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A NEW INTRAMOLECULAR BARBIER REACTION OF N-(2-IODOBENZYL)PHENACYLAMINES: A CONVENIENT SYNTHESIS OF 1,2,3,4-TETRAHYDROISOQUINOLIN-4-OLS

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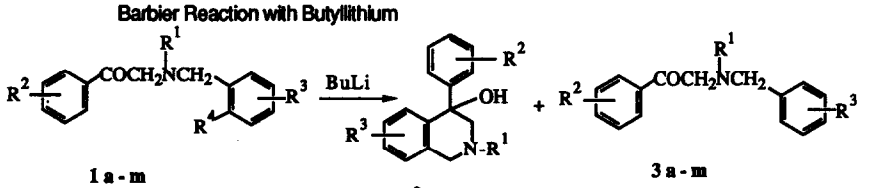
Summary: 4-Phenyl-1,2,3,4-tetrahydroisoquinolin-4-ols were prepared by an intramolecular Barbier reaction of N-(2-iodobenzyl)phenacylamines with butyllithium in good yields.

The Barbier reaction has attracted many organic chemists,[1] since this one-step reaction provides an easy method for carbon-carbon bond formation.[2] Recently, this reaction was modified using a variety of metals[3] under ultrasound irradiation.[4] Most are intermolecular reactions between allyl or benzyl halides and ketones or aldehydes and others are intramolecular cyclization reactions[3g,5] of alkyl halides containing a carbonyl group. However, there is no report on the Barbier cyclization reaction of aryl halides. We now describe the first example of the intramolecular Barbier reaction of aryl halides, N-(2-iodobenzyl)phenacylamines (**1**), with butyllithium for the convenient synthesis of biologically active 4-phenyl-1,2,3,4-tetrahydroisoquinolin-4-ols (**2**).[6]

A typical experimental procedure follows: BuLi (0.52 ml of 1.6M solution in hexane, 0.83 mmol) was added to a dry THF (5 ml) solution of **1a** (235 mg, 0.64 mmol) at -78°C under stirring and N_2. The mixture was stirred for 10 min, water was added and extracted with ether. Preparative TLC of the extract gave the cyclization product **2a** (106 mg, 69%) and the deiodinated product **3a** (28 mg, 18%). Table I summarizes the results for other phenacylamines (**1b-m**).

Table I. Synthesis of 4-Phenyl-1,2,3,4-tetrahydroisoquinolin-4-ols by Intramolecular Barbier Reaction with Butyllithium



1 a - m　　2a-m　　3 a - m

	R^1	R^2	R^{3a}	R^4	Isolated Yield of Product (%) (2)	(3)
a:	Me	H	H	I	69	18
b:	Me	4'-OMe	H	I	50	21
c:	Me	4'-OMe	6,7-$(OMe)_2$	I	77	3
d:	Me	4'-OMe	5,6-$(OMe)_2$	I	64	15
e:	Me	4'-Cl	H	I	62	8
f:	Me	3'-Cl	H	I	54	6
g:	Me	4'-Br	H	I	67	12
h:	Me	4'-F	H	I	59	9
i:	CH_2Ph	H	H	I	86	0
j:	CH_2Ph	H	6,7-$(OMe)_2$	I	71	5
k:	COOEt	H	H	I	61	0
l:	Me	4'-OMe	5,6-$(OMe)_2$	Br	14	7
m:	Me	4'-OMe	6,7-$(OMe)_2$	Br	0	28

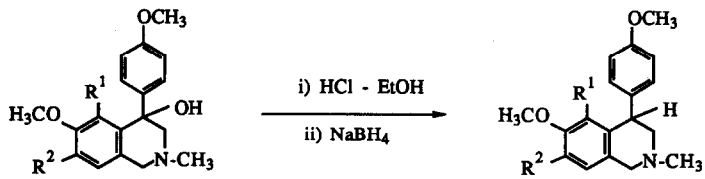
a)Numbering is for **2**.

Synthesis of **2** reported so far needed multi-step reactions[7] and we recently reported the synthesis of **2** by insertion reaction of **1** with zerovalent nickel in short steps but in low yields.[8] The present reaction is therefore the most convenient and simplest method for the preparation of **2**.

The present reaction gave good results for compounds (**1e-h**) having halogen atoms (F,Cl, Br) on the phenacyl benzene ring, contrary to the insertion reaction of **1e** and **1f** which gave dehalogenated products along with **2e**[8a] and **2f**.[9] On the other hand, this reaction was not so effective for compounds (**1l** and **1m**) containing a bromine atom on the benzyl benzene ring as for the iodo compounds.

These isoquinolin-4-ols are easily converted to pharmacologically active 4-aryl-1,2,3,4-tetrahydroisoquinolines.[10] Amaryllidaceae alkaloids, (±)-O,O-dimethylcherylline (**4**)[11a] and (±)-O,O-dimethyllatifine (**5**)[11b,c] were prepared by dehydration and reduction of **2c** and **2d** in 70 and 73% yields, respectively.

Application of this new cyclization reaction to the preparation of other benzoheterocyclic compounds is in progress.



2c: R^1=H, R^2=OCH_3
2d: R^1=OCH_3, R^2=H

4: R^1=H, R^2=OCH_3
5: R^1=OCH_3, R^2=H

References and Notes

1. a) G.Molle and P.Bauer, *J. Am. Chem. Soc.*, **104**, 3481 (1982); b) H.Choi, A.A.Pinkerton, and J.L.Fry, *J. Chem. Soc., Chem. Commun.*, **1987**, 225; c) Z.Paryzek and K.Blaszczyk, *Can. J. Chem.*, **65**, 229 (1987); d) N.-Y.Shih, P.Mangiaracina, M.J.Green, and A.K.Ganguly, *Tetrahedron Lett.*, **30**, 5563 (1989).
2. C.Blomberg and F.A.Hartog, *Synthesis*, **1977**, 18.
3. a) P.J.Pearce, D.H.Richards, and N.F.Scilly, *J. Chem. Soc. (P 1)*, **1972**, 1655; b) G.G.Cameron and A.J.S.Milton, *J. Chem. Soc. (P 2)*, **1976**, 378; c) H.Tanaka, T.Hamatani, S.Yamashita, and S.Torii, *Chem. Lett.*, **1986**, 1461; d) Y.Butsugan, J.Ito, and S.Araki, *Tetrahedron Lett.*, **28**, 3707 (1987); e) H.Tanaka, T.Nakahara, H.Dhimane, and S.Torii, *ibid.*, **30**, 4161 (1989); f) M.Wada and K.-Y.Akiba, *ibid*, **26**, 4211 (1985); g) G.A.Molander and J.B.Etter, *J. Org. Chem.*, **51**, 1778 (1986); h) J.L.Namy, J.Collin, J.Zhang, and H.B.Kagan, *J. Organomet. Chem.*, **328**, 81 (1987); i) W.Wang, L.Shi, R.Xu, and Y.Huang, *J. Chem. Soc. (P 1)*, **1990**, 424.
4. a) J.-L.Luche and J.-C.Damiano, *J. Am. Chem. Soc.*, **102**, 7926 (1980); b) J.C.S.-Barboza, J.-L.Luche, and C.Petrier, *Tetrahedron Lett.*, **28**, 2013 (1987); c) J.C.S.-Barboza, C.Petrier, and J.-L.Luche, *J. Org. Chem.*, **53**, 1212 (1988); d) Y.Goldberg, R.Sturkovich, and E.Lukevics, *Heterocycles*, **29**, 597 (1989).
5. a) J.K.Crandall and H.S.Magaha, *J. Org. Chem.*, **47**, 5368 (1982); b) K.Kakiuchi, H.Takeuchi, Y.Tobe, and Y.Odaira, *Bull. Chem. Soc. Jpn.*, **58**, 1613 (1985); c) Y.Leroux, *Bull. Soc. Chim. Fr.*, **1968**, 359; d) M.P.Cooke,Jr. and I.N.Houpis, *Tetrahedron Lett.*, **26**, 4987 (1985).
6. a) Y.Ishida, N.Koga, T.Nanbu, M.Kihara, and S.Kobayashi, *Br. J. Pharmacol.*, **94**, 19 (1988); b) M.Kihara, M.Kashimoto, S.Kobayashi, Y.Ishida, H.Moritoki and Z.Taira, *J. Med. Chem.*, "in press".
7. a) I.G.Hinton and F.G.Mann, *J. Chem. Soc.* ,**1959**, 599; b) D.V.Gardner, U.S.Pat. 4,113,869, 1978; c) B.Leseche, J.Gilbert, and C.Viel, *J. Heterocyclic Chem.*, **18**, 143 (1981); d) G.Grethe, J.L.Lee, M.Uskokovic, and A.Brossi, *J. Org. Chem.*, **33**, 491 and 494 (1968); e) S.N.Quessy, L.R.Williams, and V.G.Baddeley, *Synth. Commun.*, **8**, 45 (1978).
8. a) M.Kihara, Y.Ishida, and S.Kobayashi, *J. Chem. Research (S)*, **1987**, 236; b) M.Kihara, A.Nakanishi, and S.Kobayashi, *Heterocycles*, **29**, 957 (1989).
9. M.Kihara, Y.Kobayashi, and M.Kashimoto, unpublished results.
10. S.J.Coote, S.G.Davis, D.Middlemiss, and A.Naylor, *J. Chem. Soc. (P 1)*, **1989**, 2223 and references cited therein.
11. a) S.Kobayashi, T.Tokumoto, M.Kihara, Y.Imakura, T.Shingu, and Z.Taira, *Chem. Pharm. Bull.*, **32**, 3015 (1984); b) S.Kobayashi, T.Tokumoto, and Z.Taira, *J. Chem. Soc., Chem. Commun.*, **1984**, 1043; c) S.Kobayashi, T.Tokumoto, S.Iguchi, M.Kihara, Y.Imakura, and Z.Taira, *J. Chem. Research (S)*, **1986**, 280.

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