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A Novel and Convenient Protocol for Synthesis of Pyridazines

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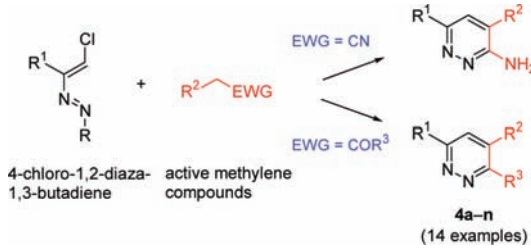
ABSTRACT



A new flexible strategy for the synthesis of diversely functionalized pyridazines from 4-chloro-1,2-diaza-1,3-butadienes and active methylene compounds is reported. The high chemoselectivity of this approach offers access to structural precursors of GABA-A antagonist analogues.

The pyridazine[1] ring is recurrent as a structural component of biologically active compounds.[2] Moreover, pyridazines are useful intermediates in the construction of several other heterocycles[3] and in physical organic chemistry[4] and recently have been explored as new α-helix mimetics.[5]

The 3-aminopyridazine unit has proven to be interesting from a pharmacological point of view.[6−9] For example, Minaprine

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1 (Cantor) is a psychotropic drug presently used as an antidepressant.[7] Various 3-aminopyridazine derivatives of γ-aminobutyric acid act as selective GABA-A receptor antagonists.[8,9] In particular, the 6-aryl-3-aminopyridazine derivative of GABA, SR 95103 [2-(3-carboxypropyl)-3-amino-4-methyl-6-phenylpyridazinium chloride], showed high specificity and potency.[9] Our synthetic efforts toward these and related compounds have focused on the preparation of diversely functionalized 6-aryl (alkyl)-3-aminopyridazine derivatives.

Because most approaches to these heterocycles suffer from many disadvantages, including inconvenient operations, a limited number of suitable substrates, harsh reaction conditions, a high number of steps, and poor yields, the development of mild and efficient methods for their synthesis is highly desirable. Effectively, the common five-step strategy for the construction of 6-phenyl-3-aminopyridazines[10] involves synthesis of the pyridazinone core based on the condensation of acetophenone with α-ketoester and requires ammonia or hydrazine as a precursor of the amino function.[7c,10a]

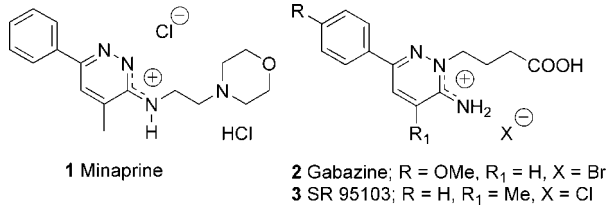
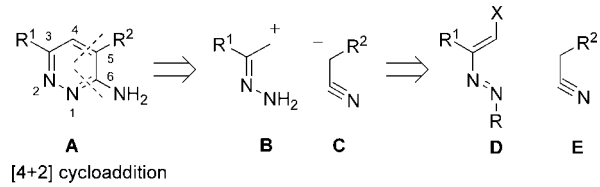


Figure 1. Structures of some pharmaceutically important 3-aminopyridazine derivatives: Minaprine **1**, Gabazine **2**, and SR 95103 **3**.

Our analysis of the 3-aminopyridazine target **A** (Scheme 1) emphasizes two strategic disconnections of the pyridazine ring, along the two carbon−carbon bonds C(4)−C(5) and C(6)−N(1). This unveils two subunits that trace the left half back to the hydrazone cation **B** and the right half to the cyano compound frame **C**. Our experience in the heterocyclic constructs entices us to correlate fragment **B** to the azo-ene systems **D**[11,12] and fragment **C** to the active methylene compounds containing cyano group **E**. In the synthetic direction, we envision the C(4)−C(5) junction first to be installed via a Michael-type addition of α-CH_2-acidic cyano compounds with chloro-1,2-diaza-1,3-butadienes, followed by completion of the heterocycle via an internal nucleophilic ring closure. Importantly, this proposed approach would directly place the requisite amino group in position 3 of the pyridazine nucleus.

Scheme 1. Retrosynthetic Analysis of 1-Aminopyridazine **A**



The presence of a leaving group on the C4 of the azo-ene skeleton plays a crucial role in the outcome of the reaction. In fact, the key step of these reactions resides in the formation of the α,β-unsatured hydrazones as a result of HX elimination. It should be noted that these reactions constitute an umpolung of the classical carbonyl reactivity, since neutral 1,2-diaza-1,3-butadienes enable analogous nucleophilic additions at the α hydrazone functionality that corresponds to the C4 carbon of azo-ene systems.

Surprisingly, there are relatively few reports on employment of 4-chloro-1,2-diaza-1,3-butadienes in organic synthesis.[13] For example, South et al. reported that haloazodienes reacted in an inverse electron demand Diels−Alder reaction with enamines to provide tetrahydropyridazine derivatives.[13e,g] In 1981, Gilchrist found that β-chloroazoalkenes reacted with 1,3-dicarbonyl compounds to yield first the addition−elimination products and then pyrroles when an excess of CH_2-acidic substrate was used.[13a] Because of these results and of our interest in certain 3-aminopyridazine targets, we set out to establish reaction conditions and/or substrates that would provide the desired 3-aminopyridazines on the basis of our current working hypothesis.

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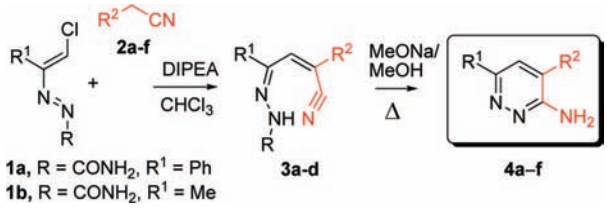
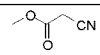
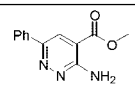
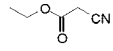
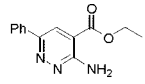
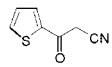
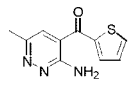
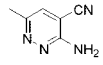
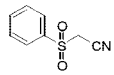
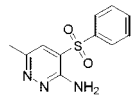
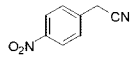
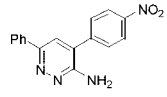
Table 1. Michael-Type Addition/Heterocyclization of Active Methylene Cyano Compounds **2a**−**f** on 1,2-Diaza-1,3-butadienes **1a,b**;[a] Syntheses of 3-Aminopyridazines **4a**−**f**



no.	1	2	3 %	4 %
1	**1a**	 **2a**		 **4a** 80[c]
2	**1a**	 **2b**		 **4b** 74[c]
3	**1b**	 **2c**	**3a** 53[b]	 **4c** 33[b,d]
4	**1b**	 **2d**	**3b** 90[b]	 **4d** 63[b,d]
5	**1b**	 **2e**	**3c** 46[c]	 **4e** 85[b,d]
6	**1a**	 **2f**	**3d** 54[c]	 **4f** 90[b,d]

[a] All reactions were carried out in $CHCl_3$ (5 mL) at rt for 1−24 h using 1,2-diaza-1,3-butadienes **1a,b** (1.0 mmol), active methylene compounds **2a**−**f** (1.0 mmol), and DIPEA (1.1 mmol) (TLC check). [b] Yields of isolated product by crystallization. [c] Isolated yield after silica gel chromatography. [d] All reactions were carried out under reflux for 3−6 h by treatment of **3a**−**d** (0.5 mmol) in MeOH (10 mL) with MeONa (0.5 mmol) (TLC check).

As a first approach to compound **4a**, the 4-chloro-1,2-diaza-1,3-butadiene **1a**, possessing an aminocarbonyl moiety on N(1), was reacted with the commercially available methyl cyanoacetate **2a** to give exclusively 3-aminopyridazine (**4a**) in 80% yield (Table 1, entry 1).

Fortunately, from this reaction we did not observe any bis-addition product or pyrrole derivative, contrary to what was previously reported by Gilchrist. The presence of an aminocarbonyl residue instead of an alkoxycarbonyl (or aryl) on the N(1) of the azo-ene system is essential for the pyridazine ring formation, showing the intrinsic preference of this group to the heterocyclization process. A brief study revealed optimized reaction conditions: $CHCl_3$ as solvent, room temperature, and DIPEA as base (1.1 equiv).

Under the above-mentionated conditions, a range of active methylene compounds **2a**−**f** containing a cyano group were tested in Michael additions with 4-chloro-1,2-diaza-1,3-butadienes **1a,b**[14] (Table 1, entries 1−6).

The ethyl cyanoacetate **2b** also worked well to give analogous 3-aminopyridazine **4b** (entry 2). 2-Thenoylacetonitrile **2c**, malononitrile **2d**, and benzensulfonilacetonitrile **2e** reacted with **1b** to form the corresponding α,β-unsatured hydrazone **3a**−**c** in good yields (entries 3−5). More precisely, the reaction furnished crude product **3a**−**c** by direct precipitation from the reaction mixture. To obtain the respective pyridazine **4c**−**e**, the same intermediates **3a**−**c** were subjected to intramolecular ring closure in the presence of a stoichiometric amount of sodium methoxide (CH_3ONa) in methanol (CH_3OH) at reflux (Table 1).

Interestingly, even 4-nitrophenylacetonitrile **2f** having in the α-position only a single carbonyl group reacted efficiently with **1a** to afford the respective addition−elimination product **3d** (entry 6). As expected, the latter hydrazone **3d** was an effective substrate, giving **4f** in excellent yield.

In light of the latest results, we next decided to explore the full potential of this methodology using a variety of structurally diverse active methylene compounds (Table 2, entries 1−8).

Active methylene compounds containing ketone groups such as acetylacetone **2g**, cycloexane-1,3-dione **2h**, ethyl acetoacetate **2i**, acetoacetanilide **2j**, *p*-acetoacetanisidide **2k**, 4-chlorophenylsulfonylacetone **2l**, *p*-toluensulfonylacetone **2m** and 4-nitrophenylacetone **2n** reacted with **1a,b** to give the corresponding α,β-unsatured hydrazones **3e**−**f** or pyridazine derivatives **4g**−**j,l,m** in high yields (entries 1−8). Following the same heterocyclization process mediated by sodium methoxide (CH_3ONa), we were able to obtain pyridazines **4k,n** in good yields (Table 2).

Among these pyridazine compounds **4g**−**n**, tetrahydrocynnoline derivative **4h** proved to be reversible inhibitors of monoamine oxidase (MAO-A and MAO-B).[15] This fact confers an extra contribution of our methodology toward synthesis of pharmacologically active molecules.

Only in the case of the reaction between **1a** and **2i**, the desired cyclization of the amide to the ketone was competing with the ring closure on the ester group, giving pyridazinone (see **5a** in Supporting Information) as a substantial byproduct (11% yield). Finally, applying the same procedure to dimethyl malonate resulted in a complicated crude mixture from which only a low yield of the α,β-unsaturated hydrazone was isolated.

In such reactions, the active methylene compound furnishes only two ring atoms (C−C), while the 1,2-diaza-1,3-butadiene partner provides the remaining four heteroring atoms (C−C−N−N) to the final pyridazine.

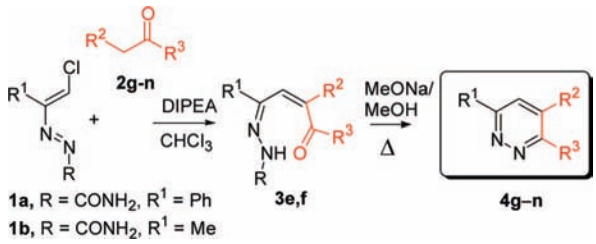
It should be noted that amino, ketone, ester, cyano, sulfone, amide, and aryl groups were all tolerated, providing the corresponding pyridazines in good to high yields. While many of the known methods are often incompatible with various functional groups or general substitution patterns, the present approach proves quite general. However, the products could be of great interest for the synthesis of many other complex heterocyclic templates.

On the basis of the obtained results, a plausible mechanism for the synthesis of variously functionalized pyridazine **4** is hypothesized (Scheme 2).

The transformation starts from the base-promoted attack of the active carbon atom of **2** at the terminal carbon of the azo-

(14) 1,2-Diaza-1,3-butadienes **1a,b** were synthesized from the corresponding dichlorohydrazones by treatment with base (see Supporting Information).

Table 2. Michael-Type Addition/Heterocyclization of Active Methylene Ketones Compounds **2g−n** on 1,2-Diaza-1,3-butadienes **1a,b**;[a] Syntheses of Pyridazines **4g−n**



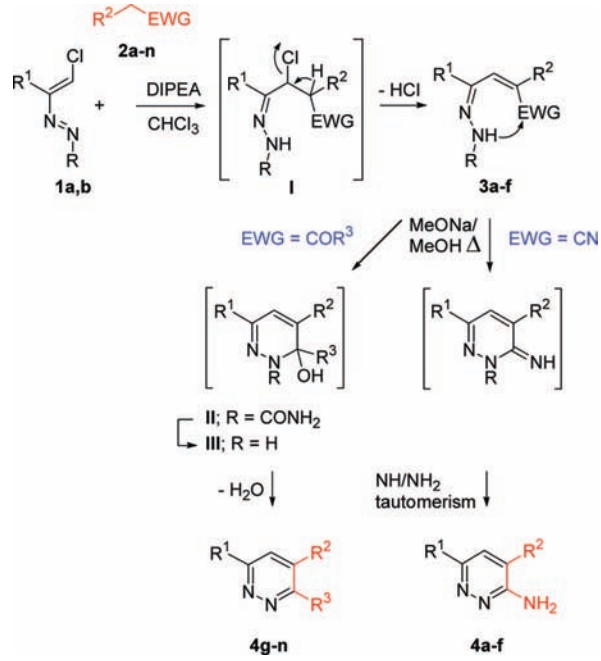
no.	1	2	3 %	4 %
1	**1a**	**2g**		**4g** 41[c]
2	**1a**	**2h**		**4h** 66[b]
3	**1a**	**2i**		**4i** 32[c,e]
4	**1a**	**2j**		**4j** 83[c]
5	**1b**	**2k**	**3e** 72[b]	**4k** 87[b,d]
6	**1a**	**2l**		**4l** 69[c]
7	**1b**	**2m**		**4m** 48[c]
8	**1b**	**2n**	**3f** 73[b]	**4n** 83[b,d]

[a] All reactions were carried out in $CHCl_3$ (5 mL) at rt for 1−24 h using 1,2-diaza-1,3-butadienes **1a,b** (1.0 mmol), active methylene compounds **2g−n** (1.0 mmol), and DIPEA (1.1 mmol) (TLC check). [b] Yields of isolated product by crystallization. [c] Isolated yield after silica gel chromatography. [d] All reactions were carried out under reflux for 3−6 h by treatment of **3e,f** (0.5 mmol) in MeOH (10 mL) with MeONa (0.5 mmol) (TLC check). [e] Pyridazinone **5a** (see Supporting Information) was also isolated in 11% yield after silica gel chromatography.

ene system of **1** (Michael-type addition) to generate an adduct intermediate (**I**) followed by a dehydroalogenation reaction to give more stable α,β-unsaturated hydrazone **3**. Subsequently, an intramolecular aza-cyclization of **3** by a nucleophilic attack of the carbamic nitrogen atom on a nitrile or carbonyl function results in the formation of a diyhdropyridazine ring (**II**). The spontaneous loss of carbamic residue resulting from the base-induced hydrolysis and decarboxylation (intermediate **III**) with consequent elimination of a water molecule (for **4g−n**) or NH/NH_2 tautomerism (for **4a−f**) leads to pyridazine compound **4**.

(15) Altomare, C.; Cellamare, S.; Summo, L.; Catto, M.; Carotti, A.; Thull, U.; Carrupt, P.-A.; Testa, B.; Stoeckli-Evans, H. *J. Med. Chem.* **1998**, *41*, 3812–3820.

Scheme 2. Mechanisms for the Formation of Pyridazines **4a−n**



It is important to note that the success of this pathway depends on the nature of moiety bonded to the terminal carbon atom of azo-ene system. In fact, in the six-membered heterocycle formation only an "external" amidic nitrogen atom can be operative with "closing" groups on the attacking nucleophiles, thus prohibiting a possible five-membered ring closure to give pyrrole derivatives. On the contrary, this latter behavior was observed when 4-alkoxy (or dialkylamino)-carbonyl-1,2-diaza-1,3-butadienes have been employed.[11]

In summary, a new (base-mediated, metal-free) and efficient synthesis yielding pyridazines **4** from readily available 4-chloro-1,2-diaza-1,3-butadienes **1** and active methylene compounds **2** has been developed. This protocol is especially attractive as it allows for the preparation of variously functionalized pyridazines in one or two steps. Moreover, the high chemoselectivity of this strategy offers access to structural precursors of GABA-A antagonist analogues (3-aminopyridazine derivatives) if practiced on a substrate bearing a cyano substituent (EWG = CN). The ease of construction of pyridazines and the broad availability of active methylene compounds implies that an extensive range of substituents/functionalities can be directly incorporated in the pyridine ring, making this procedure particularly useful for the preparation of libraries.

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Supporting Information Available: Experimental procedures and full characterization for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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