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Trapping of photochemical intermediates as a tool in organic synthesis. Preparation of spiroaziridinopyridones, a new heterocyclic system

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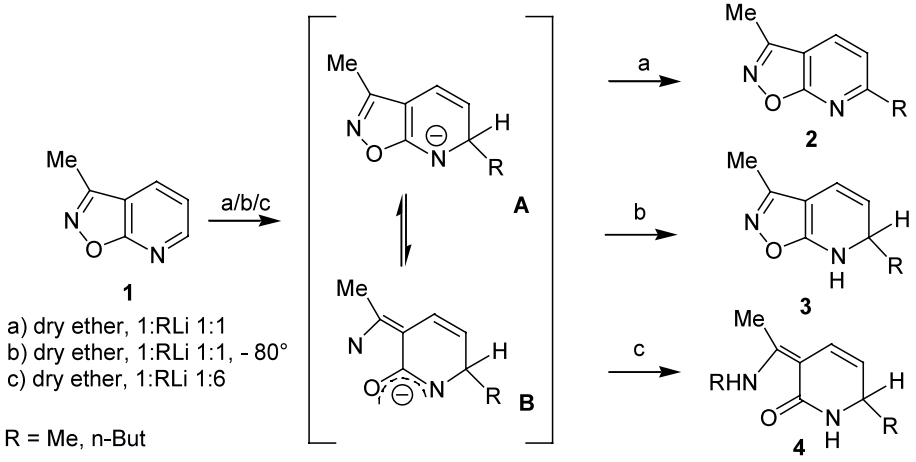
Abstract—Whereas alkyl lithium and Grignard reagents both at rt and at −80°C thermally react with 3-methylisoxazolo[5,4-*b*]pyridine giving alkylation and/or isoxazole ring opening products, sodium malonate and sodium boron hydride react only under UV irradiation. Selective trappings of ketenimine or azirine intermediates give an enaminopyridone or two diasteroisomeric spiroaziridinopirydones. Regioselective opening of the aziridine ring with perchloric acid gives 3(1-amino-ethyl)-1*H*-pyridin-2-one.

Aromatic isoxazolopyridines are useful synthons for photochemical access to several pyridino-condensed heterocycles. Isothiazolo-, pyrazolo-pyridones and pyrido-*as*-triazines can be formed by intramolecular trapping of the intermediates generated by irradiation of 4-nucleophile-substituted isoxazolopyridines.[1] Lifetimes of two of these intermediates, i.e. spiroazirine and ketenimine, measured by flash-photolysis experiments on 3-methylisoxazolo[5,4-*b*]pyridine in alcohols, are in the range of milliseconds.[2] As a consequence, it is possible to also perform intermolecular trapping experiments with suitable nucleophiles, in order to gain more insight into the mechanistic aspects and to ascertain the synthetic interest of isoxazolopyridines photoreactivity. To attain this goal the nucleophile must be thermally unreactive towards the substrate **1** and, at the same time, good enough to intercept the photochemical intermediates. In this view we experimented with some reagents of different strengths.

i. Alkyl lithium and Grignard reagents. In such a case, compound **1** reacted in the dark giving different addition products **2**–**4** (Scheme 1), depending on the amount of organometallic compound and on the reaction tempera-



Scheme 1.

Keywords: condensed pyridines; photochemical intermediates trapping; ketenimines; aziridines.
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ture.[3,4] Nucleophilic attack on pyridine ring gave the anion **A** which loses a hydride ion to afford 6-alkylpyridine **2** (path a). When this reaction was carried out at low temperature (−80°C, path b), 6-alkyl-6,7-dihydroisoxazolopyridine **3** was obtained by quenching with water and extraction with ether. It is evident that nucleophile addition occurs also at low temperature, whereas the hydride loss is thermally activated. A different result was obtained using an excess of nucleophile. In this case (path c) the *N*-alkylenamine of dihydropyridinone **4** was formed as a consequence of the attack of a second molecule of nucleophile on the nitrene **B**, deriving from the (reversible) five-membered ring opening in the isoxazolopyridine anion **A**.

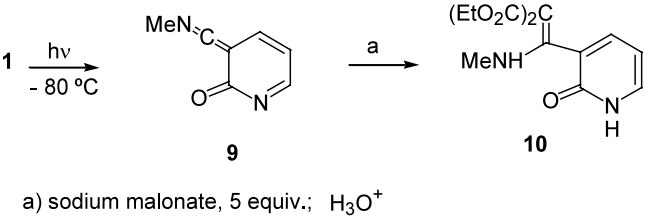
ii. Sodium malonate. This reagent, thermally unreactive towards the isoxazolopyridine **1**, can be used as a photochemical trapping agent. However, at room temperature, irradiation of **1** in ethanol containing an excess of sodium ethyl malonate[5] gave good yields of the imines **6a**,**b**[4] (Scheme 2, path b), due to thermal addition[6] of the solvent on C-2 of 2-methyloxazolo[5,4-*b*]pyridine **5**, the main photoproduct of **1** in the absence of trapping agents.[1]

It is to be noted that when the irradiation was carried out with the same reagents but at low temperature (−80°C),[5] formation of compounds **5** and/or **6** was not observed. The reaction gave, with a very low quantum yield (after 2 days of irradiation we recovered more than 80% of the starting material) the *N*-methylenamine **10**.[4] This compound was formed (Scheme 3) by malonate addition on the ketenimine **9**, which is the minor intermediate in the photorearrangements of isoxazolopyridines.[1b]

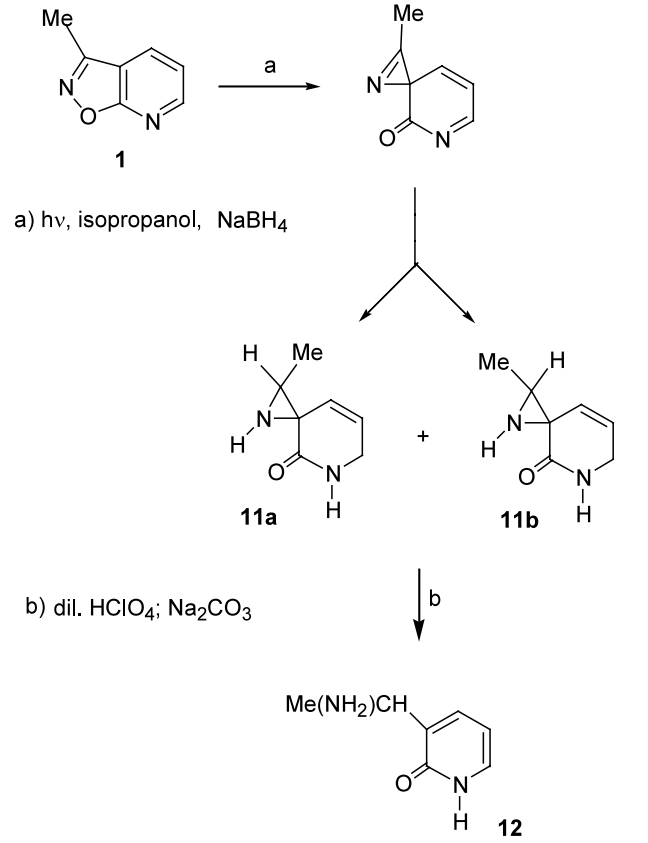
The above experiment gives more insight into the mechanistic aspect of the isoxazole photochemistry. The formation of spiroazirine intermediate, the precursor of oxazole system, is thermally activated, with an activation energy higher than for the corresponding ketenimine **9**.

iii. Sodium borohydride. Also this nucleophile is thermally inert towards **1** and, finally, it is able to trap the spiroazirine intermediate giving diasteroisomeric spiroaziridines **11a**,**b** (Scheme 4).[5] Such compounds were the main products when the photorearrangement was stopped at about 40% advancement. Otherwise, increasing amounts of the pyridones **7**[4] and **8**[4] (Scheme 3, path c) were also formed by reductive or solvolytic opening of the oxazole **5**. The progressive loss of trapping power of $NaBH_4$ due to decomposition in isopropanol is probably involved.

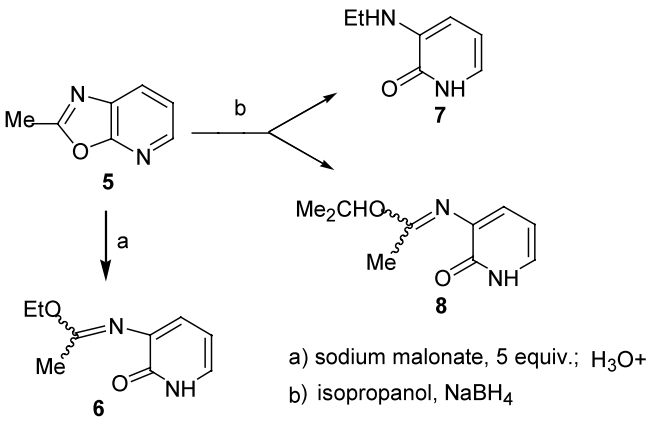
The structure of spiroaziridines **11a**,**b**, a new heterocyclic system, followed by ^1H and ^{13}C NMR data.[4] *E* configuration **11a** was assigned to the diastereoisomer which shows NOE increase of the olefin proton at 5.47 ppm by irradiation of the methyl at 1.15 ppm.



Scheme 3.



Scheme 4.



Scheme 2.

The importance of aziridines reactivity in modern organic synthesis is well documented.[7] For instance, regioselective opening of **11a**,**b** in the presence of perchloric acid[8] near quantitatively gave the amine **12** through the more stable carbocation intermediate.[9]

In conclusion, careful choice of the nucleophilic reagent and of the reaction conditions allowed us to trap the photochemical intermediates to attain the goal of synthesizing spiroaziridinopyridone compounds **11**.

The preliminary knowledge of the properties of intermediates, as lifetimes and activation energy, is mandatory to properly design the trapping reactions.

Acknowledgements

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2. Donati, D.; Ponticelli, F.; Bicchi, P.; Meucci, M. *J. Phys. Chem.* **1990**, *94*, 5271–5274.
3. To a nitrogen flushed solution of compound **1** (1 mmol) in ether (4 ml) ethereal alkyl lithium or methyl magnesium bromide was added as reported in Scheme 1. The reaction mixture was quenched with water and the organic phase evaporated to give the reaction product.
4. All new compounds gave satisfactory (within 0.3%) analytical data. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AC 200 spectrometer at 200.13 and 50.33 MHz, respectively. EI and FAB MS spectra were obtained with a VG 70 250S instrument; APCI MS spectra were recorded with a LCQ-DECA Thermo Finnigan instrument. Unless otherwise stated, the reactions are carried out until the starting material disappeared (TLC). The reported yields are relative to the reacted material.
3,6-Dimethylisoxazolo[5,4-b]pyridine **2**: yield 80%; mp 79–81°C; ^{1}H NMR ($CDCl_3$) δ: 2.60 (s, 3H, 3-CH_3), 2.72 (s, 3H, 6-CH_3), 7.20 (d, 1H, H_4), 7.91 (d, 1H, H_5); MS (EI), m/z: 148 (M^+), 133, 120, 119, 105, 92, 78, 64, 52.
3,6-Dimethyl-6,7-dihydro-isoxazolo-[5,4-b]pyridine **3**: yield 92%; unstable oil which gives on standing compound **2**; ^{1}H NMR ($CDCl_3$) δ: 1.28 (d, 3H, 6-CH_3), 2.11 (s, 3H, 3-CH_3), 4.54 (m, 1H, H_6), 4.67 (bs, 1H, NH), 5.03 (dt, 1H, H_5), 6.04 (dd, 1H, H_4); ^{13}C NMR ($CDCl_3$) δ: 9.66 (6-CH_3), 24.35 (3-CH_3), 51.70 (C_6), 89.70 (C_{3a}), 116.94 (C_4), 117.69 (C_5), 155.75 (C_3), 166.98 (C_{7a}); MS, m/z (FAB): 151 (M+1), 301 (M−H···M).
6-Methyl-3-(1-methylamino-ethylidene)-3,6-dihydro-1H-pyridin-2-one **4**: yield 90%; oil, ^{1}H NMR ($CDCl_3$) δ: 1.19 (d, 3H, 6-CH_3), 1.94 (s, 3H, CH_3), 2.94 (d, 3H, NH-$\underline{CH_3}$), 4.25 (m, 1H, H_6), 4.91 (dt, 1H, H_5), 6.19 (dd, 1H, H_4), 6.30 (bs, 1H, 1-NH), 9.80 (bs, 1H, $\underline{NH}$-CH_3); ^{13}C NMR ($CDCl_3$) δ: 13.35 (6-CH_3), 24.85 (CH_3), 29.99 ($NHCH_3$), 49.83 (C_6), 90.78 (C_3), 114.08 (C_5), 123.28 (C_4), 156.90 (C_7), 169.23 (C_2); MS (EI), m/z: 166 (M^+), 165, 151, 134, 122, 120, 106, 92, 65, 56, 42.
N-(2-Oxo-1,2-dihydro-pyridin-3-yl)-acetimidic acid ethyl ester **6**: yield 88%; mp 107–109°C; ^{1}H NMR ($CDCl_3$) δ: 1.31 (t, 3H, OCH_2 $\underline{CH_3}$), 1.88 (s, 3H, CH_3), 4.26 (q, 2H, OCH_2), 6.20 (t, 1H, H_5), 6.84 (dd, 1H, H_4), 7.09 (dd, 1H, H_6), 12.82 (bs, 1H, NH); MS (EI), m/z: 180 (M^+), 152, 135, 121, 110, 95, 82, 66, 55, 43.
3-Ethylamino-1H-pyridin-2-one **7**: yield 95%; mp 125–127°C; ^{1}H NMR ($CDCl_3$) δ: 1.28 (t, 3H, CH_3), 3.11 (q, 4H, CH_2), 4.75 (m, 1H, $\underline{NH}$-CH_2), 6.22 (t, 1H, H_5), 6.28 (dd, 1H, H_4), 6.68 (dd, 1H, H_6), 12.43 (bs, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 14.17 (CH_3), 37.61 (CH_2), 108.22, 109.42 (C_4 and C_5), 118.99 (C_6), 138.89 (C_3), 159.06 (C_2). MS (EI), m/z: 138 (M^+), 123, 110, 95, 81, 78, 68, 61, 54, 44.
N-(2-Oxo-1,2-dihydro-pyridin-3-yl)-acetimidic acid isopropyl ester **8**: yield 87%; mp 85–88°C; ^{1}H NMR ($CDCl_3$) δ: 1.34 (d, 6H, CH_3), 1.87 (s, 3H, CH_3), 5.26 (m, 1H, OCH), 6.23 (t, 1H, H_5), 6.87 (dd, 1H, H_4), 7.14 (dd, 1H, H_6), 12.96 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$) δ: 17.37, 21.72 (3 CH_3), 68.29 (OCH), 106.81, 107.68 (C_4 and C_5) 114.87–122.06 (C_6), 137.02, 139.00 (C_3 and $CH_3\underline{C}$=N), 169.01 (C_2). MS (EI), m/z: 194 (M^+), 152, 135, 111.
2-[Methylamino-(2-oxo-1,2-dihydro-pyridin-3-yl)-methylene]malonic acid diethyl ester **10**: advancing degree 20%; yield 90%; oil: ^{1}H NMR ($CDCl_3$) δ: 1.25 (br t, 6H, CH_3), 2.86 (d, 3H, $\underline{CH_3}$NH), 4.24 (br q, 4H, OCH_2), 6.29 (t, 1H, H_5), 7.36 (dd, 1H, H_4), 7.46 (dd, 1H, H_6), 9.74 (bq, 1H, $\underline{NH}CH_3$), 11.26 (br s, 1H, H_1); MS, m/z: 294 (M^+), 249, 222, 202, 175, 135.
E,Z-2-Methyl-1,5-diaza-spiro[2,5]oct-7-en-4-one **11**: advancing degree 20%; yield 85%; oil, mixture of diastereoisomers; NMR data were obtained from two chromatographic fractions enriched in **11a** or **11b**. **11a** (*E*-isomer): ^{1}H NMR ($CDCl_3$) δ: 1.15 (d, 3H, CH_3), 1.90 (bs, 1H, 1-NH), 2.60 (br q, 1H, H_2), 4.07 (m, 2H, $H_{6,6'}$), 5.47 (dt, 1H, H_8), 5.95 (dt, 1H, H_7), 6.75 (bs, 1H, 5-NH); ^{13}C NMR ($CDCl_3$) δ: 14.13 (CH_3), 38.49 (C_3), 39.72 (C_2), 43.35 (C_6), 124.70, 124.91 (C_7, C_8), 171.37 (C_4). MS, m/z: 138 (M^+), 137, 123, 109, 95. **11b** (*Z*-isomer): ^{1}H NMR ($CDCl_3$) δ: 1.43 (d, 3H, CH_3), 1.90 (bs, 1H, 1-NH), 2.12 (q, 1H, H_2), 4.07 (m, 2H, $H_{6,6'}$), 5.34 (dt, 1H, H_8), 5.84 (dt, 1H, H_7), 6.75 (bs, 1H, 5-NH). ^{13}C NMR ($CDCl_3$) δ: 12.90 (CH_3), 39.78 (C_3), 43.48 (C_2 and C_6), 123.03, 129.19 (C_7, C_8), 169.47 (C_4). MS, m/z: 138 (M^+), 137, 123, 109, 95.
3-(1-Amino-ethyl)-1H-pyridin-2-one **12**: yield 55%; cerous solid, mp 60°C: ^{1}H NMR (CD_3OD) δ: 1.35 (d, 3H, CH_3), 4.48 (q, 1H, H_7), 6.47 (t, 1H, H_5), 7.58 (dd, 1H, H_4), 7.66 (dd, 1H, H_6); ^{13}C NMR (CD_3OD) δ: 17.64 (C_8), 66.82 (C_7), 108.05 (C_5), 129.40 (C_3), 136.64 (C_6), 141.06 (C_4), 163.00 (C_2). MS (APCI), m/z: 139 (MH$^+$), 122.
5. Solutions of compound **1** in a quartz tube with the suitable solvent and nucleophile [as indicated in Scheme 2 (path c), Schemes 3 and 4] were irradiated with a low pressure

mercury lamp (253.7 nm). Chromatographic separations of the evaporated reaction mixture gave compounds reported in the schemes.
6. To a solution of sodium malonate (1 mmol) in ethanol (5 ml) or $NaBH_4$ (2 mmol) in propan-2-ol (5 ml) the oxazolopyridine **5** was added. Solvent was removed to give (Scheme 2, path b) compound **6** or (Scheme 2, path c) compounds **7** and **8** which were separated on silica gel column with $CHCl_3/CH_3OH$ 95/5 as eluent.
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8. A solution of spiroaziridines **11** (50 mg) in THF (3 ml) was treated with 70% perchloric acid (0.1 ml). Solvent was neutralized with saturated sodium carbonate and evaporated in vacuo. The residue was column chromatographed with $CHCl_3/CH_3OH$ 4/1 to give compound **12**.
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