

NOVEL AND HIGHLY SELECTIVE 1,3-DISUBSTITUTED PYRAZOLE FORMATION
WITH ONE CARBON HOMOLOGATION

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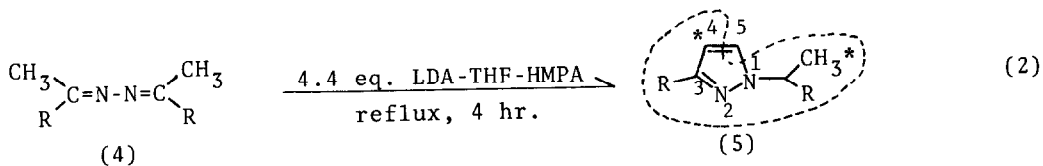
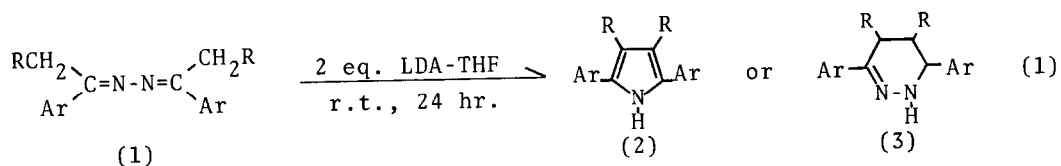
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Recently we have reported a new synthetic method of pyrroles 2 and tetrahydropyridazines 3 from alkyl aryl ketazines 1, where dianions of alkyl aryl ketazines participate in a rearrangement to form the C-C bond¹ (eq 1).

Herein we wish to report a simple and selective preparation method of 1,3-dialkylsubstituted pyrazoles 5 from dialkyl ketazines 4 (eq 2).

In marked contrast to the reaction of alkyl aryl ketazines, dialkyl ketazines were unreactive and recovered completely under the similar conditions (at room temp. for 24 hr.) or even under enforcing conditions (THF reflux for 4 hr.) While with HMPA (hexamethylphosphoric triamide), dialkyl ketazines



4a ; R = t-butyl
4b ; R = cyclopropyl
4c ; R = isopropyl
4d ; R = cyclohexyl
4e ; R = p-anisyl

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took a completely different course of reaction to give 1,3-disubstituted pyrazoles 5, selectively² (eq 2). Thus, 1-(1-t-butyl)ethyl-3-t-butylpyrazole 5a (R = t-butyl) was obtained in 46% yield from pinacolone azine 4a according to the following procedure; A solution of pinacolone azine (980 mg, 5 mmol) in HMPA (3.9 ml, 22 mmol) was added into a solution of LDA (22 mmol; lithium diisopropylamide) in 15 ml of THF at room temperature under argon. After refluxing for 4 hr., the reaction mixture was poured into water and extracted with ether, and dried over sodium sulfate. Evaporation of solvent and subsequent distillation (Kugelrohr 145-150°C/ 30 mmHg) gave pyrazole 5a.

Other ketazines (isopropyl methyl ketone, cyclopropyl methyl ketone, cyclohexyl methyl ketone, and p-methoxyacetophenone azines³) were examined and this pyrazole formation reaction was found general for ketazines of methyl sec- or tert-alkyl ketones. The reaction conditions, isolated yields, and boiling points of products are summarized in Table.

The remarkable features of this reaction are the highly selective formation of 1,3-disubstituted pyrazoles and one carbon homologation in products. (i.e., C₁₃H₂₄N₂ for 5a; C₁₂H₂₄N₂ for 4a).

As has been described in a previous communication,¹ dianion generation from alkyl aryl ketazines was confirmed by the D₂O quenching experiments. On the other hand, no deuterium incorporation was observed in the recovered pinacolone azine under the similar conditions or even under the enforcing conditions (i.e., D₂O quenching after reaction for 30 min. under the conditions which provided pyrazole). In addition, the reaction with hexadeuterio-pinacolone azine yielded pyrazole 5a without deuterium at any position.

These evidences seem to indicate that the monoanion with a short lifetime, which equilibrates with other molecules (most likely with HMPA⁴) to establish the complete proton exchange before pyrazole formation, plays an important role in the reaction of dialkyl ketazines. HMPA is indispensable to this reaction. Without this the reaction resulted in the complete recovery of ketazine even in the presence of N,N,N',N'-tetramethylethylenediamine, which had been confirmed to assist the monoanion generation.⁵

In order to pursue the origin of the extra carbon, ¹³C experiments were

Table. Reaction Conditions and Physical Data of 1,3-Disubstituted Pyrazoles^{a)}

Starting material	LDA(eq.)	Product	Yield	bp.
<u>4a</u> (R = ^t butyl)	4.4	<u>5a</u>	46	145-150°C/30 mmHg
<u>4b</u> (R = cyclopropyl)	4.4	<u>5b</u>	28	122°C/5 mmHg
<u>4c</u> (R = isopropyl)	4.4	<u>5c</u>	25	115°C/35 mmHg
<u>4d</u> (R = cyclohexyl)	4.4	<u>5d</u>	28	142°C/0.6 mmHg
<u>4e</u> (R = p-anisyl) ^b	2.2	<u>5e</u>	40	(heavy oil)

a) Ketazines were refluxed for 4 hrs with the indicated amount of LDA in the presence of 4.4 eq. of HMPA in THF. 5a-5e had the correct composition established by microanalyses and showed the satisfactory spectral data (nmr, ir, mass, and uv). b) In order to dissolve a starting ketazine, 12 eq. of HMPA was used.

undertaken with pinacolone azine, whose methyl carbon was enriched with ¹³C⁶, where ¹³C was found to distribute only both to C(4) and methyl group of substituent of N(1) in pyrazole 5a (starred in eq. 2). This indicates clearly that C(5) carbon of 5a was taken into from other molecules than ketazine 4a.

Judging from the evidences outlined above, we tentatively conclude that HMPA served not only as an assistant for anion generation but also as a carbon source of C(5).

A detailed mechanistic study and an extension to the rearrangement of the unsymmetrical ketazines are now under way.

References and Notes

- 1) Z. Yoshida, T. Harada, and Y. Tamaru, *Tetrahedron Letters*, 3823 (1976).
- 2) A study on the structural determination of pyrazole will be presented in due course.
- 3) Interestingly, p-methoxyacetophenone azine reacted to give pyrrole and/or tetrahydropyridazine under the conditions in ref. 1 (i.e., without HMPA). (Unpublished results)
- 4) a) H. Normant, T. Cuvigny, and G. I. Martin, *Bull. Soc. Chem. Fr.*, 1969, 1605.
b) P. Savignac, M. Dreux, and Y. Leroux, *Tetrahedron Letters*, 2651 (1974).
c) P. Savignac, Y. Leroux, and H. Normant, *Tetrahedron*, 31, 877 (1975).
- 5) By quenching with D₂O, mono-deuterium was introduced into one of the two methyl groups of pinacolone azine in the experiment with N,N,N',N'-tetramethylethylenediamine.
- 6) Pinacolone azine with methyl group enriched with ¹³C was synthesized from ¹³CH₃I and pivalic acid according to the following literature;
T. Mukaiyama, M. Araki, and T. Takei, *J. Amer. Chem. Soc.*, 95, 4764 (1973).