

<p>Université des Sciences et Technologies de Lille</p> 		<p>UMR CNRS 8009 COM</p>  <p>dépasser les frontières</p> <p>Synthèse Organique, Réactivité, Fonctionnalisation</p>
---	--	---

Photochemically-Induced N-N Bond Cleavage of *N,N*-Disubstituted Hydrazides

Stéphane Lebrun, Axel Couture,* Éric Deniau, Pierre Grandclaudon

UMR CNRS 8009 "Chimie Organique et Macromoléculaire",
Université des Sciences et Technologies de Lille 1, Laboratoire de Chimie Organique Physique,
Bâtiment C3(2), F-59655 Villeneuve d'Ascq Cedex, France
[*Axel.Couture@univ-lille1.fr](mailto:Axel.Couture@univ-lille1.fr)

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 off the formation of NH free lactams has been disclosed.

Introduction

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]. The most widely used technique hinges upon catalytic hydrogenolysis over Raney nickel [3], platinum [4] or palladium-based catalysts [5]. Alternative methods based upon electroreductive process, electron transfer from metals, e.g. Na or Li/NH₃ [6], or by making use of SmI₂ with HMPA as co-solvent [7] and diborane [8] have also been established. Catalytic processes based upon the use of polynuclear ruthenium clusters [9], ruthenium-based complexes [10], and tungsten or molybdenum-complexes [11] have been recently reported. However these reactions have been 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.

These results prompted 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 [12]. 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.

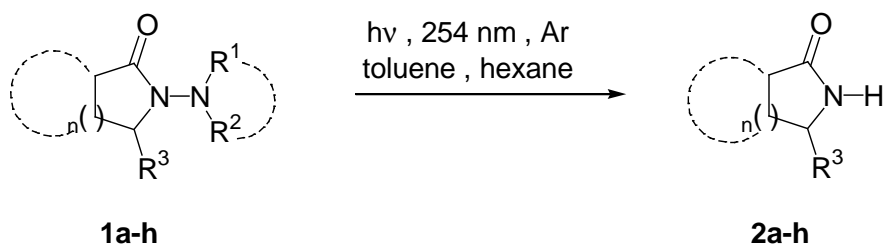
Results and Discussion

A number of structurally and constitutionally diverse hydrazides **1a-h** were selected for this study and are portrayed in Table 1.

SAMP-Hydrazides (**1a-e**) 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 [13].

1. Irradiation Conditions

A solution of the appropriate hydrazide **1a-h** (0.2 mmol) dissolved in toluene (5 mL) and freshly distilled *n*-hexane (200 mL) was purged by bubbling argon through it for 0.5 h. 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).



Scheme 1.

2. Comments on Table 1

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**.

Longer irradiation times were required for N-N bond cleavage of aromatic hydrazides (entries 1, 2) and constitutionally divers enehydrazides (entries 3, 6, 7) than for saturated analogues (entries 4, 5, 8).

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 enlactames **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.

Table 1.

Entry	Starting Hydrazide		Irradiation Time (h)	Photoproduct		Yield (%)
1		1a	10		2a	64
2		1b	10		2b	66
3		1c	8		2c	62
4		1d	8		2d	69
5		1e	6		2e	71
6		1f	10		2f	63
7		1g	12		2g	61
8		1h	6		2h	76

Conclusion

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 non-oxidative 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.

References

- [1] (a) Hinman, R. L. *J. Org. Chem.* **1957**, *22*, 148. (b) Feuer, H.; Brown, F., Jr. *J. Org. Chem.* **1970**, *35*, 1468. (c) Denmark, S. E.; Nicaise, O.; Edwards, J. P. *J. Org. Chem.* **1990**, *55*, 6219. (d) Alonso, F.; Radivoy, G.; Yus, M. *Tetrahedron* **2000**, *56*, 8673. (e) Fernandez, R.; Ferrete, A.; Lassaletta, J. M.; Llera, J. M.; Monge, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 2893. (f) Friestad, G. K.; Ding, H. *Angew. Chem., Int. Ed.* **2001**, *40*, 4491. (g) Enders, D.; Funabiki, K. *Org. Lett.* **2001**, *3*, 1575. (h) Sapountzis, I.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 897. (i) Ding, H.; Friestad, G. K. *Org. Lett.* **2004**, *6*, 637. (j) Sinha, P.; Kofink, C. C.; Knochel, P. *Org. Lett.* **2006**, *8*, 3741.
- [2] (a) Salvatore, R. N.; Yoon, C. H.; Jung, K. W. *Tetrahedron* **2001**, *57*, 7785. (b) Kienle, M.; Dubbaka, S. R.; Brade, K.; Knochel, P. *Eur. J. Org. Chem.* **2007**, 4166.
- [3] (a) Enders, D.; Schubert, H. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 365. (b) Egli, M.; Hoesch, L.; Dreiding, A. S. *Helv. Chim. Acta* **1985**, *68*, 220. (c) Denmark, S. E.; Weber, T.; Piotrowski, D. W. *J. Am. Chem. Soc.* **1987**, *109*, 2224. (d) Thiam, M.; Chastrette, F. *Tetrahedron Lett.* **1990**, *31*, 1429. (e) Alexakis, A.; Lensen, N.; Mangeney, P. *Synlett* **1991**, 625. (f) Baker, W. R.; Condon, S. L. *J. Org. Chem.* **1993**, *58*, 3277; (g) A. Solladié-Cavallo, A.; Bonne, F. *Tetrahedron: Asymmetry* **1996**, *7*, 171.
- [4] Claremon, D. A.; Lumma, P. K.; Phillips, B. T. *J. Am. Chem. Soc.* **1986**, *108*, 8265.
- [5] (a) Takahashi, H.; Tomika, K.; Noguchi, H. *Chem. Pharm. Bull.* **1981**, *29*, 3387. (b) Kim, Y. H.; Choi, J. Y. *Tetrahedron Lett.* **1996**, *37*, 5543.
- [6] (a) Rautenstrauch, V.; Delay, F. *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 726. (b) J. M. Mellor, N. M. Smith, *J. Chem. Soc.* **1984**, 2927.
- [7] (a) Burk, M. J.; Feaster, J. E. *J. Am. Chem. Soc.* **1992**, *114*, 6266. (b) Atkinson, R. S.; Kelly, B. J.; Williams, J. *Tetrahedron* **1992**, *48*, 7713.
- [8] (a) Enders, D.; Lochtman, R.; Meiers, M.; Müller, S.; Lazny, R. *Synlett* **1998**, 1182. (b) Suzuki, H.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **1994**, *35*, 6119. (c) Suzuki, H.; Aoyagi, S.; Kibayashi, C. *J. Org. Chem.* **1995**, *60*, 6114.
- [9] (a) Takei, I.; Dohki, K.; Kobayashi, K.; Suzuki, T.; Hidai, M. *Inorg. Chem.* **2005**, *44*, 3768. (b) Martínez, S.; Trepát, E.; Moreno-Mañas, M.; Sebastian, R. M.; Vallribera, A.; Mata, I.; Molins, E. *ARKIVOC* **2007**, (iv), 170.
- [10] Nakajima, Y.; Suzuki, H. *Organometallics* **2003**, *22*, 959.
- [11] Schrock, R.; Glassman, T. E.; Vale, M. G. *J. Am. Chem. Soc.* **1991**, *113*, 725.
- [12] Hoffmann, N. *Chem. Rev.* **2008**, *108*, 1052.
- [13] Job, A.; Janeck, C. F.; Bettray, W.; Peters, R.; Enders, D. *Tetrahedron* **2002**, *58*, 2253.