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

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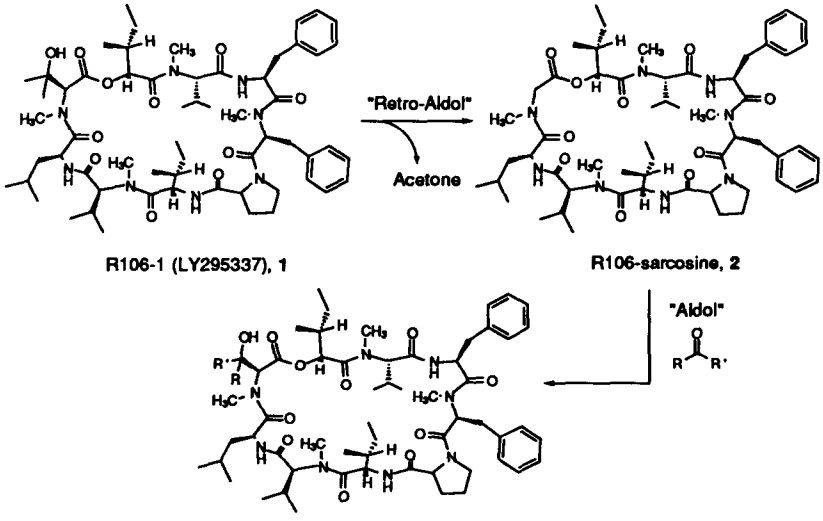
Abstract: The retro-aldol reaction of R106-1 (LY295337), **1** using trimethylamine N-oxide (TNO) facilitates the removal of the tertiary hydroxy group generating R106-sarcosine, **2** a key synthetic intermediate. The reagent is highly reproducible and provides high yields with no major side products.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

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 reported[5] 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•2H_2O) was effective in promoting the retro-aldol reaction (In addition, TNO was effective in removing a β-hydroxy group from a non-peptide substrate[6]).

TNO is a well known hydroxylating reagent[7] but its use as an "organic base" is rare. Obtaining suitable quantities of **2** using traditional reagents[8] such as NaOH/DMSO gave mixed results. The product distribution was highly variable:

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

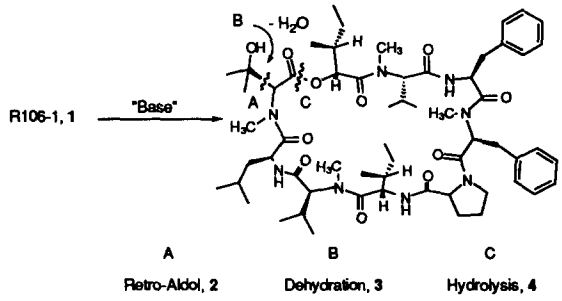


R106-1 (LY295337), **1** R106-sarcosine, **2**

New R106 Derivatives

substantial amounts of dehydration, **3** (R106-18) and lactone hydrolysis, **4** by-products were obtained[9] (Scheme 2). Unlike these reagents, TNO•2H_2O 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 dihydrate[10] 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•2H_2O 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•2H_2O (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_2O	DMF	100	3h	70 / 30 / 0
	DMF	70	12h	87 / 13/ 0
	DMF/H_2O (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

[a]HPLC percentages of crude reaction mixtures.

Typically, the reaction required heating R106-1 with 5-10 molar equivalents of TNO•2H_2O 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. $NaHCO_3$ 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.

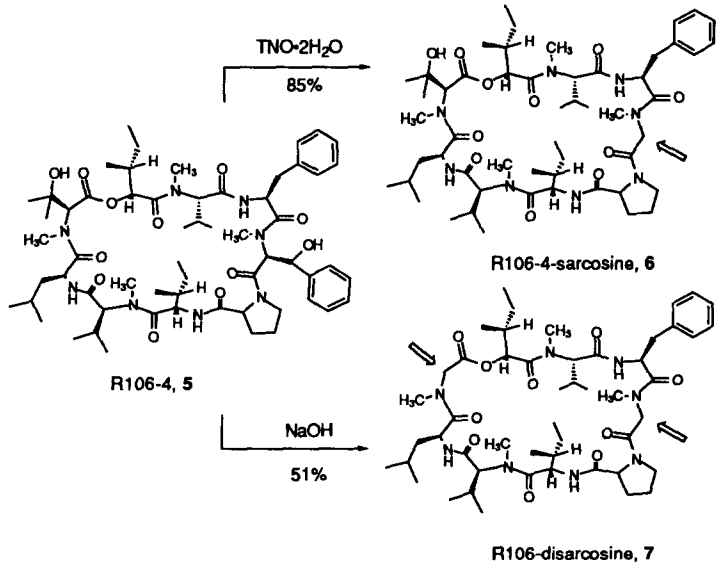
We attempted to promote the retro-aldol reaction using traditional bases such as potassium *t*-butoxide, NaOH and NaH. Although these reagents were used catalytically, higher yields of dehydration and lactone hydrolysis by-products were observed. Base catalyzed reactions using tertiary amines were also 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•2H$_2$O. The addition of water (≤ 20%) decreased the reaction rate with only a slight increase in dehydration product, **3**.

An additional feature of TNO•2H$_2$O was observed with R106-4, **5** a fermentation factor containing two β-hydroxy carbonyl functional groups[13] (Scheme 4). In this case, TNO•2H$_2$O 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•2H_2O was responsible for promoting the retro-aldol reaction. Unlike the traditional reagents, such as NaOH, KOH, triethylamine or DBU, TNO•2H_2O was found to be a mild and selective reagent for the removal of β-hydroxy groups while in the presence of other functional groups.

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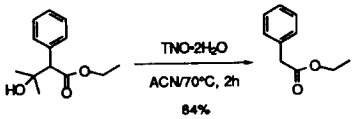
6. TNO•2H_2O was effective in promoting the retro-aldol reaction on a non-peptide model compound in good yields.



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10. Supplier: Aldrich Chemical Company

11. Reaction monitored by C-18 reverse phase chromatography (30:70 water/acetonitrile, Waters 3.9 X 300 mm μbondapak®2 mL/min, 250 nm).

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