FISCHER REACTION OF 1-ACETYL-3-OXO-2,3-DIHYDROINDOLE and 1-(*p*-TOLUENESULFONYLOXY)-3-OXO-2,3-DIHYDROINDOLE

Jean-Yves Mérour* and Laurence Savelon

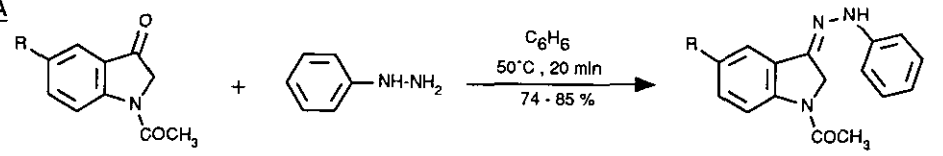
LCBA URA 499, UFR Sciences, BP 6759, Université d'Orléans,
45067 Orléans Cedex 2, France

Abstract — 1-(*p*-Toluenesulfonyloxy)-3-oxo-2,3-dihydroindole reacted with phenylhydrazine in acetic acid affording 5-(*p*-toluenesulfonyloxy)indolo[3,2-*b*]indole. By contrast 1-acetyl-3-oxo-2,3-dihydroindole in the same experimental conditions afforded 12-aminoindolo[1,2-*c*]quinazoline.

The Fischer cyclisation[1~3] of phenylhydrazones provides a simple route to indole rings. This reaction has been used to prepare polycycles as thianaphteno[3,2-*b*]indole[4] and benzofuro[3,2-*b*]indole.[5] In connection with our research program[6,7] on the reactivity of 1-acetyl-3-oxo-2,3-dihydroindole (**1a**), the Fischer reaction has been applied to this substrate.

The phenylhydrazones (**2a,b**) were prepared by heating phenylhydrazine with 1-acetyl-3-oxo-5-substituted 2,3-dihydroindoles (**1a,b**) in benzene at 50 °C and isolated as solid after cooling (method A).

Method A



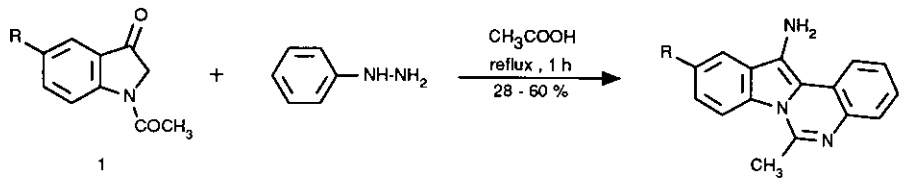
1a R = H
1b R = OCH_3

2a R = H
2b R = OCH_3

Heating, under acid catalyzed conditions (acetic acid/reflux/1 h),[8,9] of the 5-substituted phenylhydrazones (**2a,b**) afforded after cooling 12-amino-6-methyl-10-substituted indolo[1,2-*c*]quinazolines (**3a,b**) (method B).

The compounds (**3a-d**) were also directly obtained by heating 1-acetyl-3-oxo-5-substituted 2,3-dihydroindoles (**1a-d**) with phenylhydrazine in acetic acid without isolation of the phenylhydrazones (**2a-d**) (method C).

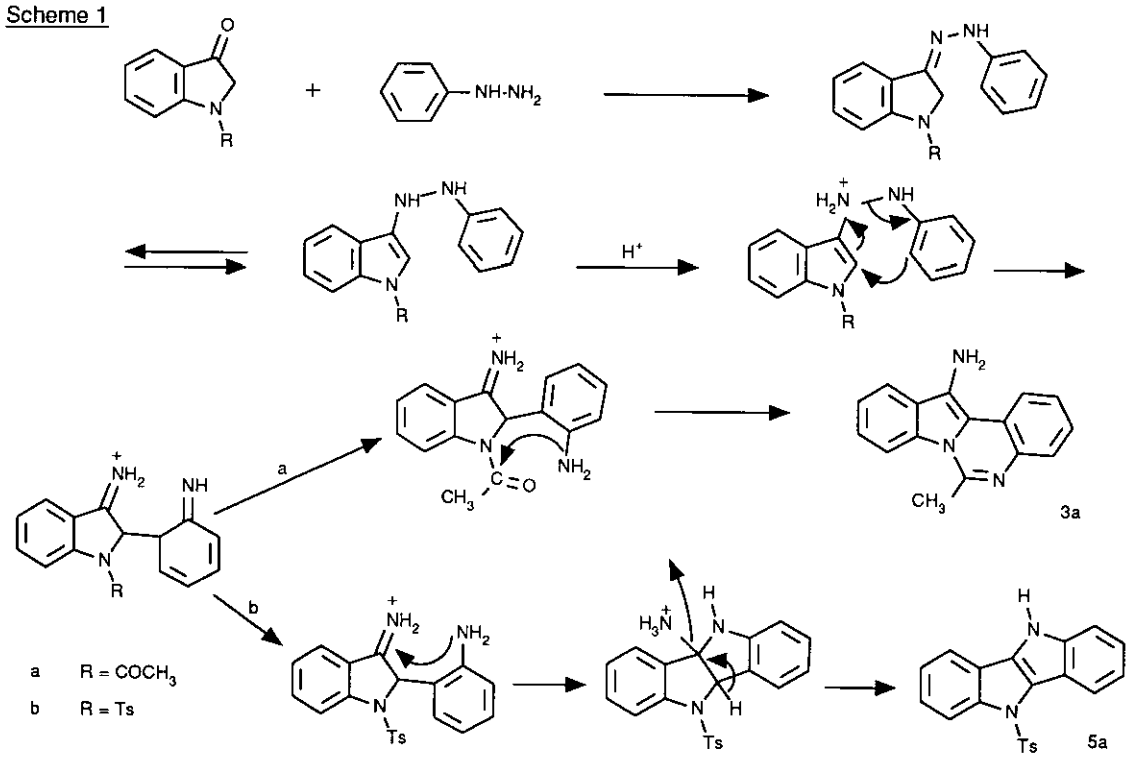
Method C



R	H	OCH_3	Cl	CH_3
1	a	b	c	d
3	a	b	c	d

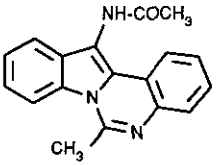
The same compounds (**3**) have also been prepared from 1-acetyl-3-acetoxy-5-substituted 2,3-dihydroindole and phenylhydrazine by Russian workers.[10] The expected product of the normal Fischer indole cyclisation, 5-acetylindolo[3,2-*b*]indole, was not observed despite the fact that smooth experimental conditions[8,9] were used. Compounds (**3a,b**) were the result of a normal nucleophilic attack of the amine function on the acetyl group, as reported on Scheme 1.

Scheme 1



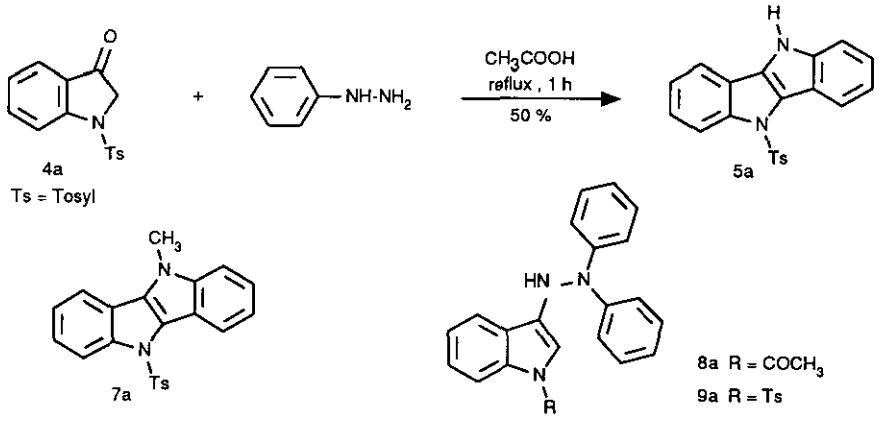
The structure of the 12-amino-6-methylindolo[1,2-*c*]quinazoline (**3a**) was in agreement with ^{1}H nmr and ^{13}C nmr in which the 6-methyl group of **3a** was observed respectively at 3.1 ppm and 25 ppm ; the ir spectrum showed the absence of carbonyl group.

Furthermore the nitrogen atom in 12 position of the compound (**3a**) was acetylated in acetic anhydride at room temperature affording compound (**6a**).[11]



6a

In order to establish the role of the acetyl group of compound (**1a**) in the formation of the compound (**3a**), 1-(*p*-toluenesulfonyloxy)-3-oxo-2,3-dihydroindole (**4a**)[12] has been prepared. Compound (**4a**) and phenylhydrazine were heated in the same conditions than before (acetic acid/reflux/1 h). The normal Fischer indole cyclisation product (**5a**), the 5-(*p*-toluenesulfonyloxy)indolo[3,2-*b*]indole, was obtained as the result of a [3,3] sigmatropic rearrangement. The examination of spectra (ir and ^{1}H nmr) allowed to confirm the structure of **5a** . The nitrogen atom in 10 position was methylated (sodium hydride, iodomethane in excess) affording compound (**7a**).[13]



The reaction of 1,1-diphenylhydrazine with compounds (**1a**) or (**4a**) in acetic acid (reflux/1 h) afforded only indolylhydrazines (**8a**) and (**9a**)[11] in 68 % and 44 % yield respectively and not indolinylhydrazones as **2** .

Compound	R	Molecular Formula	Method	Yield %	mp °C	ms (m/z) M^++1	ir (ν cm^{-1}) (KBr)	^{1}H nmr δ
2a	H	$C_{16}H_{15}N_3O$	A	74	189		3250(NH) 1640(C=O)	[b]2.2(s, 3H, $COCH_3$); 4.7(s, 2H, CH_2); 7.0(m, 9H, arom H); 9.3(s, 1H, NH).
2b	OCH_3	$C_{17}H_{17}N_3O_2$	A	85	180		3200(NH) 1650(C=O)	[b]2.2(s, 3H, $COCH_3$); 3.7(s, 3H, OCH_3); 4.7(s, 2H, CH_2); 7.0-8.2(m, 8H, arom H); 9.2(s, 1H, NH).
3a	H	$C_{16}H_{13}N_3$	B C	84 60	205	248	3300-3200(NH_2)	[a]3.1(s, 3H, CH_3); 7.3-8.4(m, 8H, arom H); 9.8(s, 2H, NH_2).
3b	OCH_3	$C_{17}H_{15}N_3O$	B C	60 32	140	278	3300-3200(NH_2)	[a]3.0(s, 3H, CH_3); 3.9(s, 3H, OCH_3); 6.9-8.5(m, 7H, arom H); 9.8(s, 2H, NH_2).
3c	Cl	$C_{16}H_{12}N_3Cl$	C	36	220		3300-3200(NH_2)	[a]2.9(s, 3H, CH_3); 7.2-8.5(m, 7H, arom H); 9.8(s, 2H, NH_2).
3d	CH_3	$C_{17}H_{15}N_3$	C	28	>250		3300-3200(NH_2)	[b]2.2(s, 3H, CH_3); 3.1(s, 3H, $COCH_3$); 7.0-8.5(m, 7H, arom H); 9.8(s, 2H, NH_2).
5a	H	$C_{21}H_{16}N_2O_2S$	C	50	180	361	3400(NH)	[a]2.2(s, 3H, CH_3); 6.8-8.6(m, 12H, arom H); 8.2(s, 1H, NH).

[a] $CDCl_3$; [b] DMSO-d_6.

REFERENCES and NOTES.

1 R. K. Brown, "The Synthesis of the Indole Nucleus", Part 1, W. J. Houlihan, John Wiley, New York, 1972, p. 414.

2 R. J. Sundberg, "The chemistry of indoles", Academic Press, New York, 1970.

3 B. Robinson, Chem. Rev., 1969, **69**, 227.

4 L. H. Werner, D. C. Schroeder, and S. Ricca Jr., J. Am. Chem. Soc., 1957, **79**, 1675.

5 D. C. Schroeder, P. O. Corcoran, C. A. Holden, and M. C. Mullígan, J. Org. Chem., 1962, **27**, 586.

6 J. Y. Mérour, J. Y. Coadou, and F. Tatiboüet, Synthesis, 1982, 1053.

7 A. Buzas, and J. Y. Mérour, Synthesis, 1989, 458.

8 C. S. Barnes, K. H. Pausaker, and C. I. Schubert, J. Chem. Soc., 1949, 1381.

9 M. L. Tomlison, J. Chem. Soc., 1951, 809.

10 G. N. Kurilo, S. Y. Ryabova, and A. N. Grinev, Khim. Geterotsikl. Soedin., 1979, 832 (Chem. Abstr., 1979, **91**, 175292c).

11 12-Acetylamino-6-methylindolo[1,2-*c*]quinazoline (**6a**).[10] Yield 36 % ; mp > 250 °C ; ms (m/z) 288 ; ir (KBr) : 3250 (NH), 1650 (CO), cm^{-1} ; ^1H nmr (DMSO-d_6) δ : 2.25 (s, 3H, $COCH_3$), 3.12 (s, 3H, CH_3), 7.3-8.5 (m, 8H, arom H), 9.88 (s, 1H, NH). 1,1-Diphenyl-2-[(1-acetylindole)-3-yl]hydrazine (**9a**). Yield 44% ; mp 205 °C ; ^1H nmr ($CDCl_3$) δ : 2.37 (s, 3H, CH_3), 7.00-7.69 (m, 10H, arom H), 7.59 (s, 1H, =CH), 8.35 (d, J=8.5Hz, 2H, arom H), 8.61 (d, J=8.5 Hz, 2H, arom H).

12 W. Hampel, J. Prakt. Chem., 1969, **311**, 78.

13 10-Methyl-5-(*p*-toluenesulfonyloxy)indolo[3,2-*b*]indole (**7a**). Compound (**4a**) (0.50 g, 1.1 mmol) was added to a suspension of sodium hydride (100%) (0.29 g, 1.2 mmol) in tetrahydrofuran (20 ml) under nitrogen at 0 °C. The mixture was stirred for 1 h at 0 °C, then 1 h at room temperature. Iodomethane (0.47 g, 3.3 mmol) was added and the mixture stirred for 20 h at room temperature and then evaporated on vacuo. Water (20 ml) was added to the residue which was extracted with dichloromethane (2 x 20 ml). After drying over magnesium sulfate and evaporation, the residue is chromatographed over silica gel (230/400 mesh) using dichloromethane as eluant ; yield 0.146 g (33 %) ; mp 215 °C ; ^1H nmr ($CDCl_3$) δ : 2.25 (s, 3H, CH_3), 4.05 (s, 3H, NCH_3), 6.9 - 8.6 (m, 12 H, arom H).

Received, 28th January, 1991