A Practical Photochemically Induced Method for N–N Bond Cleavage of N,N-Disubstituted Hydrazides

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Abstract: The development of an unprecedented methodology based upon direct photolysis of N,N-disubstituted hydrazides to secure N–N bond cleavage and to trigger the formation of NH-free lactams has been disclosed.

Key words: cleavage, photochemistry, synthetic methods, hydrazides, lactams

The cleavage of the nitrogen–nitrogen bond of hydrazine derivatives and of their *N*-acyl-protected forms is an area of current interest in chemistry and the development of synthetic methodologies to break N–N bonds and trigger off the formation of the NH free compounds is currently the object of synthetic endeavour.[1] In particular, this cleavage appears as a key transformation in a variety of asymmetric syntheses of amines and amino acids which are important pharmacophores in numerous biologically active compounds.[2] Organic chemists have at their disposal a number of synthetic methods to secure the N–N bond cleavage of N,N-disubstituted hydrazines but few general methods have demonstrated broad synthetic utility. Several reductive methods have been disclosed for this chemical transformation but they are strongly conditioned by the structural profile of the molecules, nonaromatic hydrazines being more resistant than the aromatized ones.[3] The most widely used technique hinges upon catalytic hydrogenolysis over Raney nickel,[4] platinium-[5] or palladium-based catalysts.[6] Alternative methods based upon electroreductive process, electron transfer from metals, for example, Na or Li/NH_3,[7] or by making use of SmI_2 with HMPA as co-solvent[8] and diborane[9] have also been established. Catalytic processes based upon the use of polynuclear ruthenium clusters,[10] ruthenium-based complexes,[11] and tungsten or molybdenium complexes[12] have been recently reported. And finally, the N–N bond cleavage of N,N-disubstituted hydrazines has been incidentally observed upon treatment with naphthol analogues under simply thermal conditions.[13] To circumvent limitations and difficulties related to the strong reducing conditions that are incompatible with a number of functionalities or protecting groups, alternative oxidative methods for the N–N bond cleavage of N,N-disubstituted hydrazides by peracids have been recently developed by J. M. Lassaletta and co-workers.[14] All these reactions have been claimed to proceed with varying degrees of success and some of them may be fraught with difficulties associated with the lack of reactivity, the acidic or basic conditions required and the use of hazardous reagents, namely hydrogen under pressure even though hydrogenations using in situ generated hydrogen have been also described.[15] And finally, partial racemization of neighboring stereogenic centers has been sometime observed upon this ultimate chemical operation.

These results prompt us to develop a mild, efficient, and versatile method for the deamination of hydrazides through N–N bond cleavage that is based upon the use of light as an energy source. Although well established in biochemistry, photochemically removable groups have been scarcely used in organic synthesis.[16] Such groups are particularly interesting since they do not need acidic, basic, or metal-assisted activation for cleavage. Indeed photochemical substrate activation often occurs without additional reagents and under especially mild conditions that renders this process particularly appealing in the context of green chemistry.

A number of structurally and constitutionally diverse models **1a**–**h** were selected for this study and are portrayed in Table 1. SAMP-hydrazides **1a**–**e** (entries 1–5) were favored since this chiral auxiliary ranks high in the hierarchy of temporary activating agents involved in asymmetric syntheses of a wide range of amino derivatives.[17]

Experimentally, a solution of the appropriate hydrazide **1** (0.2 mmol) dissolved in toluene (5 mL) and freshly distilled *n*-hexane (200 mL) was purged by bubbling argon through it for 30 minutes. Photolyses were carried out in a water-cooled quartz reactor equipped with dry argon inlet and magnetic stirrer. The solution was placed in a Rayonet RPR 208 photochemical reactor containing eight RUL 2537 Å lamps. Degassing and stirring of the solution was maintained until complete consumption of the starting material (TLC). To remove traces of tarry material the solution was passed through a Celite pad that was subsequently washed with CH_2Cl_2 (5 mL). The solvents were removed and the residual photoproduct was chromatographied on a silicagel column (Merck, Kieselgel 0.040–0.063 mm particle size) using ethyl acetate (for **2d**,**e**,**h**) and mixtures of ethyl acetate–hexanes (for **2a**–**c**,**f**,**g**), as eluent. A representative series of compounds, which have

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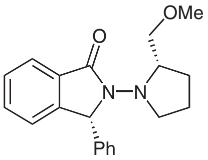
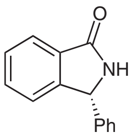
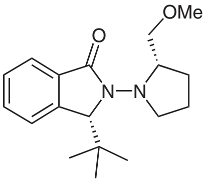
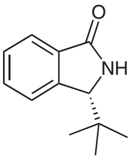
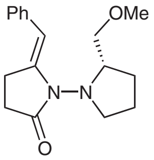
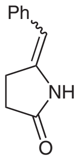
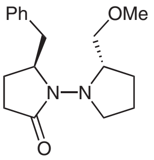
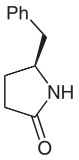
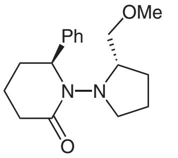
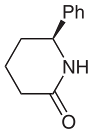
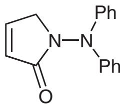
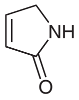
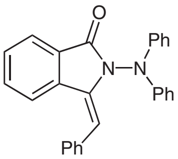
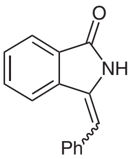
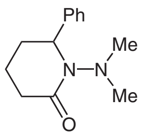
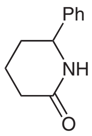
been prepared by this technique, are presented in Table 1 where it may be seen that this simple procedure affords satisfactory yields of the NH-free lactams **2a–h**.

Examination of Table 1 deserves some comments. Longer irradiation times were required for N–N bond cleavage of aromatic hydrazides (entries 1, 2) and constitutionally diverse enehydrazides (entries 3, 6, 7) than for saturated analogues (entries 4, 5, 8). The photochemical process spared the stereochemistry of the stereogenic centers α to the nitrogen atom embedded in the structurally different models (entries 1, 2, 4, 5). Thus enantiopure compounds **2a**,**b**,**d**,**e** were obtained as single enantiomers by photolysis of the parent diastereopure compounds **1a**,**b**,**d**,**e**. Unexpectedly, the photochemically-induced release of the $N(Ph)_2$ moiety (entries 6, 7) was significantly more difficult than for the structurally diverse cyclized or opened N,N-dialkyl units (entries 5–8). This synthetic strategy tolerates the presence of endo- and exocyclic unsaturated moieties (entries 6, 7) and photolysis of enehydrazides **1c**,**g** was accompanied with partial *E*/*Z* photoisomerization of the corresponding free NH enelactames **2c**,**g** (entries 3, 7). In the case of diarylated compounds **1f**,**g** (entries 6, 7) the presence of tetraphenylhydrazine could be identified in the crude photoproduct so that one can reasonably assume that the photochemical process involves homolytic N–N bond scission. This mode of cleav-

Table 1 Photoproducts **2a–h** from N–N Bond Cleavage of Hydrazides **1a–h**

Entry	Starting hydrazide	1a–h	Photoproduct	2a–h	Irradiation time (h)	Yield (%)
1		**1a**[18]		**2a**[18]	10	64
2		**1b**[18]		**2b**[18]	10	66
3		**1c**[19]		**2c**[20]	8	62
4		**1d**[19]		**2d**[19]	8	69
5		**1e**[21]		**2e**[21]	6	71
6		**1f**[22]		**2f**[23]	10	63
7		**1g**[24]		**2g**[26]	12	61
8		**1h**[27]		**2h**[21]	6	76

age is a logical consequence of the low energy requirements of the nitrogen–nitrogen bond.[28] Dissipation of carbonyl excitation energy upon irradiation at 254 nm is sufficient to induce rupture of the least stable bond in the vicinity of the chromophore, so that the primary photoreaction is the N–N cleavage. Unfortunately radical recombination precludes recovery of the chiral auxiliary (entries 1–5).

In summary a mild, efficient, and conceptually new synthetic method that enriches the repertoire of the synthetic approaches to the cleavage of N–N bond of N,N-disubstituted hydrazides has been disclosed. In practice, this methodology that hinges upon a photo-induced nonoxidative N–N bond cleavage giving rise to secondary amides is advantageous over traditional methods since it tolerates the presence of functionalities sensitive to reducing conditions and is compatible for substrates equipped with stereogenic centers. We also believe that this strategy could be applied for the deamination of a variety of substrates and might find wide application in preparation of many valuable aminated compounds.

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(24) 2-Diphenylamino-3-[1-phenylmeth-(*E*)-ylidene]-2,3-dihydroisoindol-1-one (**1g**) was prepared from 2-diphenylamino-isoindole-1,3-dione[25] and benzylmagnesium bromide following a reported procedure.[19]
Analytical Data
Mp 225–226 °C. ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 6.93$ (s, 1 H, CH=), 7.05 (t, $J = 7.0$ Hz, 2 H, H$_{\text{arom}}$), 7.20–7.51 (m, 15 H, H$_{\text{arom}}$), 7.55 (d, $J = 7.6$ Hz, 1 H, H$_{\text{arom}}$), 7.91 (d, $J = 7.5$ Hz, 1 H, H$_{\text{arom}}$) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): $\delta = 111.7$, 119.5 (4 × CH), 123.3, 123.5 (2 × CH), 124.0, 128.0, 128.5, 128.7 (2 × CH), 129.4 (4 × CH), 129.5 (2 × CH), 129.7, 133.1, 132.5, 133.7, 134.6, 144.6 (2 × C), 164.5 (CO) ppm. Anal. Calcd for $C_{27}H_{20}N_2O$: C, 83.48; H, 5.19; N, 7.21. Found: C, 83.62; H, 5.12; N, 7.00.

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(27) 1-Dimethylamino-6-phenylpiperidin-2-one (**1h**) was prepared from benzaldehyde hydrazone [*N*,*N*-dimethyl-*N*′-(1-phenylmethylidene)hydrazine] following a previously described synthetic sequence:[21] addition of allyllithium, amidation with acryloyl chloride, RCM, hydrogenation (Pd/C).

Analytical Data
Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.54–1.88 (m, 3 H), 2.04–2.11 (m, 1 H), 2.47–2.55 (m, 1 H), 2.75 (s, 6 H, 2 × CH_3), 4.65 (t, J = 5.4 Hz, 1 H), 7.25–7.31 (m, 5 H, H_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.9, 32.8, 34.0, 64.8, 126.9, 127.3, 128.3, 142.4, 170.7 (CO) ppm. Anal. Calcd for $C_{13}H_{18}N_2O$: C, 71.53; H, 8.31; N, 12.83. Found: C, 71.71; H, 8.49; N, 13.09.

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