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DEPROTONATIVE ZINCATION OF HETEROAROMATICS USING ZnI_2 AND *tert*-Bu-P4 BASE

Tatsushi Imahori, Koichi Suzawa, and Yoshinori Kondo*

Graduate School of Pharmaceutical Sciences, Tohoku University, Aobayama, Aoba-ku, Sendai 980-8578, Japan

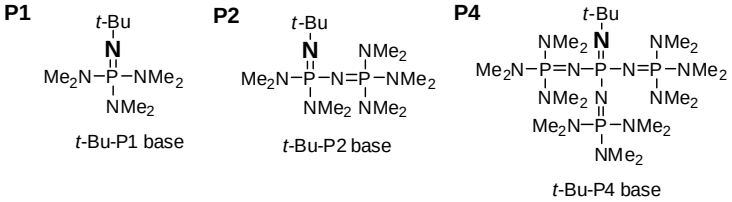
Dedicated to Professor Ryoji Noyori on the occasion of his 70th Birthday

Abstract – The direct deprotonative zincation of diazines was accomplished using the combination of ZnI_2 and *t*-Bu-P4 base and unique regioselectivities of zincation were observed.

Selective functionalization of nitrogen heteroaromatic compounds has been regarded as one of the most important subjects in heterocyclic chemistry oriented toward drug discovery research. Organometallic chemistry have played an important role and various heteroarylmetal compounds have been prepared for the selective bond formation to introduce substituents.[1] Deprotonation using a metallic base is a common method for the preparation of heteroarylmetal and is known to show high regioselectivity.

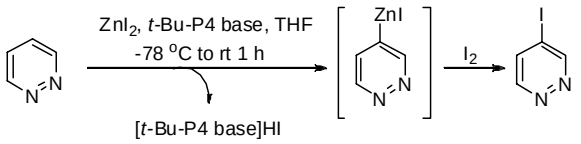
Especially, deprotonative lithiation has been intensively investigated and the reaction generally proceeds at adjacent position of heteroaroms in heteroaromatic compounds.[2] The lithiated heteroaromatic compounds can be easily converted to heteroarylzinc compounds by the treatment with zinc halides. Synthetic utility of organozinc compounds are well recognized as a useful coupling partner in palladium catalyzed cross coupling reaction of aryl and alkenyl halides and also in copper mediated coupling reactions with various electrophiles.[3] Organozinc compounds usually have high compatibility with various electrophilic functional groups and considered to be suitable reactive molecules for medicinal chemistry. In connection with our recent interests on aromatic and heteroaromatic carbanion chemistry using deprotonative zincation,[4] we investigated zincation of diazines using the combination of organic super base and zinc halide.

Phosphazene bases developed by Schwesinger are known as strong non-metallic organic bases.[5] Among them, *t*-Bu-P4 base shows extremely high basicity and has been used for various selective deprotonative transformation and other catalytic reactions.[6,7]



We recently reported novel deprotonative functionalization of aromatic and heteroaromatic compounds using *t*-Bu-P4 base and unique regioselectivities in the deprotonation of diazines were disclosed.[7f] It is well known that the conventional deprotonation using lithium tetramethylpiperidide (LTMP) proceeds at α position adjacent to ring nitrogen,[8] and in contrast to this, the deprotonation using *t*-Bu-P4 base proceeded at the most remote position from the ring nitrogen. Based on these backgrounds, we investigated direct zincation of diazines using *t*-Bu-P4 base in the presence of zinc iodide.

Table 1. Deprotonative Zincation of Pyridazine

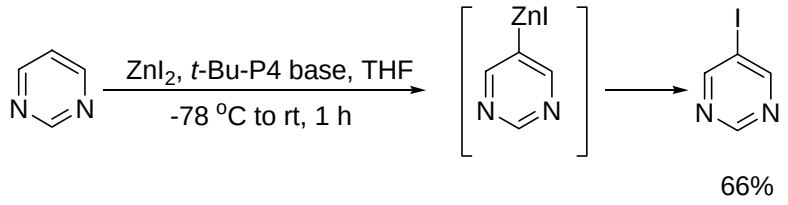


entry	*t*-Bu-P4 base (eq)	ZnI_2 (eq)	Yield (%)
1	1.0	1.0	0
2	1.0	1.6	trace
3	1.0	2.0	14
4	1.5	3.0	46
5	3.0	6.0	83

First, pyridazine was chosen as a substrate and was reacted with zinc iodide and *t*-Bu-P4 base in THF at –78 °C followed by warming up to room temperature under various ratio of reagents as shown in Table 1. The formation of pyridazinylzinc iodide was monitored by the treatment of the organozinc with I_2 to form iodopyridazine. When 1equiv. *t*-Bu-P4 base and 1 equiv. ZnI_2 was used for the reaction followed by the quench with I_2, no formation of 4-iodopyridazine was observed (Table 1, entry 1). This fact suggests that no pyridazinylzinc iodide was formed under this reaction condition. The reaction was then conducted with 1 equiv. *t*-Bu-P4 base and 2 equiv. ZnI_2 followed by treatment with I_2, and 4-iodopyridazine was obtained in 14% yield (Table 1, entry 3). In order to optimize the yield of iodopyridazine, the molar ratios of *t*-Bu-P4 base and ZnI_2 were further increased and the conditions with 3equiv. *t*-Bu-P4 base and 6 equiv. ZnI_2 gave the iodide in 83% yield (Table 1, entry 5). Under this condition, the conversion of pyridazine to pyridazinylzinc iodide is considered to be reasonable. Here the regioselectivity of the metallation is important and the zincation proceeded exclusively at the 4-position of pyridazine.

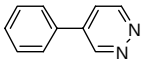
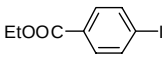
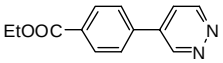
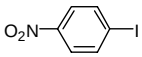
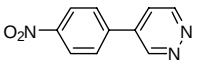
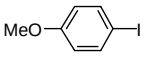
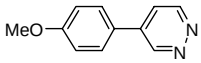
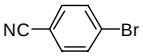
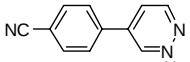
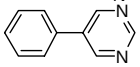
Pyrimidine was then reacted under the similar reaction conditions, namely by treatment with 3equiv. *t*-Bu-P4 base and 6 equiv. ZnI_2, 5-pyrimidinylzinc iodide was formed, which was treated with I_2 to give 5-iodopyrimidine in 66% yield (Scheme 1). Here the unique regioselectivity at 5-position was observed in contrast to the conventional deprotonative lithiation.

Scheme 1 Deprotonative Zincation of Pyrimidine



These diazinylzinc compounds prepared from the direct zincation using *t*-Bu-P4 base and ZnI_2, were reacted with aryl halides in the presence of palladium catalyst to give heterobiaryl compounds. Excellent one-pot arylations of diazines was achieved.

Table 2 Palladium Catalyzed Coupling Reaction of Heteroarylzinc Derivatives

Entry	Het-Ar-H	Ar-X	Hetr-Ar-Ar	Yield (%)
1				76
2				91
3				89
4				92
5				71
6				73

Pyridazine was reacted with zinc iodide and *t*-Bu-P4 base in THF at –78 °C followed by warming up to room temperature and the pyridazinylzinc iodide was treated with iodobenzene in the presence of $Pd(PPh_3)_4$ at room temperature for 24 h to give 4-phenylpyridazine in 76% yield (Table 2, entry 1). Other aryl halides with functional groups, such as ethyl 4-iodobenzoate, 4-iodonitrobenzene, 4-iodoanisole, 4-bromobenzonitrile reacted smoothly with the pyridazinylzinc iodide to give 4-arylpyridazines in good yields (Table 2, entries 2-5). Pyrimidine was also reacted with zinc iodide and *t*-Bu-P4 base in THF at –78 °C followed by warming up to room temperature and the pyrimidinylzinc iodide was treated with iodobenzene in the presence of $Pd(PPh_3)_4$ at room temperature for 24 h to give 5-phenylpyrimidine in 73% yield (Table 2, entry 6).

In summary, direct deprotonative zincation of diazines was accomplished using the combination of ZnI_2 and *t*-Bu-P4 base and unique regioselectivities were observed. To the best of our knowledge, simple 4-pyridazinylzinc halide and 5-pyrimidinylzinc halide without substituents on the rings were first prepared by the present method. Further investigations for the scope and limitation of the aromatic zincation and the mechanistic studies of the reaction are underway.

ACKNOWLEDGMENT

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