Cyclocondensation of activated *ortho*-chloroarylacetylenes with hydrazine: a novel route to substituted indazoles

Sergey F. Vasilevsky*[a] and Tat'yana A. Prikhod'ko[b]

[a] *Institute of Chemical Kinetics and Combustion, Siberian Branch of the Russian Academy of Sciences, 630090 Novosibirsk, Russian Federation. Fax: +7 383 235 2350; e-mail: vasilev@kinetics.nsk.su*

[b] *Department of Chemistry, Novosibirsk State University, 630090 Novosibirsk, Russian Federation. Fax: +7 383 235 5237*

The reaction of *ortho*-chloroarylacetylenes activated by electron-withdrawing substituents with $NH_2NH_2{\cdot}H_2O$ affording substituted indazoles is reported.

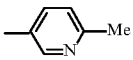
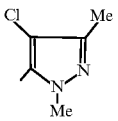
One approach to the synthesis of condensed polynuclear heteroaromatics is based on the cyclization of *vic*-functionalized aryl- and hetarylacetylenes.[1–6] To the best of our knowledge, heterocyclization of *ortho*-acetylenic aryl hydrazines has not been especially studied. Ames and Bull[7] have described the reactions of 4-chloro-, 4-phenoxy- and 4-diethylamino-3-phenylethynylcinnoline with NH_2NHR leading, according to the structure of R in the reagent, to the formation of a pyrazole or pyrrole ring in 20–39% yield. The reaction may proceed *via* a 4-hydrazino intermediate, but the authors did not explain the reasons for the different courses of the reaction. Since the cyclization was realized using only one example of a rather reactive 4-chlorocinnoline, the question of to what extent the reaction is common remained unclear. Nevertheless, at present the direction of the *vic*-acetylenylarylhydrazine cyclization cannot be predicted because there are two nucleophilic nitrogen atoms in the function of the initial compounds and either is capable of attacking both the α- and β-carbon atom of the vicinal acetylenic substituent. In this case, the closing of both 5-(pyrrole, pyrazole) and the six-membered cyclic 1,2-dihydro-1,2-diazine is possible. Baldwin's rules, however, do not allow one to discriminate between the alternative formation of five-membered or six-membered rings when either is possible.[8]

In this connection we have initiated a systematic study of the reaction between *ortho*-acetylenylchloroarenes **1a–d** and $NH_2NH_2{\cdot}H_2O$. Compounds **1a–d** were prepared in 75–85% yield by condensation of the aryl iodides **2,3** with the terminal acetylenes **4a–d** in the presence of $(PPh_3)_2PdCl_2$, CuI and Et_3N (Scheme 1). The reactions of **1a–d** with $NH_2NH_2{\cdot}H_2O$ were carried out in refluxing butanol. Under these conditions, *o*-chlorotolane **1a** did not react with $NH_2NH_2{\cdot}H_2O$ and could be recovered almost quantitatively even after heating for more than 30 h.

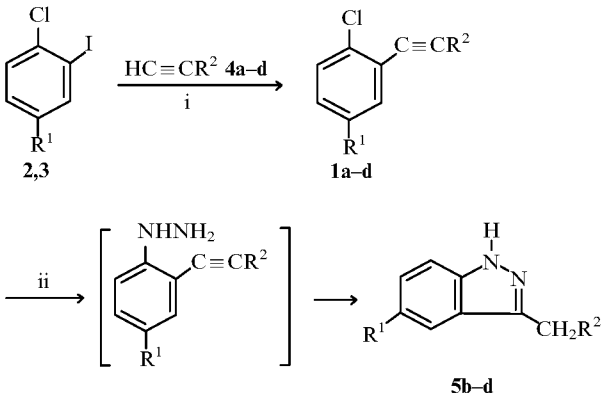
Substrate activation by a single nitro group has also appeared to be insufficient. Thus, boiling *o*-chloro-*m*′-nitrotolane for 60 h gave a complex mixture of products; TLC, IR and NMR control showed that the major component was the initial tolane.

Only the acetylenic chlorides **1b–d** turned out to be reactive, obviously due to the enhanced lability of the chlorine atom under the influence of a *para*-nitro group; they were transformed into 3,5-disubstituted indazoles **5b–d**[†] within 1–6 h in 65–88% yields (Table 1).

Table 1 Cyclocondensation of arylacetylenes **1** with $NH_2NH_2{\cdot}H_2O$ (Scheme 1).

Acetylene **1**	R^1	R^2	Indazole **5**	Yield (%)
a	H	Ph	[a]	–
b	NO_2	*p*-$NO_2C_6H_4$	**b**	88
c	NO_2		**c**	65
d	NO_2		**d**	66

[a] **1a** (91%) was recovered after heating for 34 h.



Scheme 1 *Reagents and conditions*: i, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, benzene, 25–80 °C, 4–11 h; ii, $NH_2NH_2{\cdot}H_2O$, BuOH, reflux, 1–6 h.

Such a course of cyclization (pyrazole formation) is assigned to the triple bond polarization caused by the influence of both the acceptor group of the acetylene fragment and the donor group ($NHNH_2$). Under these conditions the α-atom to the C≡C bond has a relatively large positive charge.

To confirm that substitution of the chlorine atom is the first stage of the cyclocondensation, rather than nucleophilic addition of NH_2NH_2 to the activated triple bond, we introduced piperidine into the reaction with **1d**. The action of this N-nucleophile on **1d** ought to be similar to that of $NH_2NH_2{\cdot}H_2O$, but neither of the two possible products is

[†] All compounds synthesized gave satisfactory analytical and spectroscopic data.

5b: mp 213–214 °C (from acetone); ^{1}H NMR ([$^2H_6$]acetone) δ 4.64 (s, 2H, CH_2), 7.70–8.30 (m, 6H, $C_6H_4NO_2$, H-6,7), 8.72 (d, $J_{4,6}$ 1.6 Hz, 1H, H-4), 12.60 (br.s, 1H, NH); IR (KBr) ν/cm^{-1} 1370, 1400, 1530, 1570 (NO_2), 3450 (br., NH).

5c: mp 218–219 °C (from EtOH); ^{1}H NMR ([$^2H_6$]acetone) δ 2.43 (s, 3H, Me), 4.45 (s, 2H, CH_2), 7.16 (d, $J_{\beta,\gamma}$ 7 Hz, 1H, β-H Py), 7.65 (d, $J_{\gamma,\beta}$ 7 Hz, 1H, γ-H Py), 7.72 (d, $J_{7,6}$ 7.2 Hz, 1H, H-7), 8.21 (dd, $J_{6,7}$ 7.2 Hz, $J_{6,4}$ 1.6 Hz, 1H, H-6), 8.55 (s, 1H, α-H Py), 8.70 (d, $J_{4,6}$ 1.6 Hz, 1H, H-4), 12.70 (br.s, 1H, NH); IR (KBr) ν/cm^{-1} 1370, 1510 (NO_2), 3450 (br., NH).

5d: mp 243–244 °C (from EtOH); ^{1}H NMR ([$^2H_6$]acetone) δ 2.75 (s, 3H, CMe), 3.70 (s, 3H, NMe), 4.45 (s, 2H, CH_2), 7.65 (d, $J_{7,6}$ 9 Hz, 1H, H-7), 8.15 (dd, $J_{6,7}$ 9 HZ, $J_{6,4}$ 2.2 Hz, 1H, H-6), 8.70 (d, $J_{4,6}$ 2.2 Hz, 1H, H-4), 12.50 (br.s, 1H, NH); IR (KBr) ν/cm^{-1} 1330, 1510 (NO_2), 3400 (br., NH).

capable of cyclization. The formation of only 4-chloro-1,3-dimethyl-5-(5-nitrophenylethynyl-2-piperidino)pyrazole **6**,[‡] (94.3%) confirms the correctness of the assumed reaction scheme.

In conclusion, cyclocondensation of activated *ortho*-chloroarylacetylenes with $NH_2NH_2 \cdot H_2O$ leads to substituted indazoles and is a novel method of synthesis of these compounds.

We thank Professor M. S. Shvartsberg for highly valuable advice on and discussion of this work.

The work was supported by grant no. 95-03-08928a from the Russian Foundation for Basic Research.

References

1 M. S. Shvartsberg, I. D. Ivanchikova and L. G. Fedenok, *Tetrahedron Lett.*, 1994, **35**, 6749.
2 S. F. Vasilevsky and E. V. Tretyakov, *Liebigs Ann. Chem.*, 1995, 775.
3 S. F. Vasilevsky, A. V. Pozdnyakov and M. S. Shvartsberg, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1985, 1367 (*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1985, **34**, 1250).
4 T. Sakamoto, Y. Kondo and H. Yamanaka, *Heterocycles*, 1988, **27**, 2225.
5 T. A. Prikhod'ko, S. F. Vasilevsky and M. S. Shartsberg, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1984, 2602 (*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1984, **33**, 2383).
6 A. V. Piskunov and M. S. Shvartsberg, *Mendeleev Commun.*, 1995, 155.
7 D. E. Ames and D. Bull, *Tetrahedron*, 1982, **38**, 383.
8 J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 1976, 734.

[‡] **6**: mp 113–114 °C (from EtOH); ^{1}H NMR ($CDCl_3$) δ 1.75 [m, 6H, $C(CH_2)_3C$], 2.35 (s, 3H, CMe), 3.45 (m, 4H, CH_2NCH_2), 3.95 (s, 3H, NMe), 6.95 (d, $J_{3,4}$ 8 Hz, 1H, H-3), 8.15 (d, $J_{4,3}$ 8 Hz, 1H, H-4), 8.40 (s, 1H, H-6); IR (KBr) ν/cm^{-1} 1330, 1540 (NO_2), 2220 (C≡C).

Received: Moscow, 7th December 1995
Cambridge, 6th February 1996; Com. 5/08183A