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

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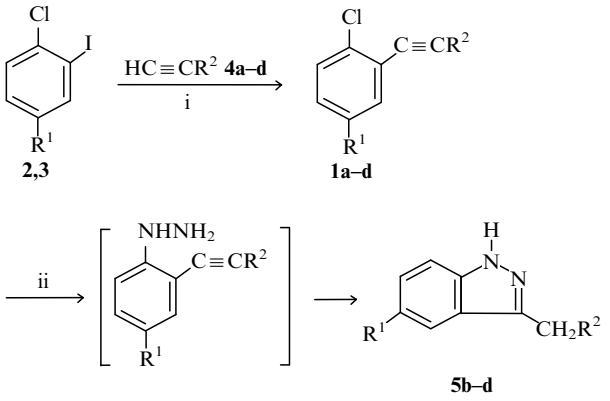
The reaction of *ortho*-chloroarylacetylenes activated by electron-withdrawing substituents with $NH_2NH_2{\cdot}H_2O$ affording substituted indazoles is reported.

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.

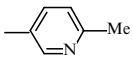
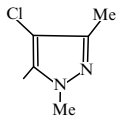
Substrate activation by a single nitro group has also appeared to be insufficient. Thus, boiling *o*-chloro-*m*′-nitrotolane for 60 h gave a complex mixture of products; TLC, IR and NMR control showed that the major component was the initial tolane.

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).



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.

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.

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.

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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).

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