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CYCLIC 1,2-DINITROGEN COMPOUNDS THROUGH *N,N'*-DI(METHOXYCARBONYL)HYDRAZINIUM INTERMEDIATES

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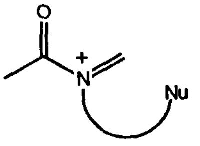
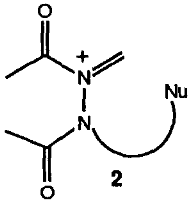
Abstract: Acid catalyzed cyclization of methoxymethyl substituted acyclic hydrazides **4** provides cyclic hydrazides **5** in moderate to good yields through the intermediacy of *N,N'*-di(methoxycarbonyl)hydrazinium intermediates.

Recent years have witnessed an increasing interest in the biological properties of cyclic hydrazine derivatives. Such compounds are attractive objects of study, both in their own right,[1] and as analogues of bioactive mono-nitrogen compounds.[2] Cyclic hydrazines also occur in nature, although infrequently.[3] From a synthetic perspective, cyclic hydrazines have proved useful for the preparation of other dinitrogen compounds through cleavage of the N-N bond.[4]

The synthesis of cyclic hydrazines usually proceeds by one of the following methods:[5] (1) the double substitution reaction of hydrazines with α,ω-dihalides, α,ω-halocarbonyl compounds, or α,ω-dicarbonyl compounds; (2) the addition of hydrazines to α,β-unsaturated carbonyl compounds; (3) 1,3-dipolar cycloadditions of diazoalkanes and nitrile imines; and (4) hetero Diels Alder reactions of azodicarboxylates. The scope of these methods is rather limited in terms of ring size and substitution pattern. In conjunction with our work[6] on the use of *N*-acyliminium ions **1** (Nu = nucleophile) as intermediates in cyclization reactions, we decided to probe the possible application of similar methodology to the synthesis of cyclic hydrazines by way of the corresponding hydrazinium ions **2**. To the best of our knowledge the latter intermediates have not been investigated before. In this communication we report some of our first results in this area.



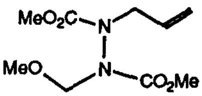
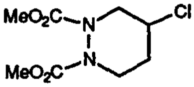
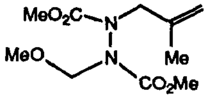
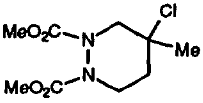
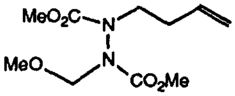
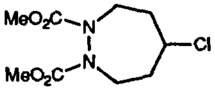
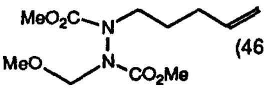
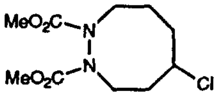
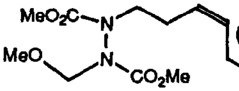
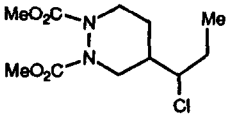
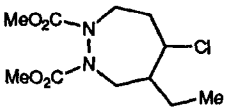
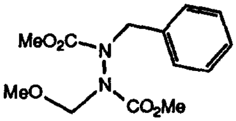
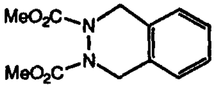
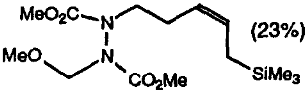
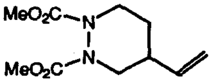
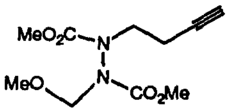
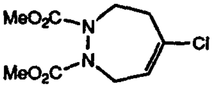
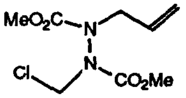
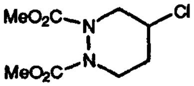
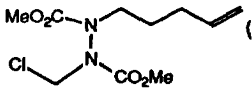
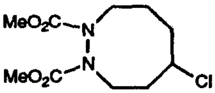
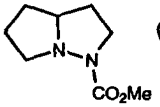
1



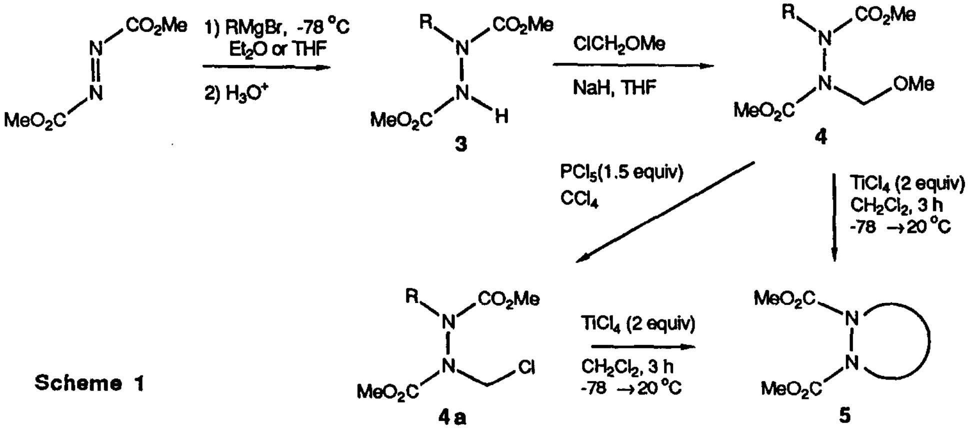
2

The general synthetic outline is presented in Scheme 1. To dimethyl azodicarboxylate was added the appropriate Grignard derivative[7] furnishing the monosubstituted hydrazide **3**. The latter derivative upon treatment with chloromethyl methyl ether and sodium hydride in THF provided the desired precursor **4** which was then reacted with Brønsted or Lewis acid to generate the electrophilic intermediate **2**. The choice of the nucleophilic component was primarily aimed at determining the scope of the new C-C bond formation. As can be seen from the results in

Table

entry	precursor (yield)[a,b]	product(s) (yield)[b]
1	 (23%)	 (32%)
2	 (60%)	 (54%)
3	 (42%)	 (80%)
4	 (46%)	 (15%)
5	 (35%)	  (39%)[c]
6	 (70%)	 (98%)
7	 (23%)[d]	 (54%)[e]
8	 (47%)[f]	 (80%)
9	 (62%)	 (70%)
10	 (94%)	 (8%)  (39%)

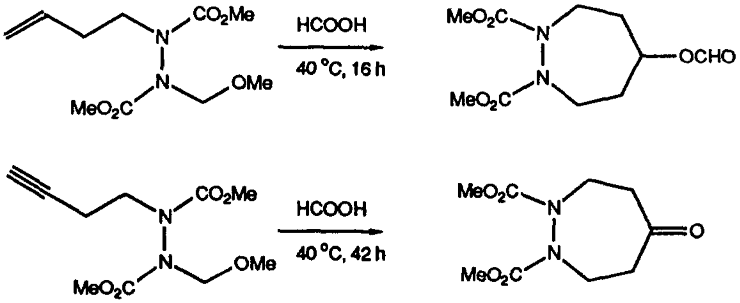
a) Combined yield of RMgX addition and reaction with $ClCH_2OMe$, except for entries 9 and 10, which show the yield for the methoxy to chloro conversion. b) Yield after flash chromatographic purification; for reaction conditions see Scheme 1. c) Mixture of regio- and stereoisomers. d) Starting bromide prepared according to ref. 12. e) $BF_3\,OEt_2$ was used as Lewis acid, because $TiCl_4$ gave mainly protodesilylation. f) The Grignard reagent derived from 1-bromo-4-trimethylsilyl-3-butyne (ref. 13) was used; the yield includes fluoride mediated desilylation.



Scheme 1

the Table, this novel method offers a good opportunity to synthesize a variety of hitherto unknown cyclic hydrazine derivatives 5.[8] Although yields have not been optimized, the results in entries 3 and 7 are remarkable in terms of structure, yield and transition state for the cyclization. Furthermore, the synthesis of the reduced phthalazine derivative (entry 6) is also noteworthy, because the possibilities for varying the aromatic nucleophile are manifold.[9] The lower yields in entries 1, 4, and 5 are connected in part with the anticipated more difficult formation of the ring system and/or the occurrence of side reactions. The latter could be avoided in part by facilitating the formation of the intermediate by substituting the OMe by a better leaving group. Introduction of a chlorine atom[10] gave a more reactive precursor 4a and, indeed, improved the cyclization outcome, as is apparent from comparison of entries 1 and 9. Also in line with this result is the observation that upon use of the less reactive Lewis acid $SnCl_4$ in the cyclization of the methallyl derivative (entry 2) only a slow and incomplete ring closure took place. Remarkably, the formation of the eight-membered system starting from the more reactive chloro-precursor (entry 10) was accompanied by a transannular reaction to produce a bicyclic derivative.[11] This process was not observed in the cyclization of the methoxy-precursor (entry 4) although the yield of the latter reaction was rather low.

Also in line with the expected slow generation of the hydrazinium intermediate is the observation, that at room temperature no reaction occurred upon treatment of the OMe precursor with HCOOH. Upon warming, however, both the butenyl and butynyl derivatives effectively cyclized in yields of 76% and 83%, respectively (Scheme 2).



Scheme 2

The present data indicate the advantageous use of the *N,N'*-di(methoxycarbonyl)hydrazinium intermediate **2** for the construction of cyclic hydrazines. Moreover, the easy availability of linear and cyclic starting materials of type **4** allows the construction of a wide variety of cyclic derivatives. Studies concerning the scope as well as the more detailed mechanistic background of the new process are currently underway in our laboratory.

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