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# Lewis Acid Catalyzed α-Functionalization of Ketals for the Regioselective Synthesis of α-Carbamoyl Ketals

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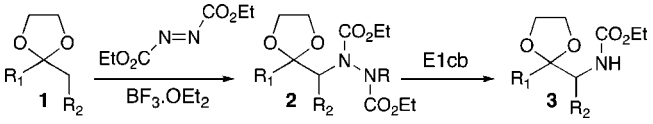
## ABSTRACT




**Treatment of 1 with DEAD in the presence of $BF_3 \cdot OEt_2$ gave 2 (R = H), which was *N*-alkylated to give 2 (R = $CH_2CO_2Et$), and insitu eliminated (E1cb) to give α-carbamoyl ketals.**

During the past several years we have investigated methods for the introduction of amine functionality into organic molecules.[1a−c] More recently, we have examined the "ene reaction" of dialkyl azodicarboxylates to give allylic hydrazine derivatives, and the subsequent cleavage of the N−N′ bond to give allylic carbamates by an E1cb elimination process rather than the usual reductive methods.[2,3a−c] Attempts to apply this type of methodology to ketones **1** in the form of their α-*N*,*N*′-dialkyldicarboxylate hydrazine derivatives **2**[4a−m] was thwarted by selectivity problems in the E1cb N−N′ bond cleavage reaction that resulted in **4** as the major product (and tautomer) rather than **3** (Figure 1).[5] Attempts to rectify this situation by using silyl enol ethers was unsuccessful because of desilylation in the *N*-alkylation step (migration of the $R_3Si$ group to the terminal *N* atom) and consequently loss of selectivity in the elimination step.

To solve this unwanted reactivity, it was decided to examine the reaction of ethylene ketals with diethyl azodicarboxylate in the presence of a Lewis acid. This would in effect remove enolizable α-ketone hydrogen atoms.

It was expected that the open enol form of **5** (Scheme 1) would react with the diethyl azodicarboxylate to form an oxonium ion that will reclose the cyclic ketal and result in α-hydrazination of the ketal to give **5a**. This type of ketal reactivity has analogy in the bromination of ethylene ketals as described in 1962 by Eaton.[6a−c]

It was found that treatment of **5** with DEAD in the presence of $BF_3 \cdot OEt_2$ (0.2 equiv) in 1,2-dichloroethane (DCE) and quenching the reaction with ethylene glycol gave **5a** (80%). These conditions were applied to other substrates with varying amount of $BF_3 \cdot OEt_2$ (Scheme 2,

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(4) For reactions of ketones and derivatives with dialkyl azodicarboxylates, see: (a) Leblanc, Y.; Fitzsimmons, B. J. *Tetrahedron Lett.* **1989**, *30*, 2889–2892. (b) Gmiener, B.; Bollinger, B. *Tetrahedron Lett.* **1991**, *32*, 5927–5930. (c) Gmeiner, P.; Bollinger, B. *Tetrahedron* **1994**, *50*, 10909–10922. (d) Enders, D.; Joseph, R.; Poiesz, C. *Tetrahedron* **1998**, *54*, 10069–10078. (e) Yamashita, Y.; Ishitani, H.; Kobayashi, S. *Can. J. Chem.* **2000**, *31*, 666–672. (f) Kumaragurubaran, N.; Juhl, K.; Zhuang, W.; Bøgevig, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 6254–6255. (g) Duthaler, R. O. *Angew. Chem., Int. Ed.* **2003**, *42*, 975–978. (h) Dessole, G.; Bernardi, L.; Bonini, B. F.; Capito, E.; Fochi, M.; Herrera, R. P.; Ricci, A.; Cahiez, G. *J. Org. Chem.* **2004**, *69*, 8525–8528. (i) Matsubara, R.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 7993–7995. (j) Thomassigny, C.; Prim, D.; Greck, C. *Tetrahedron Lett.* **2006**, *47*, 1117–1119. (k) Lacoste, E.; Vaique, E.; Berlande, M.; Pianet, I.; Vincent Jean-Marc, V. J.; Landais, Y. *Eur. J. Org. Chem.* **2007**, 167–177. (l) Sun, X.-W.; Wang, W.; Xu, M.-H.; Lin, G.-Q. *Tetrahedron Lett.* **2008**, *49*, 5807–5809. (m) Gennari, C.; Colombo, L.; Bertolini, G. *J. Am. Chem. Soc.* **2011**, *108*, 6394–6395.

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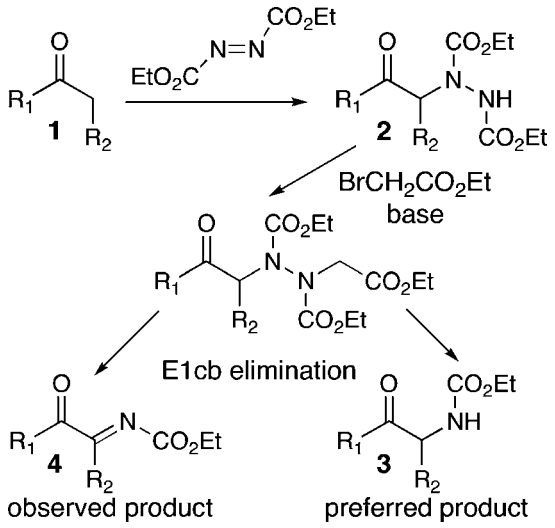
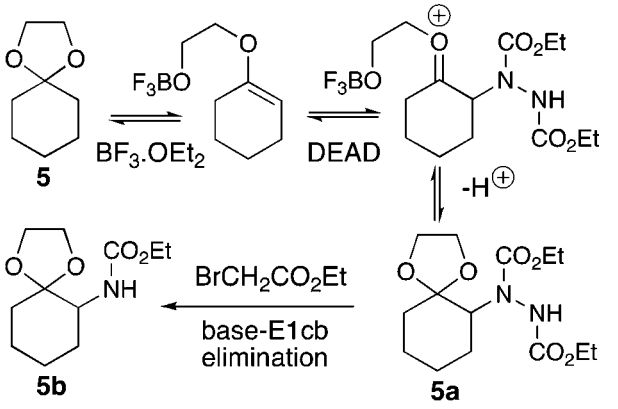



**Figure 1.** E1cb elimination of the N−N′ bond.

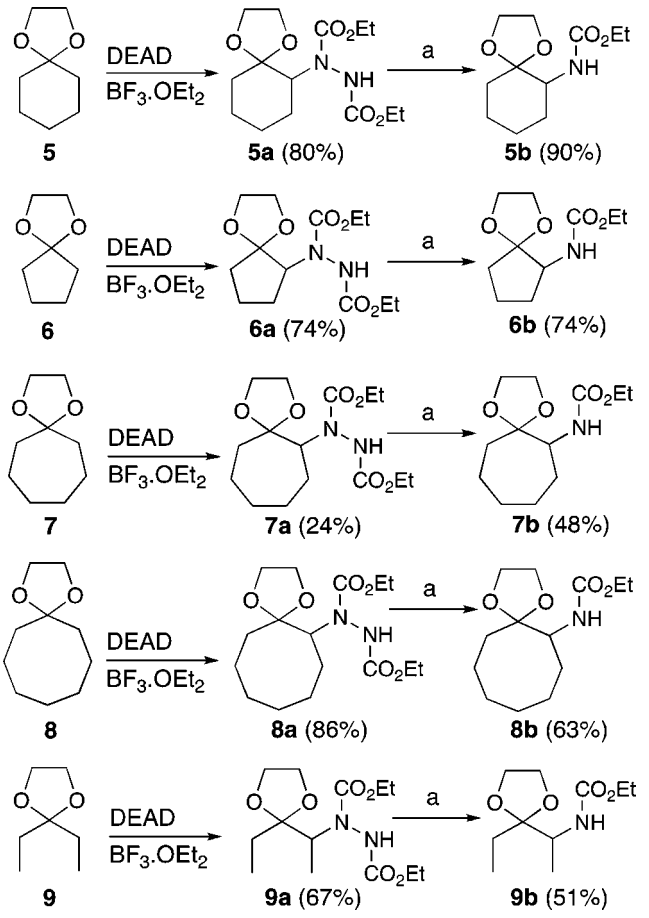
see the Supporting Information for full experimental details). It was found that using these hydrazination conditions on different substrates resulted in lower yields, and the desired product was accompanied by varying amounts (5−20%) of diethyl hydrazine dicarboxylate ($DEADH_2$), even though the starting DEAD reagent was pure. Dialkyl azodicarboxylates react competitively as hydride acceptors and oxidation reactions are not uncommon.[7a,b] In particular, DEAD has been used to oxidize primary and secondary alcohols into aldehydes and ketones, respectively.[8a,b] Unfortunately, efforts to prevent the formation of $DEADH_2$ were unsuccessful.

**Scheme 1.** α-Functionalization of Ketals and E1cb Elimination To Cleave the N−N′ Bond




Treatment of **5** with methyl bromoacetate, $Cs_2CO_3$, and $CH_3CN$ led to incomplete alkylation of the terminal hydrazino nitrogen atom.[2] Even the use of large excesses of base and/or alkylating reagent resulted in substantial amounts of isolated starting material. It seemed plausible that the *N*-alkylation event was accompanied by competitive *O*-alkylation and that the *O*-alkylated products hydrolyzed back to starting material during workup. Changing to a base with a smaller counterion than cesium and carrying out the reaction in a less polar solvent than $CH_3CN$ would, in principle, promote *N*-alkylation. It was found that NaH in diglyme at 0 °C led to the anticipated improvements and allowed the *N*-alkylation to proceed in excellent conversion.

**Scheme 2.** Two-Step Formation of α-Carbamoyl Ketals[a]




[a] Conditions a: NaH (3 equiv), $BrCH_2CO_2Et$ (1.5 equiv), diglyme, 0−50 °C.

In addition to solving the alkylation difficulties, these new conditions were easily adapted to a one-pot alkylation/cleavage procedure. Increasing the temperature of the alkylation reaction of compound **5a** from 0 to 50 °C gave the α-carbamoyl ketal **5b** in 90% yield.[9] These same

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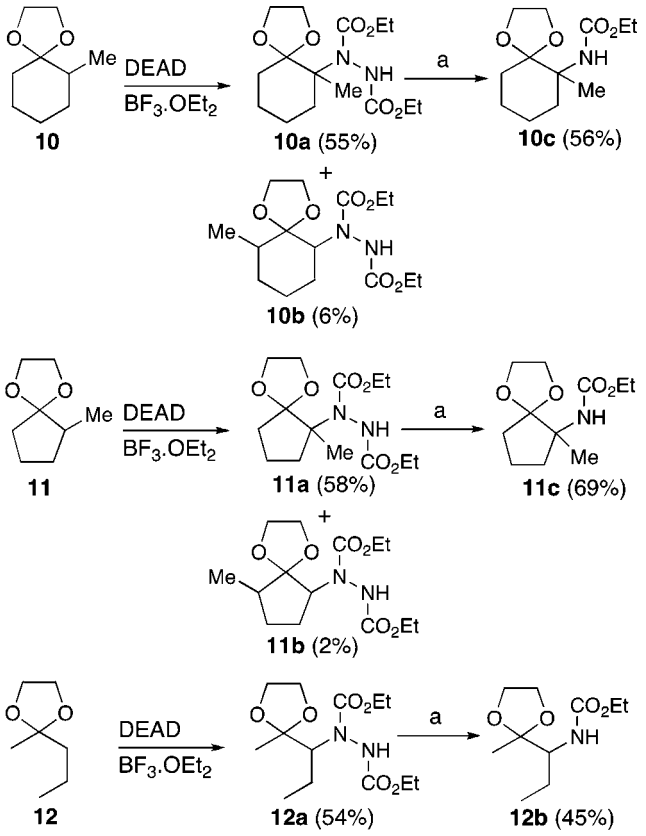
**Scheme 3.** Regioselective Formation of α-Carbamoyl Ketals[a]




[a] Conditions a: NaH (3 equiv), $BrCH_2CO_2Et$ (1.5 equiv), diglyme, 0−50 °C.

conditions were extended to the other α-hydrazino ketals (Schemes 2 and 3) with varying efficiency.

It was further found that during the development of the one-pot procedure it was also necessary to change from methyl to ethyl bromoacetate as the alkylating reagent. When methyl bromoacetate was used, we observed significant ethoxy to methoxy transfer in the carbamoyl group of the product (trans-esterification). These results suggest that the excess ethyl bromoacetate is hydrolyzing in situ, liberating methoxide. It is also notable that the α-carbamoyl ketals were not *N*-alkylated under the $N-N'$ bond cleavage reaction conditions. This result suggests that the excess alkylating reagent decomposes before $N-N'$ bond cleavage occurs.

To examine the regioselectivity of the $BF_3 \cdot OEt_2$-mediated reaction with DEAD, we treated some unsymmetrical ketals to the standard reaction conditions (Scheme 3). As expected from the proposed enol ether mechanism (Scheme 1), the more highly substituted adducts (thermodynamic) were the major products **10a**, **11a**, and **12a**, respectively. The less substituted adducts **10b** and **11b** were very minor products and, in the case of the reaction of **12**, were not detected. The major products were treated to the $N-N'$ bond cleavage conditions to produce the corresponding α-carbamoyl ketals **10c**, **11c**, and **12b**, respectively. These adducts would be particularly difficult to access by other methods.

In summary, a regioselective C−N bond-forming reaction operating through the Lewis acid activation of ethylene ketals has been developed. This chemistry was used in concert with a one-pot anionic $N-N'$ bond cleavage reaction forming α-carbamoyl ketals. It is expected that this rare functional array will find synthetic applications where orthogonal amine−ketone protection is required.

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**Supporting Information Available.** Complete experimental details and compound characterization. This information is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.