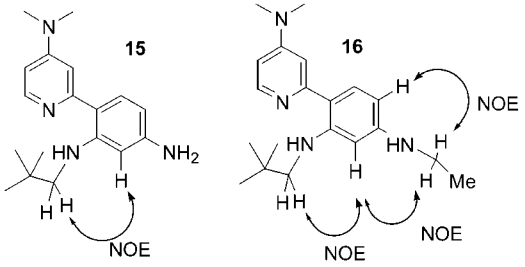


Figure 6. NOEs observed for compounds **15** and **16**.

Subsequently, and to our greater satisfaction, we succeeded in obtaining crystals of **13** suitable for X-ray diffraction analysis (Figure 7) and so our assignments were further verified.

To provide evidence that the observed regioselectivity was only due to intramolecular involvement of the DMAP unit and that no other effects were responsible for the different reactivity of the two aniline groups, compound **7** was

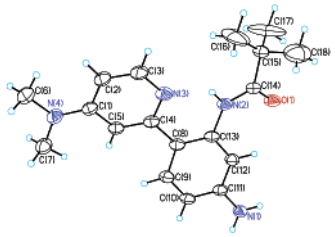


Figure 7. Structure of compound **13** as determined by X-ray diffraction of a single crystal.[17]

submitted to conditions identical with those used for the acylation of **6**. As anticipated, upon treatment of compound **7** with 1 equiv of either pivaloyl or acetyl chloride, a mixture of the two possible monoacylated products plus starting material and doubly acylated product was obtained (ca. 2:1:2:2 in both cases: see Supporting Information).

In conclusion, the results of this study show that it is possible to achieve regioselective delivery of an acyl group to one of two amine groups within the same molecule by introducing a suitably positioned DMAP moiety that acts as the catalyst in the acylation process. Incorporation of these concepts into a molecular motor is currently underway.

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Supporting Information Available: Key experimental procedures and spectral characterization data for new compounds, additional details of experimental procedures used during acylation experiments, ^{1}H NMR spectra of crude mixtures for each acylation experiment, additional X-ray diffraction information, and NOESY and COSY spectra of pertinent compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Changes in chemical shifts for protons H_2' and H_3' (Figure 3) on acylation of either of the two amine groups were expected to be quite different: acylation of the amine closer to the DMAP group would be expected to have a larger effect on the chemical shift for H_3' but not for H_2'; acylation of the other amine group would result in a large chemical shift change for both hydrogens. In practice, we observed the first effect, indicating that the process was working as predicted, but we secured additional proof.

(15) Robin, M. B.; Bovey, F. A.; Basch, H. In *The Chemistry of Amides*; Zabicky, J., Ed.; Wiley-Interscience: New York, 1970; p 1.

(16) The ^{1}H NMR spectra of compounds **12** and **13** are very similar in the aromatic region and therefore structure-elucidation studies concentrated on **13** and the structure of **12** was assigned by analogy.

(17) Crystal data for compound **13**: $C_{24}H_{32}N_{5.33}O_{1.33}$ (unit cell), M_r = 416.55, monoclinic space group $C2/c$, a = 32.285(4) Å, b = 16.713(3) Å, c = 20.190(4) Å, U = 3456.2(8) Å^3, D_c = 1.201 g/cm^3, Z = 6, absorption coefficient = 0.077 mm^{-1}, 2250 unique data were produced from 7107 measured reflections (R_{int} = 0.0680), R_1 = 0.0814, wR_2 = 0.2219. CCDC-185843 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Center, 12, Union Road, Cambridge CB2 1EZ, UK; fax (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).