A CONVENIENT SYNTHESIS OF 1-ARYL- AND 1-ALKYL-1,4,5,6-TETRAHYDROPYRIDAZIN-3(2*H*)-ONES

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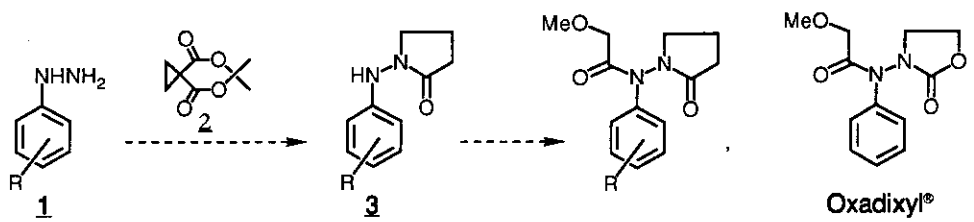
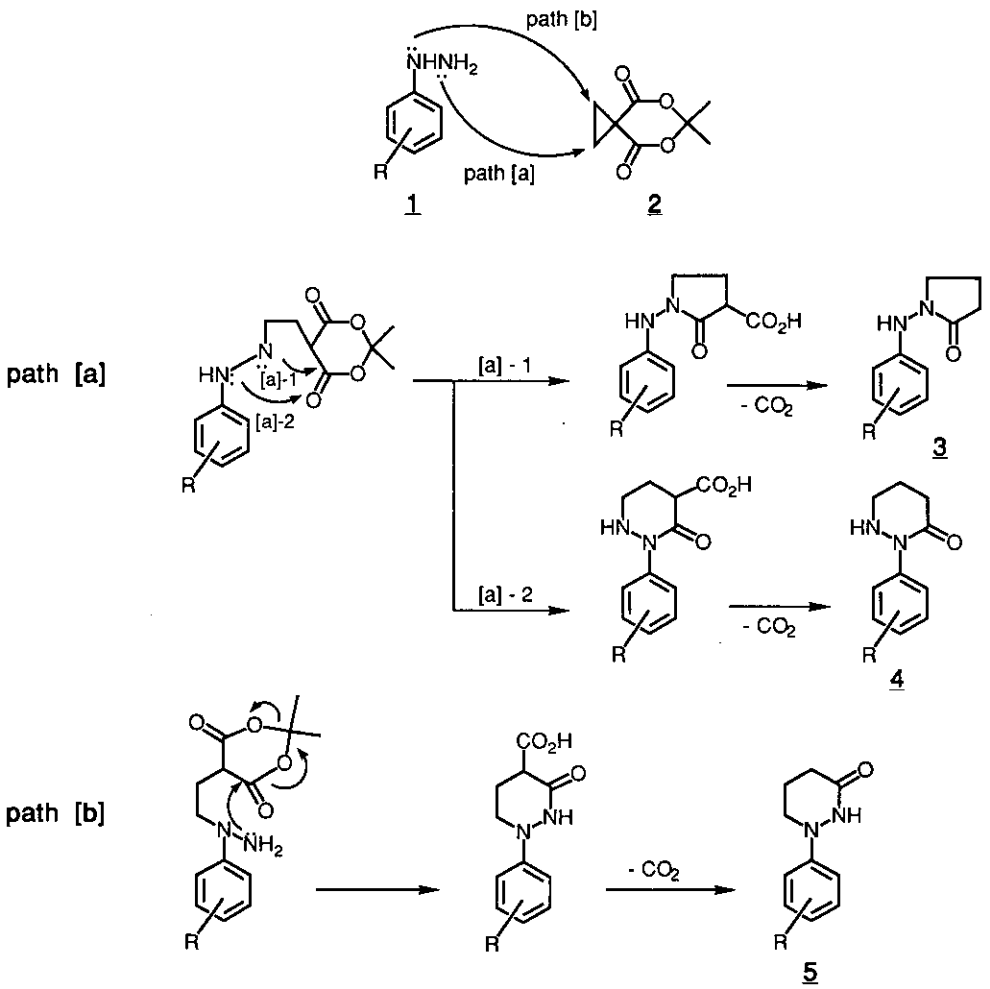
Abstracts - Aryl- and alkylhydrazines react with readily available cyclopropanedicarboxylate (2) in refluxing acetonitrile to afford the corresponding 1-substituted 1,4,5,6-tetrahydropyridazin-3(2*H*)-ones (5) directly *via* nitrogen-carbon bond formation, cyclization and decarboxylation of the cyclized intermediates.

In 1975, Danishefsky *et al.*[1] reported a novel synthesis of 5-membered lactam starting from aniline and cyclopropanedicarboxylate (2). With his case in mind, we were interested in the reaction between hydrazine (1) and 2 to construct 5-membered ring (3), which can be utilized as a intermediate for the carbon analogue of commercial fungicide Oxadixyl.[2]



During the course of our attempted efforts to synthesize 3, however, we have observed that six membered pyridazinone (5) was produced rather than expected 5-membered compound (3). A possible structure of the compounds which could be derived from the reaction of hydrazines with 2 is depicted in Scheme 1. Before we carried out experiment, we assumed that more nucleophilic and less hindered terminal nitrogen of phenylhydrazine will attack electrophile (2) to give either 3 or 4 (path [a]). By preliminary experiment, however, we ruled out the possibility of 5-membered

structure (3) judging from the ir carbonyl stretching frequency ($\upsilon_{C=O}$ = 1662 cm^{-1} rather than over 1700 cm^{-1}).[3]

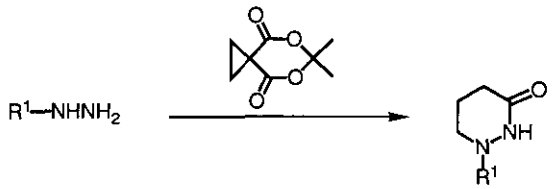


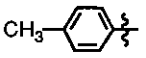
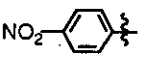
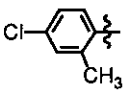
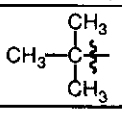
Scheme 1

Then, to determine the structure clearly between the remaining 6-pyridazinone (4) and 3-pyridazinone (5), the following literature precedence was very helpful. Namely, in 1987, Dowlatshahi[4] reported the synthesis of 1-phenyl-1,4,5,6-tetrahydropyridazin-3(2*H*)-one (5, R=H) in three steps

in 41 % overall yield. Blokhina *et al.*[5] also reported a successful preparation of compound (5) *via* several lengthy steps. By comparing the mp and other physical properties of the compounds prepared in our reaction conditions with those of reported compound,[4] they turned out to be 5 rather than 4. Only trace amount (less than 5 percent) of 4 when R is 4-chloro-2-methyl was detected. The nmr spectrum of N-H proton of compound (5) displayed absorption at around 8 ppm in all cases. In contrast the spectrum of the above mentioned minor compound displayed no such signal, although mass spectrum is same as its counterpart (5) So the minor compound is believed to be 4. This tendency to form the pyridazin-3-one (5) is also valid even when aliphatic hydrazine was used (Entry 5, Table 1).

Table 1. Preparation of 1-substituted 1,4,5,6-tetrahydropyridazin-3(2*H*)-ones (5)



Entry	R^1	ir (cm^{-1})	nmr (ppm)[a]	Yield(%)[b]	mp (°C)
1		3154, 1662	1.9(m, 2H), 2.4(m, 2H), 3.7 (t,[c] 2H) 7.8-7.4(m, 5H), 8.2(s, 1H)	58	152-153
2		3154, 1650	2.0(m, 2H), 2.3(m, 5H), 3.8(t,[c] 2H), 6.8-7.2(m, 4H), 8.6(s, 1H)	54	133-134
3		3244, 1697	2.0(m, 2H), 2.4(m, 2H), 3.6(t,[c] 2H), 6.7(d,[c] 2H), 8.2(d,[c] 2H), 8.7(s, 1H)	38	183-185
4		3178, 1663	1.7(m, 2h), 2.3(s, 3H), 2.5(t,[c] 2H), 3.3(t,[c] 2H), 7.1(m, 3H), 8.2(s, 1H)	30	185-186
5		3155, 1654	1.1(s, 9H), 1.9(m, 2h), 2.4(m, 2H), 3.0(t,[c] 2h), 7.5(s, 1H)	68	95-97

a) Spectra were recorded on either Varian Gemini 200 or JEOL JNM-PMX 60 instrument with TMS as reference in $CDCl_3$.

b) Yield is not optimized.

c) J=6Hz.

The typical reaction conditions to get 5 is simply to mix hydrazine and 1 equivalent of 2 in acetonitrile and to reflux for 3-5 h. Several complicated reactions occur in a single one-pot operation to end up with pyridazin-3-one (5) A normal work-up followed by a column chromatography gives the results shown in Table 1. The moderate yield is thought to be caused by unstable nature of the starting hydrazines.

In conclusion, we observed that the major reaction between hydrazine and 2 involves the nucleophilic attack by the more substituted nitrogen of the hydrazine toward electrophile (2) to give pyridazin-3-one (5) rather than pyridazin-6-one (4). Additionally the present method is demonstrated to be useful for the preparation of the pyridazin-3-one (5) by simple and more convenient manner compared with the previously known methods.

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   For the preparation of 2, see S. Danishefsky and R. K. Singh, *Org. Syn.*, 1981, **60**, 66.
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