Tetrahedron Letters 53 (2012) 2822–2824

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Solvent dependency of the yield of an N-monosubstituted diaziridine: a GC–MS study

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ARTICLE INFO

Article history:
Received 29 February 2012
Revised 21 March 2012
Accepted 26 March 2012
Available online 4 April 2012

Keywords:
Diaziridines
Solvent parameters
GC–MS
Optimization

ABSTRACT

Due to the growing importance of diaziridines in the drug design and the increasing popularity of diazirines as carbene precursors, the solvent influence on the yield of an N-monosubstituted diaziridine has been studied. It was observed that data points within every solvent class are clustering and the yield in general is the highest in apolar aprotic solvents.

Diaziridines without alkyl substituents on the nitrogen atoms are fairly labile and reactive due to their strain, and the reactivity is enhanced when the nitrogens are unsymmetrically substituted. These facts make diaziridines powerful alkylating agents and such compounds have therefore been tested as inhibitors of enzymes such as monoamine oxidase (MAO)[1] and α-glycosidase[2], respectively. This could provide a medicinal treatment against psychic disorders and diabetes mellitus type 2, respectively.

Moreover, diaziridines can be used in heterocyclic chemistry as building blocks for the synthesis of hetero atom-containing five-membered rings.[3] Finally, oxidation of C,C-disubstituted diaziridines provides easy access to diazirines,[4] which are popular precursors for the generation of carbenes for example in photoaffinity labeling experiments.[4f]

Most C,C-disubstituted diaziridines[4g] are available only in poor to moderate yields.[5–10] This is often due to steric hindrance caused by substituents and probably stereoelectronic factors that are not known in detail. Thus, it is desirable to have a better understanding of the reaction in general and the importance of the solvent used to improve yields. Therefore, it seemed prudent to examine the solvent influence on diaziridine synthesis with respect to the yield.

From the literature it is known that in general diaziridine syntheses with hydroxylamine-*O*-sulfonic acid (HOSA) have been performed either in water,[11a] methanol,[11b] or pure liquid ammonia.[11c]

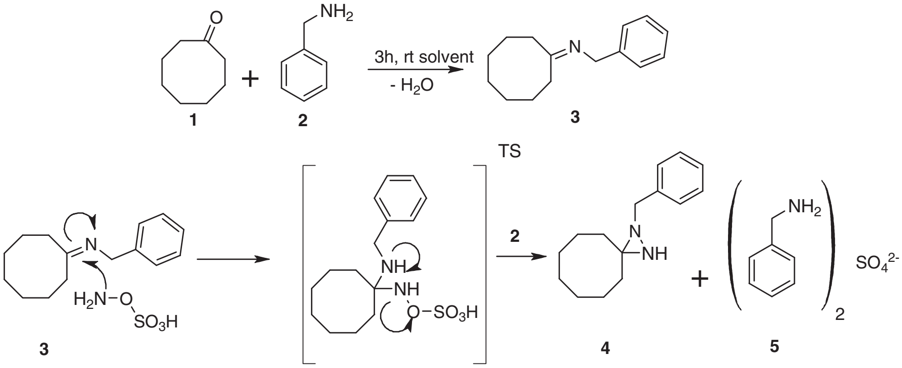

Figure 1. Proposed mechanism of formation of diaziridine **4**.

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http://dx.doi.org/10.1016/j.tetlet.2012.03.105

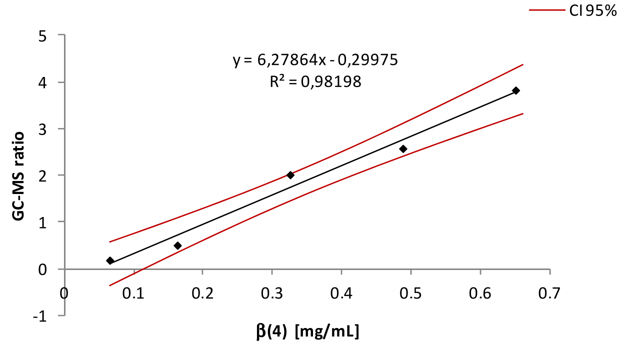

Figure 2. Calibration curve plot showing the dependency of the GC–MS ratio according to the mass concentration of **4**.

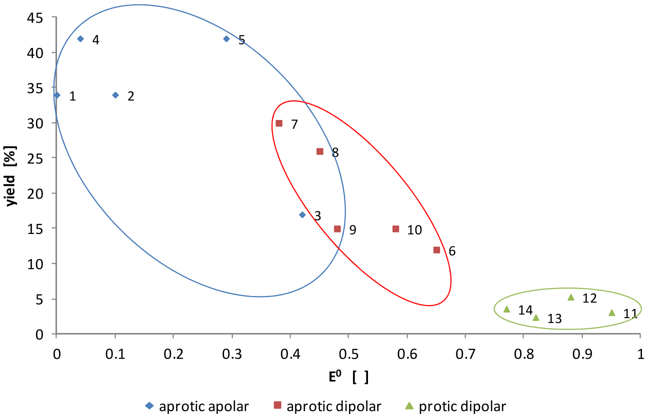

Figure 3. Correlation of eluting power versus yield.

The synthesis of diaziridines was reported by three research groups between 1959 and 1961.[11] All these groups carried out the reactions in methanol–ammonia solutions. In 1961 Schmitz and Ohme made diaziridines commercially available.[11k]

As for the mechanism of diaziridine generation these three research groups invoked the intermediate formation of an imine, which is nucleophilically attacked by HOSA. Thereby an aminal is formed, which eliminates the very good leaving group hydrogen sulfate via an intramolecular nucleophilic substitution reaction followed by a proton elimination step (Fig. 1).

1-Benzyl-1,2-diazaspiro[2.7]decane (**4**) was used as model diaziridine (Fig. 1). It is obtained from the reaction of cyclooctanone (**1**), benzylamine (**2**), and HOSA, which was performed similar to the procedure of Schmitz and Ohme.[11k,12]

The reason for this decision was based on the fact that the yield of the corresponding C,C-disubstituted diaziridine, 1,2-diazaspiro[2,7]decane, with 22% is quite low.[5] Thus, any improvement or worsening of this yield should easily be detected. In order to cover important solvent properties, five different solvents of the following solvent classes (aprotic apolar, aprotic dipolar, and protic dipolar) were used: pentane (*n*Pen), hexane (*n*Hex), dichloromethane (DCM), cyclohexane (*c*Hex), toluene (Tol), acetonitrile (MeCN), diethyl ether (Et_2O), tetrahydrofuran (THF), methyl *tert*-butyl ether (TBME), ethyl acetate (EA), methanol (MeOH), ethanol (EtOH), isopropyl alcohol (*i*PrOH), 1-butanol (*n*BuOH), 1,4-butanediol (*n*Bu(OH)$_2$).

For the determination of yields, a GC–MS calibration curve with xylene as internal standard was made. For this purpose one reaction batch was worked up, the content of diaziridine **4** was determined via ^{1}H NMR with dimethyl malonate as internal standard and the crude product was used for the construction of the GC–MS calibration curve. In order to verify the yields of all other reaction batches, the diaziridine content from each reaction mixture was determined by using this curve.

Figure 2 demonstrates the linear dependency between the GC–MS ratio (r_{GC-MS}) and the diaziridine concentration. With a value of 0.982 the regression coefficient R^2 is quite satisfactory. Furthermore, the confidence intervals (CI) at a confidence level of 95% are given.

In order to find out how diaziridine yields depend on the solvent used, yields were assigned for four solvent parameters: the relative dielectric constant (ε_{rel})[13], the dipole moment (μ)[13], the eluting power (E^0)[14], and the calculated polarizability (cα) (calculated with ChemSketch 12.0). No correlation could be observed between any of those solvent parameters and the calculated yields. One of these correlations is depicted in Figure 3. All other correlations are given in the Supplementary data (see Figs. 4–6). The values for the data points are given in Table 1.

It turns out that none of the solvent parameters used is able to describe the obtained yields by its own. However, from Table 1 it is obvious that the experimentally observed diaziridine yield is the highest in apolar aprotic solvents. With a yield of 42% it is at its maximum in *c*Hex and Tol, which is an enormous improvement compared to the usually used solvent MeOH, where the yield amounts to 3.1% only (Table 1). No literature data for the yield of **4** in MeOH as solvent is available.

In conclusion, for diaziridine formation from ketones, benzylamine, and HOSA it is recommended to apply apolar aprotic sol-

Table 1
Solvents used, their parameters,[13,14] and experimentally observed GC–MS ratios

Entry	Solvent	[14]E^0	cα (Å^3)	μ[13] (D)	[13]ε_{rel}	r_{GC-MS}	Yield[a] (%)
1	*n*Pen	0.00	10.0	0.00	1.84	0.692	34 ± 0.2
2	*n*Hex	0.01	11.8	0.00	1.88	0.677	34 ± 0.2
3	DCM	0.42	6.49	1.55	8.93	0.192	17 ± 0.2
4	*c*Hex	0.04	11.0	0.00	2.02	0.927	42 ± 0.2
5	Tol	0.29	12.3	0.429	2.38	0.905	42 ± 0.2
6	MeCN	0.65	4.45	3.44	37.5	0.039	12 ± 0.2
7	Et_2O	0.38	8.85	1.30	4.34	0.538	30 ± 0.2
8	THF	0.45	7.95	1.75	7.60	0.458	26 ± 0.2
9	TBME	–	10.7	–	4.50	0.139	15 ± 0.2
10	EA	0.58	8.86	1.88	6.00	0.127	15 ± 0.2
11	MeOH	0.95	3.26	1.70	32.2	0.309	3.1 ± 0.03
12	EtOH	0.88	5.09	1.70	24.5	0.613	5.3 ± 0.03
13	*i*PrOH	0.82	6.91	1.66	19.9	0.135	2.4 ± 0.03
14	*n*BuOH	0.77	8.77	1.75	17.5	0.335	3.6 ± 0.03
15	*n*Bu(OH)$_2$	0.42	11.0	3.98	31.5	0.039	2.0 ± 0.03

[a] Yields were calculated from the calibration curve of Figure 2. Measurement uncertainties were calculated via Gaussian's propagation of uncertainty.

vents such as cyclohexane and toluene. Use of such solvents in the reaction to prepare diaziridine **4** clearly leads to superior results, when compared to reactions in water, methanol, or pure liquid ammonia as was suggested originally.[11a–c]

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.03.105.

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12. *General procedure for the preparation of* ***4***: 1.00 mol equiv of cyclooctanone (**1**) was dissolved in dry solvent at ambient temperature to yield a concentration of about 0.5 M. 3.15 mol equiv of benzylamine (**2**) were added and the resulting turbid solution was stirred for 3.5 h. After that 1.05 mol equiv of HOSA were added at once. After 10 min, 9 μL of the reaction mixture were taken up with a Gilson pipette and added to a solution consisting of 900 μL internal GC–MS standard solution (0.25 mg/mL of xylene in EA) and 91 μL of pure EA placed into a GC–MS vial.

    For the determination of the NMR yields, the reaction mixture was filtered, evaporated on a rotary evaporator and a small weighted amount of the remaining oil was mixed with a small weighted amount of the internal NMR standard (diethyl malonate) and the resulting mixture was dissolved in $CDCl_3$.
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