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An efficient preparation of 1,2-dihydropyridazines through a Diels-Alder/palladium-catalysed elimination sequence

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ABSTRACT

A convenient, scalable synthesis of 1,2-dihydropyridazines is presented, based on the Diels-Alder cycloaddition of 1-acetoxy-1,3-butadiene with a variety of azo compounds, followed by a palladium-catalysed elimination. The products are produced on multigram scale and the new method is particularly efficient and atom-economical when compared with previous preparations of 1,2-dihydropyridazines.

1,2-Dihydropyridazines **2** represent potentially interesting molecular building blocks, but have only rarely been described in the literature [1–6]. Indeed, preliminary studies have shown that 1,2-dihydropyridazines undergo electrocyclic reactions [1a,2–4,7], (producing bicyclic diazetidines, 2-aminopyrroles and conjugated imines) as well as Diels-Alder reactions with 4-phenyl-1,2,4-triazole-3,5-dione (PTAD) [5,8]. In addition, substituted 1,2-dihydropyridazines have been used as precursors to pyridazine derivatives [9], and unusual photochemical reactions of several 1,2-dihydropyridazines have been reported [10].

To enable a more comprehensive study of the synthetic potential of 1,2-dihydropyridazines **2**, we required an efficient synthesis suitable for multigram scale. Initially, we assessed previously described routes to 1,2-dihydropyridazines **2**, starting with an approach first reported by Altman and co-workers [1], and later employed by other authors [2–4], which involves the Diels-Alder cycloaddition of 1,3-butadiene with dimethyl azodicarboxylate to give tetrahydropyridazine **1**, followed by allylic bromination then dehydrobromination to generate **2** (Scheme 1). Whilst the initial Diels-Alder cycloaddition proceeded as expected with a range of azodicarboxylate reagents, the requirement for carbon tetrachloride (a toxic and ozone-depleting chemical) in the allylic bromination step is a major disadvantage. Unfortunately, our attempts to identify more sustainable reaction conditions for the allylic bromination were unsuccessful, thus we turned our attention to a related approach [5,6], in which tetrahydropyridazine **1** is converted into dihydropyridazine **2** through a two-step sequence involving bromination then double dehydrobromination (Scheme 1). However, the process proved capricious, and only poor yields of impure dihydropyridazines could be obtained. As the existing synthetic routes to **2** were unsuitable for larger-scale work, we sought to develop a new scalable approach to **2** by incorporating a suitable leaving group (LG) into the diene **3**, thereby allowing elimination directly from the resulting cycloadduct **4**, negating the need for bromination procedures.

At the outset, the Diels-Alder cycloadditions of diisopropyl azodicarboxylate (DIAD) with a range of substituted dienes **3** (LG = OAc, OBz, OPiv or OCO_2Et) were studied, generating tetrahydropyridazine intermediates bearing a leaving group (Scheme 1). Of the dienes tested, 1-acetoxy-1,3-butadiene (**3a**; LG = OAc) gave the most promising results in terms of the stability and the isolated yield of the resulting cycloadduct **4**, which was sufficiently stable to purification by flash column chromatography (although some degradation during purification was observed, pure samples of **4** were readily obtained). Next, attention turned to the elimination of intermediates **4** to give 1,2-dihydropyridazine **2a**. Initially, the elimination was attempted under a range of mild acidic or basic conditions, but in these cases the starting material was recovered unchanged. When more forcing acidic or basic conditions were employed, **2a** was not obtained, and significant decomposition of the starting material took place. Therefore, we wondered whether the desired transformation could be carried out using palladium catalysis. Whilst the palladium-catalysed elimination of allylic

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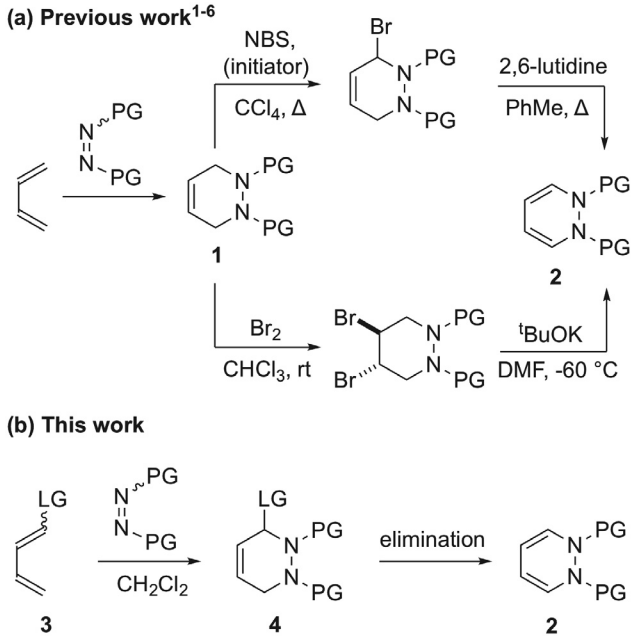
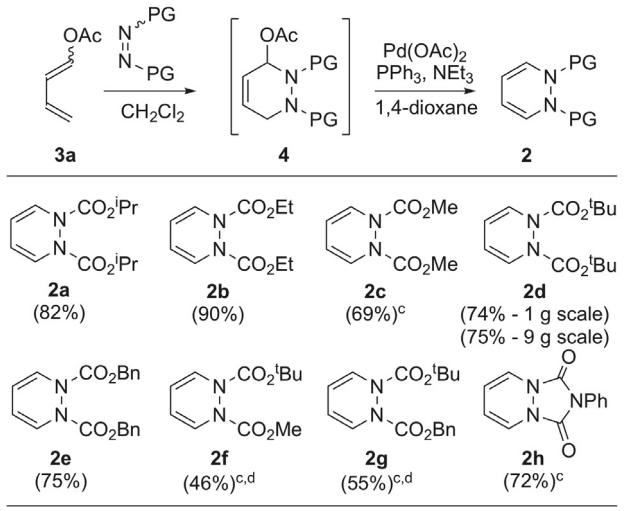


Scheme 1. Synthetic approaches to 1,2-dihydropyridazines (PG = protecting group, LG = leaving group, NBS = *N*-bromosuccinimide).

acetates is well known [11], to our knowledge there is no precedent for palladium-catalysed elimination in heterocyclic systems such as **4**. Pleasingly, the application of a variety of palladium catalysts resulted in conversion of **4a** into **2a**, although in some cases, rearrangement of the starting material (to produce allylic acetate **5a**) was observed in addition to the desired elimination (Table 1). Interestingly, the palladium-catalysed elimination of allylic acetate **5a** to **2a** was extremely sluggish (incomplete conversion and significant degradation were observed after **5a** was subjected to any of the conditions described in Table 1 for one week), hence it was crucial to suppress the formation of **5a** to allow efficient conversion of **4a** to **2a**. Several different palladium catalysts were tested, with $Pd(OAc)_2$ proving optimal, although the choice of ligand had a strong effect on the selectivity for **2a** over **5a**. Thus, whilst the use of dppp gave approximately equal amounts of **2a** and **5a** (Table 1, entry 4), Xantphos and triphenylphosphine led selectively to **2a** in 76% yield (Table 1, entry 5). However, when using Xantphos, reducing the catalyst loading from 10 mol% to 1 mol% switched the selectivity to give **5a** as the major product (Table 1, compare entries 5 and 6). In contrast, no such loss in selectivity was observed when $Pd(OAc)_2$/triphenylphosphine was employed at low catalyst loading, and the desired product **2a** could be selectively obtained in 83% yield using only 1 mol% $Pd(OAc)_2$ (Table 1, entry 7). In this case, the inclusion of two equivalents of triethylamine led to more reproducible results. After further optimization of the elimination conditions (see the Supporting Information), $Pd(OAc)_2$, triphenylphosphine, triethylamine and 1,4-dioxane emerged as the optimal catalyst, ligand, base and solvent respectively.

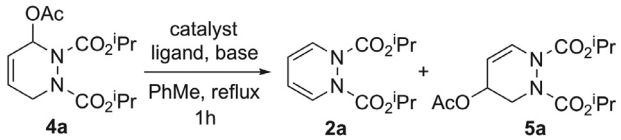
Having identified optimized conditions for the elimination, the two-step cycloaddition-elimination sequence was next applied to a range of different azo compounds. Thus, in addition to DIAD, diene **3a** also underwent successful cycloaddition with five other symmetrical azodicarboxylate reagents to generate the corresponding acetoxytetrahydropyridazines **4**, each bearing different carbamate protecting groups (Table 2). Moreover, two non-symmetrical

Table 2
Preparation of 1,2-dihydropyridazines through Diels-Alder reaction/palladium-catalysed elimination.



[a]Reaction conditions: **3a** (1.5 equiv.), azo compound (1.0 equiv.; 4.0–7.0 mmol), CH_2Cl_2 (2.5–5.0 M), rt or 40 °C, 1–40 h, then $Pd(OAc)_2$ (1 mol%), PPh_3 (4 mol%), NEt_3 (2.0 equiv), 1,4-dioxane (0.5 M), reflux, 1 h.
[b]Isolated yields over two steps after column chromatography.
[c]As footnote a, but yield calculated over three steps also including synthesis of the azo compound from the corresponding hydrazine.
[d]As footnote a, but using 2 mol% $Pd(OAc)_2$ and 8 mol% PPh_3.

Table 1
Optimisation of the palladium-catalysed elimination of allylic acetate **4a**.



Entry	Catalyst	Ligand	Base	Yield[a] **2a** (%)	Yield[a] **5a** (%)
1	$Pd(PPh_3)_3$ (10 mol%)	–	–	73	15
2	$Pd_2(dba)_3$ (10 mol%)	PPh_3 (40 mol%)	–	48[b]	–
3	$Pd(OAc)_2$ (10 mol%)	PPh_3 (40 mol%)	–	77	–
4	$Pd(OAc)_2$ (10 mol%)	dppp (20 mol%)	–	42[c]	39[c]
5	$Pd(OAc)_2$ (10 mol%)	Xantphos (20 mol%)	–	76	–
6	$Pd(OAc)_2$ (1 mol%)	Xantphos (2 mol%)	–	17	47
7	$Pd(OAc)_2$ (1 mol%)	PPh_3 (4 mol%)	NEt_3	83	–

[a] Isolated yield after chromatography.
[b] Difficulties encountered in separating **2a** from dibenzylideneacetone.
[c] Reaction time of 2 h.

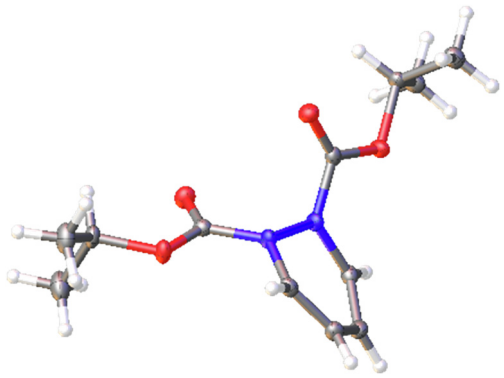


Fig. 1. Solid-state molecular structure of **2a** with thermal ellipsoids drawn at 50% probability.

azodicarboxylate reagents were also investigated, yielding tetrahydropyridazine products **4f** and **4g**, each bearing two orthogonal protecting groups. The acetoxytetrahydropyridazine intermediates **4** required only a rapid purification through a short plug of silica (to remove excess diene **3a**) before being subjected to elimination to give the desired 1,2-dihydropyridazines **2** (Table 2).

The cycloaddition-elimination sequence allows the preparation of the corresponding 1,2-dihydropyridazines **2** on gram-scale in generally high yields (Table 2). Product yields are calculated over two steps (the Diels-Alder cycloaddition and the subsequent elimination), when using commercially available azodicarboxylate reagents (i.e. for **2b**, **2c**, **2d** and **2e**), whereas for 1,2-dihydropyridazines **2a**, **2f**, **2g** and **2h**, the yields are calculated over three steps, including the in-situ preparation of the azodicarboxylate reagent from the corresponding hydrazine through oxidation with iodobenzene diacetate. In the case of **2f** and **2g**, lower yields were obtained than those for the other 1,2-dihydropyridazines, due to the competing formation of rearrangement products **5f** and **5g** respectively. Doubling the catalyst loading resulted in improved yields of **2f**/**2g** compared withthose obtained under the standard conditions (46% yield compared with 22% yield for **2f**; 55% yield compared with 43% yield for **2g**), but in these cases the rearrangement pathway could not be completely suppressed. It should also be noted that in general, the presence of water tends to promote the formation of rearrangement products **5**, therefore the cycloadducts **4** were generally dried in a vacuum desiccator prior to the elimination step. Overall, the two-step reaction sequence is easy to perform and is scalable, as demonstrated by the four-fold scale-up of the synthesis of 1,2-dihydropyridazine **2d**, which produced nine grams of **2d** in comparable yield to that obtained on gram-scale.

The ^{1}H and ^{13}C NMR spectra of 1,2-dihydropyridazines **2a**–**g** are complex, and deserve some comment. At room temperature, broad signals are generally observed, and at least two species are apparent that are in the immediate exchange regime on the NMR timescale. At 75 °C, (partial) coalescence of the peaks occurs, thus simplifying the spectra considerably (see the Supporting Information for variable-temperature NMR studies on 1,2-dihydropyridazine **2b**), whilst upon heating to over 100 °C, degradation occurs. These observations match a previous report on diethyl 3,6-diphenyl-1,2-pyridazinedicarboxylate, for which a dynamic ring-twisting process was proposed [12], similar to those reported for 1,3-cyclohexadiene [13]. This conclusion was further supported by a crystal structure of **2c**, which is similar to that reported by Kaftory and co-workers [14], and the twisted conformation is apparent in the solid-state structure of **2c** due to the large C—N—N—C torsion angle of 44.74(11)° as well as the C=C—C=C torsion of 17.87(14)° (Fig. 1). In contrast, dihydropyridazine **2h** does not exhibit this dynamic behaviour (a single set of resonances is observed by ^{1}H and ^{13}C NMR spectroscopy), presumably due to the lack of conformational freedom afforded by its fused bicyclic structure. It should be noted that several detailed spectroscopic analyses on tetrahydropyridazines have been reported [15], which display similar dynamic behaviour to dihydropyridazines **2a**–**g**.

In conclusion, we have developed a new method for the preparation of 1,2-dihydropyridazines based on a novel Diels-Alder/palladium-catalysed elimination sequence, which is particularly efficient and easy to perform when compared with the previously published synthetic routes. The two-step sequence is readily scalable, producing multigram quantities of 1,2-dihydropyridazines, and this convenient synthetic approach will enable detailed studies into the synthetic potential of these interesting heterocycles. Indeed, further work towards this goal is already underway, and will be reported in due course.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.04.054.

References

[1] (a) J.L. Altman, M.F. Semmelhack, R.B. Hornby, J.C. Vederas, Chem. Commun. (1968) 686–687;
(b) J.L. Altman, M.F. Semmelhack, R.B. Hornby, J.C. Vederas, Org. Prep. Proc. Int. 7 (1975) 35–37.
[2] R.N. Warrener, E.E. Nunn, M.N. Paddon-Row, Aust. J. Chem. 32 (1979) 2659–2674.
[3] R.A. Stearns, P.R. Ortiz de Montellano, J. Am. Chem. Soc. 107 (1985) 234–240.
[4] D.W. Whitman, B.K. Carpenter, J. Am. Chem. Soc. 102 (1980) 4272–4274.
[5] T. Sheradsky, R. Moshenberg, J. Org. Chem. 50 (1985) 5604–5608.
[6] M. Rink, S. Mehta, K. Grabowski, Arch. Pharm. 292 (1959) 225–233.
[7] J. Rigaudy, J.C. Brelière, Bull. Soc. Chim. Fr. (1968) 455–457.
[8] W. Ried, U. Reiher, Chem. Ber. 120 (1987) 1597–1599.
[9] C.J. Ball, J. Gilmore, M.C. Willis, Angew. Chem. Int. Ed. 51 (2012) 5718–5722.
[10] (a) T. Sheradsky, R. Moshenberg, J. Org. Chem. 49 (1984) 587–590;
(b) T. Sheradsky, R. Moshenberg, J. Org. Chem. 51 (1986) 3123–3125.
[11] (a) E.J. Smutny, J. Am. Chem. Soc. 89 (1967) 6793–6794;
(b) J. Tsuji, T. Yamakawa, M. Kaito, T. Mandai, Tetrahedron Lett. 19 (1978) 2075–2078;
(c) B.M. Trost, T.R. Verhoeven, J.M. Fortunak, Tetrahedron Lett. 20 (1979) 2301–2304.
[12] J.E. Anderson, J.-M. Lehn, Tetrahedron 24 (1968) 137–149.
[13] a) S.S. Butcher, J. Chem. Phys. 42 (1965) 1830–1832;
b) M. Traetteberg, Acta Chem. Scand. 22 (1968) 2305–2312;
c) H. Oberhammer, S.H. Bauer, J. Am. Chem. Soc. 91 (1969) 10–16;
d) W. Auf der Heyde, W. Lüttke, Chem. Ber. 111 (1978) 2384–2395.
[14] M. Kaftory, T.H. Fisher, S.M. Dershem, J. Chem. Soc. Perkin Trans. II (1989) 1887–1891.
[15] (a) J.C. Brelière, J.-M. Lehn, Chem. Commun. (1965) 426–427;
(b) R. Daniels, K.A. Roseman, Tetrahedron Lett. 7 (1966) 1335–1342;
(c) C.H. Bushweller, Chem. Commun. (1966) 80–81;
(d) B. Price, I.O. Sutherland, F.G. Williamson, Tetrahedron 22 (1966) 3477–3490;
(e) R. Daniels, K.A. Roseman, Chem. Commun. (1966) 429;
(f) J.E. Anderson, J.-M. Lehn, J. Am. Chem. Soc. 89 (1967) 81–87;
(g) J.E. Anderson, J.-M. Lehn, Tetrahedron 24 (1968) 123–135;
(h) E.W. Bittner, J.T. Gerig, J. Am. Chem. Soc. 94 (1972) 913–922;
(i) K. Bynum, R. Rothchild, Spectrosc. Lett. 30 (1997) 1713–1732.