

Trimethylamine N-oxide: A Novel Reagent for the Promotion of the Retro-Aldol Reaction of R106-1 (LY295337)

Michael J. Rodriguez* and Mark J. Zweifel

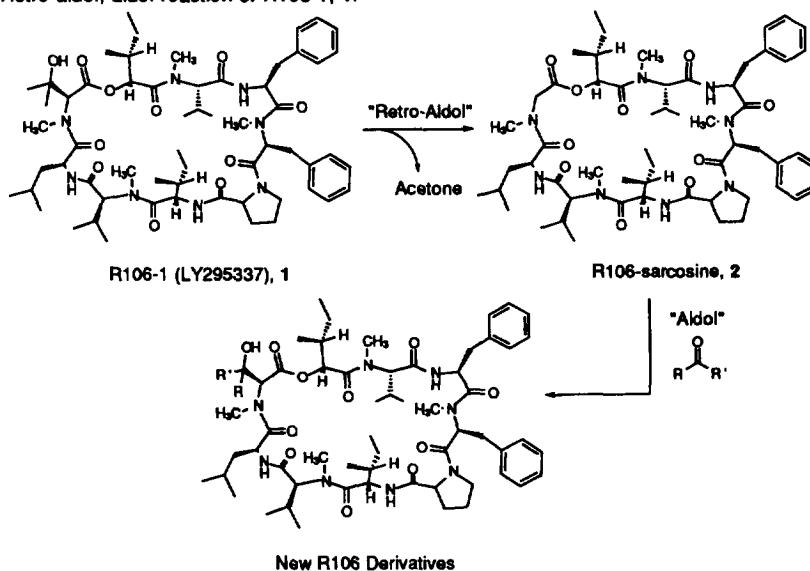
Infectious Diseases Research, Lilly Research Laboratories,
 Eli Lilly and Company, Indianapolis, Indiana 46285, USA

Abstract: The retro-aldol reaction of R106-1 (LY295337), **1** using trimethylamine N-oxide (TNO) facilitates the removal of the tertiary hydroxy group generating R106-sarcosine, **2** a key synthetic intermediate. The reagent is highly reproducible and provides high yields with no major side products. A side by side comparison of TNO vs. traditional bases is described.
 Copyright © 1996 Elsevier Science Ltd

R106-1 (LY295337), **1** is part of a family of antifungal agents produced by fermentation of the microorganism *Aureobasidium pullulans* R106.¹ R106-1 is the most potent and abundant of the eighteen factors and is effective against the clinically important fungal pathogen, *Candida albicans*.² These compounds have been the target of much synthetic interest not only due to their potent antifungal properties but also because of their unique structure.³ The tertiary alcohol is the only functional group available for direct modification. It has been recognized that this site is also important for biological activity.⁴ We recently reported⁵ a semisynthetic approach to utilize the tertiary alcohol to generate new hydroxylated analogs via a tandem retro-aldol, aldol reaction (Scheme 1) but the methodology to synthesize the key synthetic intermediate R106-sarcosine, **2** was complicated by side reactions. In our attempts to optimize the formation of **2**, we discovered that trimethylamine N-oxide dihydrate (TNO·2H₂O) was effective in promoting the retro-aldol reaction (In addition, TNO was effective in removing a β-hydroxy group from a non-peptide substrate⁶).

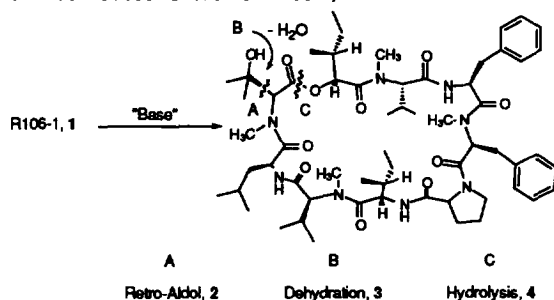
TNO is a well known hydroxylating reagent⁷ but its use as an "organic base" is rare. Obtaining suitable quantities of **2** using traditional reagents⁸ such as NaOH/DMSO gave mixed results. The product distribution was highly variable:

Scheme 1. Retro-aldol, aldol reaction of R106-1, **1**.



substantial amounts of dehydration, **3** (R106-18) and lactone hydrolysis, **4** by-products were obtained⁹ (Scheme 2). Unlike these reagents, TNO-2H₂O promotes the retro-aldol reaction in excellent yields. The results of the retro-aldol reaction of R106-1 using traditional bases and TNO are summarized in Table 1. We observed major differences between the commercially available nonhydrate and dihydrate¹⁰ TNO reagents in promoting the retro-aldol reaction. The non-

Scheme 2. Product profile of base induced reaction of R106-1, **1**.



hydrated reagent appears to be less effective in maximizing yields of R106-sarcosine [TNO-2H₂O vs. TNO (DMF/70°C) 87% vs. 54%]. Longer reaction times were required to drive the reaction to completion and we isolated substantial amounts of dehydration product, **3**. The isolation of **3** is observed with TNO-2H₂O (ACN/70°C) but accounts for only 3% of the overall reaction mixture. The use of aryl and cyclic N-oxides [i.e. pyridine and methylmorpholine N-oxides] were investigated but were found to be ineffective in promoting the retro-aldol reaction.

Table 1. TNO vs. Traditional Bases.

Reagent	Solvent	Temp °C	Rxn Time	% 2 / 3 / 4 ^a
TNO-2H ₂ O	DMF	100	3h	70 / 30 / 0
	DMF	70	12h	87 / 13 / 0
	DMF/H ₂ O (4:1)	70	18h	83 / 17 / 0
	ACN	70	18 h	97 / 3 / 0
TNO (nonhydrate)	DMF	70	days	54 / 46 / 0
Triethylamine	DMF	70	o.n.	0 / 0 / 0
NaH	THF	rt	1-2 h	33 / 33 / 0
Trimethylamine (75% aq)	DMF	70	o.n.	33 / 33 / 0
Trimethylamine (anhydrous)	DMF	70	days	0 / 0 / 0
Potassium t-butoxide	DMSO	rt	30 min	70 / 2 / 28
DBU	THF	rt	days	0 / 0 / 0
NaOH	DMSO	rt	40 min	77 / 2 / 21

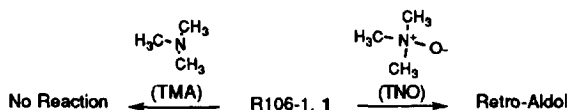
^aHPLC percentages of crude reaction mixtures.

Typically, the reaction required heating R106-1 with 5-10 molar equivalents of TNO-2H₂O in an aprotic solvent such as DMF or ACN at 70°C for 12-18 h after which the mixture was allowed to cool to room temperature and was concentrated under vacuum to ~1/2 volume. The crude residue was dissolved in 200 mL ethyl acetate and washed with cold 10% aq. HCl followed by saturated aq. NaHCO₃ and brine. The organic layer was concentrated and the crude residue was purified by C-18 reverse phase preparative HPLC. Acetonitrile gave the best results yielding 97% R106-

sarcosine, **2** (92% isolated yield).¹¹ We found the ideal temperature to be 70°C. The reaction was somewhat sluggish at temperatures below 60°C. Reaction times were substantially reduced with higher temperatures, but temperatures nearing 100°C provided higher yields of by-products.

We attempted to promote the retro-aldol reaction using traditional bases such as potassium *t*-butoxide, NaOH and NaH. Although these reagents were used catalytically, higher yields of dehydration and lactone hydrolysis by-products were observed. Base catalyzed reactions using tertiary amines were also investigated. We initially suspected that trimethylamine was generated *in situ* under the reaction conditions and was responsible for the retro-aldol reaction since TNO was described in the literature to decompose into secondary and tertiary amines at elevated temperature.¹² However, the use of commercially available anhydrous trimethylamine gave only starting material (Scheme 3) unless water was added to the reaction [75% aqueous TMA gave 33% retro-aldol, See Table 1]. Unlike traditional bases, where

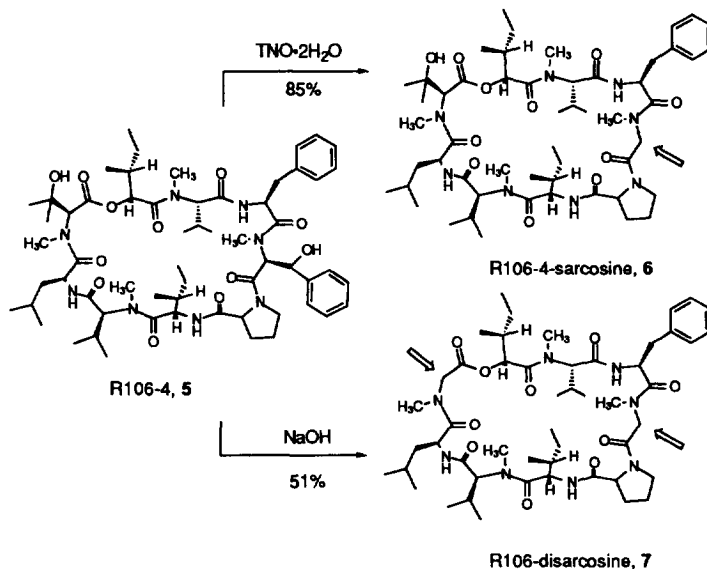
Scheme 3.



lactone hydrolysis has been promoted by the presence of trace amounts of water, the addition of water did not have a detrimental effect on the yields of **2** with TNO-2H₂O. The addition of water ($\leq 20\%$) decreased the reaction rate with only a slight increase in dehydration product, **3**.

An additional feature of TNO-2H₂O was observed with R106-4, **5** a fermentation factor containing two β -hydroxy carbonyl functional groups¹³ (Scheme 4). In this case, TNO-2H₂O selectively converted the β -hydroxy-phenylalanine

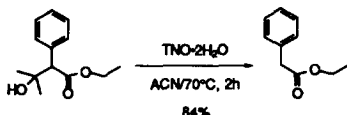
Scheme 4.



to sarcosine over the β -hydroxy-valine to produce R106-4-sarcosine, **6** (85% isolated yield). In contrast, NaOH/DMSO produced low yields of the R106-disarcosine derivative, **7**.¹⁴ We suspected that the selectivity difference was due in large part to the accessibility of the RO-H proton towards the reagents. The results thus far suggested that TNO-2H₂O was responsible for promoting the retro-aldol reaction. Unlike the traditional reagents, such as NaOH, KOH, triethylamine or DBU, TNO-2H₂O was found to be a mild and selective reagent for the removal of β -hydroxy groups while in the presence of other functional groups.

References and Notes.

1. Yoshikawa, Y.; Ikai, K.; Umeda, Y.; Ogawa, A.; Takesako, K.; Kato, I.; Naganawa, H. *J. Antibiotics* **1993**, *46* (9), 1347-1354.
2. Takesako, K.; Kuroda, H.; Inoue, T.; Haruna, F.; Yoshikawa, Y.; Kato, I.; Uchida, K.; Hiratani, T.; Yamaguchi, H. *J. Antibiotics*, **1993**, *46* (9), 1414-1420.
3. (a) Kurome, T.; Inami, K.; Inoue, T.; Ikai, K.; Takesako, K.; Kato, I.; Shiba, T. *Chem. Lett.*, **1993**, *11*, 1873-1876. (b) Ishida, T.; In, Y.; Fujikawa, A.; Urata, H.; Inoue, M.; Ikai, K.; Takesako, K.; & Kato, I. *J. Chem. Soc., Chem. Comm.* **1992**, *17*, 1231 ~ 233.
4. (a) Yamaguchi, H.; Nakamura, T.; Uchida, K.; Takesako, K.; Ikai, K.; Yamamoto, J.; & Shimanaka, K. US. 5200505. (b) Awazu, N.; Ikai, K.; Yamamoto, J.; Nishimura, K.; Mizutani, S.; Takesako, K.; & Kato, I. *J. of Antibiotics*, **1995**, *48*: 525 ~ 527.
5. Rodriguez, M. J.; Zweifel, M.J.; Loncharich, R. J. "Aldol Promoted Reaction of R106-Sarcosine: Synthesis and Conformational Analysis of Novel R106 Analogs". *J. of Org.Chem.*, **1996**, *61*(5), 1564-1572.
6. TNO-2H₂O was effective in promoting the retro-aldol reaction on a non-peptide model compound in good yields.



7. (a) Reinaud, O.; Capdevielle, P.; Maumy, M. *J. Mol. Catal.* **1991**, *68*(2), L13-L15. (b) Capdevielle, P.; Sparfel, D.; Baranne-Lafont, J.; Nguyen, K. C.; Maumy, M. *J. Chem. Soc., Chem. Commun.* **1990**, *7*, 565-566. (c) Reinaud, O.; Capdevielle, P.; Maumy, M. *J. Chem. Soc., Chem. Commun.* **1990**, *7*, 566-568. (d) Nakajima, S.; Kawai, H.; Sakakibara, M.; Tatsuta, K.; Otake, N. *Tetrahedron Lett.*, **1989**, *30* (36), 4857-4858. (e) Ray, R.; Matteson, D. *Tetrahedron Lett.* **1980**, *21*(5), 449-450.
8. Ikai, K.; Takesako, K.; Shiomi, K.; Moriguchi, M.; Umeda, Y.; Yamamoto, J.; Kato, I.; Naganawa, H. *J. of Antibiotics*, **1991**, *44*(9), 925-933.
9. Ikai, K.; Shiomi, K.; Takesako, K.; Mizutani, S.; Yamamoto, J.; Ogawa, Y.; Ueno, M.; Kato, I. *J. of Antibiotics*, **1991**, *44*(11), 1187-1198.
10. Supplier: Aldrich Chemical Company
11. Reaction monitored by C-18 reverse phase chromatography (30:70 water/acetonitrile, Waters 3.9 X 300 mm μ bondapak[®]2 mL/min, 250 nm).
12. (a) Nakagawa, S.; Shizuhiko, M. *Hiroshima-Kenritsu Shokuhin Kogyo Gijyutsu, Senta Kenkyu Hokoku*, **1993**, *20*, 1-7. (b) Toshio, T. *Nippon Suisan Gakkaishi*, **1975**, *41*(5), 535-546.
13. Ishida, T.; In, Y.; Kujikawa, A.; Urata, H.; Inoue, M.; Ikai, K.; Takesako, K.; Kato, I. *J. Chem. Soc., Chem Commun.*, **1992**, *17*, 1231-1233.
14. Compounds **6** and **7** are known compounds previously prepared by Takara Shuzo Company. Haruna, F.; Yamaguchi, H., Nakamura, T.; Uchida, K.; Takesako, K.; Ikai, K.; Yamamoto, J.; Shimanaka, K. Takara Shuzo Co., LTD. EP91300438.8.

(Received in USA 13 March 1996; revised 18 April 1996; accepted 25 April 1996)