ХИМИЯ ГЕТЕРОЦИКЛИЧЕСКИХ СОЕДИНЕНИЙ. — 2000. — № 6. — С. 806—815

S. Ostrowski, A. M. Wolniewicz

AN APPROACH TO FUSED PYRIMIDINE DERIVATIVES *VIA* SCHIFF BASES OF AROMATIC *ortho*-NITROCARBALDEHYDES. AN INVESTIGATION OF SUBSTITUENT EFFECTS ON THE REACTION COURSE

The synthesis of fused pyrimidines from the Schiff bases of aromatic *ortho*-nitrocarbaldehydes is reported. The Schiff bases after selective reduction of the nitro group on 10% Pd/C, followed by condensation of the amines formed with orthoesters, are transformed to corresponding imidates. Heating of the latter in a sealed tube with an excess of ammonia (or with ammonia in ethanol) gives fused pyrimidines. The influence of various substituents in an aromatic ring of imine moiety of the Schift bases with regard to the overall yield of fused pyrimidine derivatives have been investigated. Moderate electron-withdrawing groups gave the best results.

Keywords: fused pyrimidines, Schiff bases, catalytic hydrogenation.

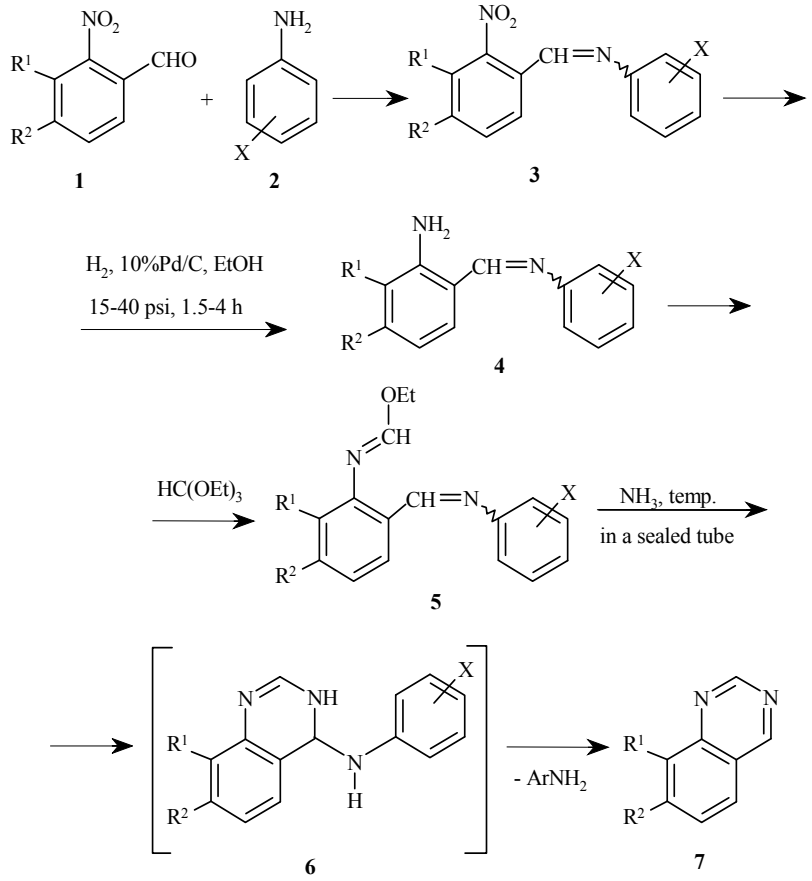
Many simple fused pyrimidines (*e.g*. purines, pteridines) are biologically active themselves or are essential components of important natural substances such as nucleic acids. For example, a pyrimidine nucleus is embedded in a large number of alkaloids, drugs, antibiotics, agrochemicals, and antimicrobial agents [1], and since the early years of this century, several studies on the synthesis and structure-activity relationships of pyrimidine derivatives have been reported [1, 2]. The limiting factor for their preparation is the availability of starting materials [3–6].

In the previous papers [7–9] we have presented efficient syntheses of fused pyrimidines, starting with *ortho*-nitroarene carboxime derivatives or with *ortho*-(isocyanomethyl)nitroaromatic / nitro-heteroaromatic compounds, which were readily available by Vicarious Nucleophilic Substitution of Hydrogen (VNS) [10]. On the other hand, the construction of pyrimidine ring utilizing the Schiff bases of 4-nitroimidazole-5-carbaldehydes was also described [9]. In that case, a moderate influence of the X substituent in the aromatic ring of the imine moiety was observed on the total yield of fused pyrimidine ring formation.

Herein, the approach to the fused pyrimidine skeleton (*via* Schiff bases) is reported (for preliminary results see [11]), and the investigations on two model compounds (**1a**, **1b**) are undertaken to explain how the character of X substituent influences the reaction yield.

The aldehydes of type **1** on interaction with anilines **2** can be easily transformed into the Schiff bases **3**. The latter (in contrast to oximes [7, 9]), after simple transformations *via* aminoimines **4** to imidates **5**, were used in the cyclocondensation with ammonia (Scheme 1).

Scheme 1



In this approach, heating of imidates **5** in a sealed tube with an excess of ammonia (80–90 °C, 8–12 h) or with saturated solution of ammonia in ethanol gives fused pyrimidines **7**. Perhaps the first step of this cyclocondensation is the addition of the ammonia moiety to the carbon atom on the >C=N double bond of the Schiff base, and then intramolecular replacement of the OEt group by the amino group by addition-elimination to give intermediate **6**.

If this postulated reaction sequence operates as drawn on Scheme 1, then the last step of this transformation must be the elimination of arylamino moiety from the dihydro compound **6**. This could indeed be the case, as small amounts of these types of intermediates (see [9]) were identified by the MS method in the post-reaction mixtures along with the main products **7**. It is worth mentioning that the ArNH moiety, in basic conditions, is a rather poor leaving group. Hence, one can expect difficulties in the elimination step leading to the corresponding fused pyrimidine ring.

The transformations from imines **3** to pyrimidines **7**, due to the instability of the intermediates, were carried out step by step without the isolation of **4** and **5**. The reaction of the Schiff base, prepared from the 2-nitrobenzaldehyde (**1a**) and aniline (**2a**; X = H), afforded the fused pyrimidine **7a** in low overall yield (*ca* 5%). The use of naphthalene aldehyde (**1b**) and aniline derivatives (**2k**, **2l**, X = CH_3) gave the appropriate fused pyrimidine **7b** in moderate total yields (23% and 28%, respectively, Table 1). Similar results (21%) were obtained for the Schiff base **3br** prepared from the bulky trityl amine. One should expect the electron-withdrawing groups X in the aryl substituents to make the elimination **6** → **7** faster. An arylamine capable to be a source of good leaving group is desired to prepare the Schiff base, and a *para*-cyanoaniline (**2o**; X = *para*-CN) was selected to check this postulated substituent effect and to improve the yields of pyrimidine derivatives. Initially, it was found that the CN group was resistant to reduction in the catalytic conditions applied for transformation **3** → **4**. However, in the preliminary reaction, when the methyl substituent in the *para*-position (Hammett constant: $\sigma_{para}(CH_3) = -0.170$ [12]) was replaced by the strong electron-withdrawing CN group ($\sigma_{para}(CN) = 0.660$ [12c]), the yield of the pyrimidine **7b** decreased dramatically (8%), while in the post-reaction mixture, the starting *para*-cyanoaniline (**2o**) and its *N*-formylated derivative were found (10–15%). Similar results were obtained, or no product was detected, for *ortho*-bromo (**3ab**), *ortho*-chloro (**3ac**), *para*-phenylsulphonyl (**3af**) substituents as well for 2,4,6-tribromoaniline (**3ag**), 2,4-difluoroaniline (**3bp**), 2-aminopyridine (**3ai**), and 3-aminopyridine (**3aj**) moieties.

We tried to ascertain the influence of X-substitution on the reaction course, and it was found that the strong electron-withdrawing groups (*i.e.* X = CN, SO_2Ph, 2,4-difluoro-, etc.) increased the reactivity of the imine >C=N double bond; hence, under the reaction conditions applied for reduction of **3**, its hydrogenation (**3** → **8** + **2**) probably occurred, thus decreasing the overall yield. For example, after completion of the reaction sequence (treatment of the crude mixture after reduction of **3** with $HC(OEt)_3$, and cyclocondensation with ammonia), the *N*-formyl derivative of **9** (R^1,R^2 = H) was identified. This derivative (**9a**) must come from the "aldehyde part" of **3**, supporting the hypothesis of hydrogenation of the Schiff base in the early stage of this synthesis. Additionally, the degradation of the labile >C=N double bond (X = electron-withdrawing group) by NH_3, EtOH or traces of water during the transformation **5** → **7** can compete with cyclocondensation, giving some amounts of aniline derivative **2**. Then, aniline derivative **2** as well as **8** can be partially formylated by the orthoester. All the discussed transformations are outlined in Scheme 2.

The yields of fused pyrimidine **7b** (from the Schiff bases in naphthalene series) were higher as compared to **7a** from the benzo derivatives. This can be explained by the easier aromatization of the higher conjugated fused system. Hence, one can expect a limitation of this method for the synthesis of bicyclic fused pyrimidines. For this reason, for some cases in the benzene series (entries **ad**, **ae**, **ah**; Table 1) and in the thiophene series (entry **cr**), the transformations of imines **3** to fused pyrimidines were not realized.

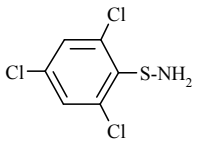
Table 1

Intermediates and Products

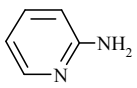
R^1, R^2	X	Alde-hyde	Aniline deri-vatives	Inter-media-tes **3—6**	Fused Pyrimi-dines & Yields [%]*
H, H	H	**1a**	**2a**	**aa**	**7a**, *ca* 5
H, H	*o*-Br	**1a**	**2b**	**ab**	**7a**, 3
H, H	*o*-Cl	**1a**	**2c**	**ac**	**7a**, traces
H, H	*m*-Br	**1a**	**2d**	**ad**	*[3]
H, H	*m*-Cl	**1a**	**2e**	**ae**	*[3]
H, H	*p*-SO_2Ph	**1a**	**2f**	**af**	**7a**, —
H, H	2,4,6-trbromo	**1a**	**2g**	**ag**	**7a**, —
H, H	2,4,6-trichloro	**1a**	**2'h**[*2]	**ah**	*[3]
H, H	—	**1a**	**2'i**[*2]	**ai**	**7a**, traces
H, H	—	**1a**	**2'j**[*2]	**aj**	**7a**, 12
–CH=CH–CH=CH–	*m*-CH_3	**1b**	**2k**	**bk**	**7b**, 23 [39][*4]
–CH=CH–CH=CH–	*p*-CH_3	**1b**	**2l**	**bl**	**7b**, 28
–CH=CH–CH=CH–	*p*-Br	**1b**	**2m**	**bm**	**7b**, 37
–CH=CH–CH=CH–	*p*-Cl	**1b**	**2n**	**bn**	**7b**, 28
–CH=CH–CH=CH–	*p*-CN	**1b**	**2o**	**bo**	**7b**, 8
–CH=CH–CH=CH–	2,4-difluoro-	**1b**	**2p**	**bp**	**7b**, 7
–CH=CH–CH=CH–	—	**1b**	$H_2N–CPh_3$ **2r**	**br**	**7b**, 21
2-nitro-3-thiophenecarbaldehyde		**1c**	$H_2N–CPh_3$ **2r**	**cr**	*[3]

* Calculated for the Schiff base 3 (3 steps).

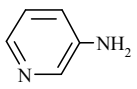
*2



2'h



2'i

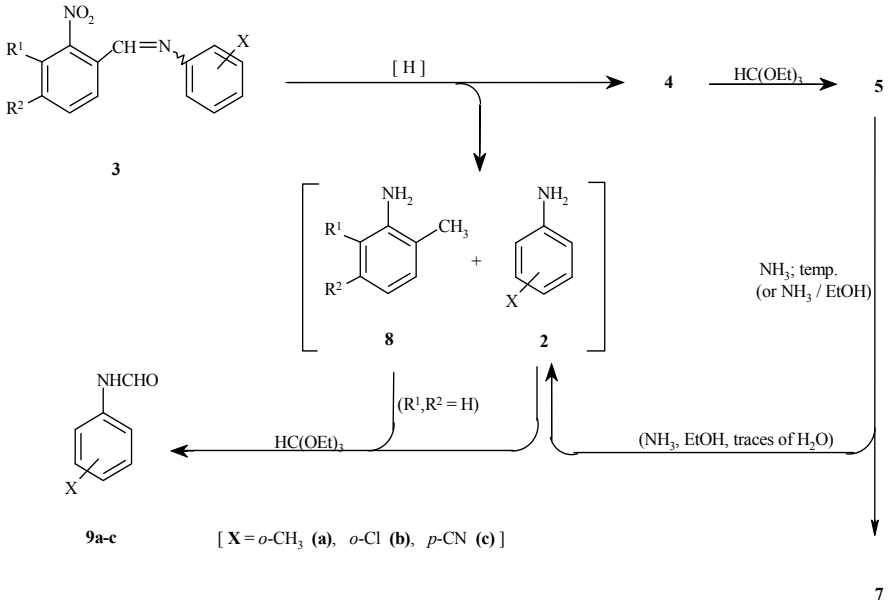


2'j

*3 The transformations to pyrimidine derivatives were not realized due to decomposition in the earlier step.

*4 [In brackets] optimized yield.

Scheme 2



[**X** = *o*-CH_3 **(a)**, *o*-Cl **(b)**, *p*-CN **(c)**]

On the other hand, the best results were obtained in the naphthalene series in the case of the moderate electron-withdrawing groups: X = *para*-Br, $\sigma = 0.232$ [12] (imine **3bm**, 37%), X = *para*-Cl, $\sigma = 0.227$ [12] (imine **3bn**, 28%) or for X = Me; $\sigma_{para} = -0.170$, $\sigma_{meta} = -0.069$ [12] (imines **3bk**, **3bl**; 23% and 28%, respectively). Optimization of this transformation for the Schiff base **3bk** resulted in a yield of up to 39% product, and in the case of purine synthesis, described elsewhere [9], when X = *para*-Br, the use of this methodology resulted in a product yield even higher (47%), as compared to investigations on the model compounds presented in this paper.

The ability to access fused pyrimidines is of great utility due to biological activity of these systems. The approach *via* the Schiff bases described herein can also be applied for their preparation. The scope and limitations of this method were investigated, particularly the influence of X substituent on the overall reaction yield was examined, and we observed the best results for X = moderate electron-withdrawing groups. In this case, the presented approach can be also considered as a preparative method for the synthesis of polycyclic fused pyrimidines.

EXPERIMENTAL

General Methods. NMR spectra were recorded on a Varian Gemini-200 spectrometer (200 MHz for ^{1}H and 50 MHz for ^{13}C). Mass spectra were measured on an AMD 604 (AMD Intectra GmbH, Germany) spectrometer (electron impact and LSIMS (+) methods). Melting points are uncorrected. TLC analysis was performed on aluminium foil plates pre-coated with silica gel 60F 254 (Merck). Silica gel 200–300 mesh (Merck AG) was used for column chromatography.

The starting 1-nitronaphthalene-2-carbaldehyde (**1b**) and 2-nitrothiophene-3-carbaldehyde (**1c**) were prepared from the corresponding commercially available aromatic nitrocompounds according to the procedures described in the literature [13]. 2,4,6-Trichlorophenylsulfenamide (**2'h**) was prepared from 2,4,6-trichlorobenzenethiol sodium salt according to the typical procedure [14]. 4-(Phenylsulfonyl)aniline (**2f**) was obtained by catalytic reduction of 4-nitrophenyl phenyl sulfone (10% Pd/C, 20 psi, 3 h, in EtOH; quantitatively), m.p. 174—175 °C (EtOH), lit. [15a] 173—175 °C and *para*-cyanoaniline (**2o**) was obtained by catalytic reduction of *para*-nitrobenzonitrile (10% Pd/C, 40 psi, 2 h, in EtOH; quantitatively), m.p. 90—91 °C (EtOH), lit. [15b] m. p. 86 °C. Aminopyridines (**2'i**, **2'j**), tritylamine (**2r**), and other aniline derivatives used are commercially available. 2,4-Difluoroaniline (**2p**) can be also obtained from 2,4-difluoronitrobenzene by catalytic reduction on 10% Pd/C (40 psi, 2 h, in EtOH). The Schiff bases **3** were prepared according to typical procedures [16, 17], optimized in our laboratory.

Preparation of Schiff Bases 3. General Procedures

Procedure A. — Aromatic aldehyde (**1a**, **1b**, **1c** respectively, 3.0 mmol), the proper aniline derivative (3.30 mmol), a catalytic amount of *p*-TsOH acid (2 mg, 0.01 mmol) and $Si(OEt)_4$ (15 ml) were dissolved in toluene (30 ml), and the reaction mixture was refluxed for 10—20 h, until the aldehyde disappeared (TLC monitoring; n-hexane/$CHCl_3$ — 1 : 1). After cooling, the solvent and most of the $Si(OEt)_4$ were evaporated. The solid residue (after 2 days in refrigerator) was filtered off, washed with n-hexane and recrystallized from chloroform/n-hexane (**3ab**, **3ac**, **3ad**, **3ae**, **3ag**, **3ah**, **3aj**, **3bo**), or the residue was purified by column chromatography (**3af**, **3ai**, **3bk**, **3br**, **3cr**; eluent: n hexane/$CHCl_3$ — 1 : 1) to give pure Schiff bases (mixtures of *E/Z*-isomers).

Procedure B. — To a solution of aromatic aldehyde (3.0 mmol) and aniline derivative (3.6 mmol) in toluene (30 ml), a catalytic amount of *p*-TsOH acid (10 mg, 0.06 mmol) was added, and the mixture was refluxed for *ca* 8 h (TLC monitoring; $CHCl_3$). After cooling and evaporation to dryness, the crude products were purified by chromatography (eluent: from n-hexane/$CHCl_3$ — 5 : 1 to $CHCl_3$) to give a mixture of *E/Z*-isomers (products **3aa**, **3bl**, **3bm**, **3bn**, and **3bp** were obtained).

(*E/Z*)-*N*-(2-Nitrobenzylidene)aniline (3aa). Solid, yield 71%. ^{1}H NMR ($CDCl_3$): 8.95 (s, 1H, C**H**=N), 8.32 (d, *J* = 7.7 Hz, 1H, H-Ar), 8.09 (d, *J* = 8.1 Hz, 1H, H-Ar), 7.82—7.57 (m, 2H, H-Ar), 7.49—7.34 (m, 2H, H-Ar), 7.34—7.20 ppm (m, 3H, H-Ar). MS, *m/z* (% rel. int.): 226 ($M^{+\bullet}$, 46), 210 (15), 209 (100), 195 (6), 180 (13), 179 (76), 178 (29), 167 (10), 153 (38), 152 (55), 151 (16), 134 (6), 105 (12), 104 (11), 92 (12), 77 (57), 76 (15), 51 (23); HR-MS calculated for $C_{13}H_{10}N_2O_2$: 226.0742, found: 226.0763.

(*E/Z*)-*N*-(2-Nitrobenzylidene)-2-bromoaniline (3ab). Solid, yield 82%. ^{1}H NMR ($CDCl_3$): 8.98 (s, 1H, C**H**=N), 8.59—8.52 (m, 2H, H-Ar), 8.31 (dd, *J* = 7.7, 1.6 Hz, 1H, H-Ar), 8.11 (dd, *J* = 8.1, 1.4 Hz, 1H, H-Ar), 7.83—7.56 (m, 3H, H-Ar), 7.37 ppm (ddd, *J* = 8.1, 4.7, 0.8 Hz, 1H, H-Ar). MS, *m/z* (% rel. int.): 306 (29), 304 (29) [isotopic $M^{+\bullet}$], 290 (9), 289 (63), 288 (9), 287 (63), 260 (4), 259 (25), 258 (5), 257 (26), 208 (10), 195 (14), 181 (17), 180 (100), 179 (15), 178 (52), 177 (15), 167 (10), 158 (2), 157 (20), 156 (2), 155 (20), 152 (43), 151 (28), 134 (8), 104 (12), 91 (8), 77 (17), 76 (38), 75 (24), 63 (11), 51 (14), 50 (15). Found, %: C 51.06; H 2.77; N 9.05; Br 26.20. $C_{13}H_9BrN_2O_2$ (305.13). Calculated, %: C 51.17; H 2.97; N 9.18; Br 26.19.

(*E/Z*)-*N*-(2-Nitrobenzylidene)-2-chloroaniline (3ac). Solid, yield 90%. ^{1}H NMR ($CDCl_3$): 8.90 (s, 1H, C**H**=N), 8.38 (dd, *J* = 7.7, 1.6 Hz, 1H, H-Ar), 8.12 (dd, *J* = 8.1, 1.3 Hz, 1H, H-Ar), 7.83—7.61 (m, 2H, H-Ar), 7.47 (dd, *J* = 7.6, 1.6 Hz, 1H, H-Ar), 7.38—7.11 ppm (m, 3H, H-Ar). MS, *m/z* (% rel.int.): 262 (13) & 260 (45) [isotopic $M^{+\bullet}$], 245 (29), 243 (88), 215 (19), 213 (55), 208 (8), 195 (10), 179 (15), 178 (45), 177 (18), 167 (7), 152 (100), 151 (26), 139 (11), 134 (11), 126 (12), 113 (8), 111 (28), 104 (11), 89 (6), 77 (11), 76 (17), 75 (25), 63 (7), 51 (10), 50 (9). Found, %: C 59.87; H 3.19; N 10.68; Cl 13.43. $C_{13}H_9ClN_2O_2$ (260.68). Calculated, %: C 59.90; H 3.48; N 10.75; Cl 13.60.

(*E/Z*)-*N*-(2-Nitrobenzylidene)-3-bromoaniline (3ad). Solid, yield 86%. ^{1}H NMR ($CDCl_3$): 8.95 (s, 1H, C**H**=N), 8.31 (dd, *J* = 7.7, 1.7 Hz, 1H, H-Ar), 8.13 (dd, *J* = 7.9, 1.6 Hz, 1H, H-Ar), 7.85—7.64 (m, 2H) & 7.50—7.21 ppm (m, 4H) [H-Ar]. MS, *m/z* (% rel. int.): 306 (35) & 304 (36) [isotopic $M^{+\bullet}$], 290 (15), 289 (95), 288 (16), 287 (100), 274 (5), 260 (5), 259 (25), 258 (5), 257 (24), 208 (12), 195 (10), 180 (67), 179 (20), 178 (68), 177 (19), 167 (11), 158 (3), 157 (29), 156 (5), 155 (30), 152 (54), 151 (32), 134 (18), 119 (7), 104 (18), 77 (24), 76 (48), 75 (41), 63 (15), 51 (17), 50 (19), 39 (9). Found, %: C 51.14; H 2.77; N 9.13; Br 26.28. $C_{13}H_9BrN_2O_2$ (305.13). Calculated, %: C 51.17; H 2.97; N 9.18; Br 26.19.

(*E/Z*)-*N*-(2-Nitrobenzylidene)-3-chloroaniline (3ae). Solid, yield 94%. ^{1}H NMR ($CDCl_3$): 8.95 (s, 1H, C**H**=N), 8.32 (dd, *J* = 7.7, 1.7 Hz, 1H, H-Ar), 8.14 (dd, *J* = 8.1, 1.3 Hz, 1H, H-Ar), 7.85—7.64 (m, 2H, H-Ar), 7.44—7.16 ppm (m, 4H, H-Ar). MS, *m/z* (% rel. int.): 262 (13) & 260 (40) [isotopic $M^{+\bullet}$], 245 (32), 243 (100), 229 (3), 215 (12), 213 (30), 208 (6), 195 (4), 178 (24), 177 (9), 152 (38), 151 (10), 134 (7), 113 (5), 111 (14), 104 (5), 77 (4), 76 (5), 75 (9), 63 (2), 51 (4). Found, %: C 59.31; H 3.20; N 10.46; Cl 12.43. $C_{13}H_9ClN_2O_2$ (260.68). Calculated, %: C 59.90; H 3.48; N 10.75; Cl 13.60.

(*E/Z*)-*N*-(2-Nitrobenzylidene)-4-(phenylsulfonyl)aniline (3af). Solid, unstable, yield *ca* 55%, it was directly used for the next steps; for crude product ^{1}H NMR and MS spectra were recorded. ^{1}H NMR ($CDCl_3$): 8.88 (s, 1H, C**H**=N), 8.26 (dd, *J* = 7.7, 1.7 Hz, 1H, H-Ar), 8.11 (dd, *J* = 8.0, 1.2 Hz, 1H, H-Ar), 8.04—7.94 (m, 4H, H-Ar), 7.82—7.66 (m, 2H, H-Ar), 7.64—7.51 (m, 3H, H-Ar), 7.35—7.27 ppm (m, 2H, H-Ar). MS, *m/z* (% rel. int.): 366 ($M^{+\bullet}$, 26), 350 (23), 349 (100), 334 (6), 319 (9), 195 (5), 180 (8), 179 (10), 178 (17), 166 (5), 152 (11), 151 (11), 134 (7), 125 (16), 104 (7), 77 (30), 51 (5).

(*E/Z*)-*N*-(2-Nitrobenzylidene)-2,4,6-tribromoaniline (3ag). Solid, yield 84%. ^{1}H NMR ($CDCl_3$): 8.80 (s, 1H, C**H**=N), 8.38 (dd, *J* = 7.6, 1.7 Hz, 1H, H-Ar), 8.17 (dd, *J* = 7.9, 1.3 Hz, 1H, H-Ar), 7.87—7.66 (m, 2H, H-Ar), 7.76 ppm (s, 2H, $C_6\mathbf{H_2}Br_3$). MS, *m/z* (% rel. int.): 466 (11), 464 (30), 462 (30) & 460 (11) [isotopic $M^{+\bullet}$], 450 (5), 449 (22), 448 (11), 447 (58), 446 (12), 445 (63), 444 (3), 443 (22), 419 (6), 417 (15), 415 (15), 413 (6), 366 (2), 355 (5), 354 (2), 353 (9), 351 (4), 340 (47), 339 (15), 338 (100), 337 (11), 336 (61), 330 (10), 328 (11), 310 (10), 287 (3), 285 (3), 274 (3), 272 (3), 259 (6), 258 (6), 257 (20), 256 (4), 255 (15), 246 (5), 236 (6), 234 (13), 232 (7), 193 (6), 183 (6), 177 (20), 165 (8), 156 (3), 155 (17), 154 (4), 153 (16), 150 (15), 134 (11), 104 (15), 89 (7), 88 (7), 77 (12), 76 (10), 75 (14), 74 (17), 63 (7), 51 (10). Found, %: C 34.04; H 1.79; N 5.85; Br 51.33. $C_{13}H_7Br_3N_2O_2$ (462.92). Calculated, %: C 33.73; H 1.52; N 6.05; Br 51.78.

(*E/Z*)-*N*-(2-Nitrobenzylidene)-2,4,6-trichlorophenylsulfenamide (3ah). Solid, yield 65%. ^{1}H NMR ($CDCl_3$): 8.24 (s, 1H, C**H**=N), 8.08 (dd, *J* = 7.8, 1.6 Hz, 1H, H-Ar), 8.00 (dd, *J* = 8.2, 1.2 Hz, 1H, H-Ar), 7.70—7.46 (m, 2H, H-Ar), 7.54 ppm (s, 2H, $C_6\mathbf{H_2}Cl_3$). MS, *m/z* (% rel. int.): 366 (<1), 364 (3), 362 (8) & 360 (8) [isotopic $M^{+\bullet}$], 282 (1), 280 (2), 252 (2), 229 (4), 227 (5), 225 (1), 214 (13), 213 (11), 212 (13), 211 (11) 190 (2), 180 (3), 178 (15), 176 (18), 149 (9), 133 (100), 119 (3), 103 (10), 91 (5), 79 (6), 65 (8), 51 (5). Found, %: C 42.92; H 1.84; N 8.00; Cl 29.64; S 9.07. $C_{13}H_7Cl_3N_2O_2S$ (361.63). Calculated, %: C 43.18; H 1.95; N 7.75; Cl 29.41; S 8.85.

(*E/Z*)-*N*-(2-Nitrobenzylidene)-2-aminopyridine (3ai). Solid, unstable, yield *ca* 14%, it was directly used for the next steps; for crude product ^{1}H NMR and MS spectra were recorded. ^{1}H NMR ($CDCl_3$): 9.56 (s, 1H, C**H**=N), 8.52 (ddd, *J* = 4.8, 1.9, 0.8 Hz, 1H, H-Ar), 8.34 (dd, *J* = 7.6, 1.6 Hz, 1H, H-Ar), 8.17—7.23 ppm (m, 6H, H-Ar). MS, *m/z* (% rel. int.): 227 ($M^{+\bullet}$, 17), 210 (55), 197 (18), 182 (40), 181 (84), 180 (48), 179 (33), 168 (43), 152 (37), 134 (7), 127 (15), 121 (42), 104 (26), 94 (30), 79 (51), 78 (100), 67 (16), 51 (30).

(*E/Z*)-*N*-(2-nitrobenzylideno)-3-aminopyridine (3aj). According to Procedure A; solid, yield 94%. ^{1}H NMR ($CDCl_3$): 8.86 (s, 1H, C**H**=N), 8.40 (dd, *J* = 7.7, 1.6 Hz, 1H, H-Ar), 8.12 (dd, *J* = 8.1, 1.3 Hz, 1H, H-Ar), 7.83—7.61 (m, 3H, H-Ar), 7.42—7.33 (m, 1H, H-Ar), 7.18—7.08 ppm (m, 2H, H-Ar). MS, *m/z* (% rel. int.): 227 ($M^{+\bullet}$, 28), 210 (100), 180 (36), 179 (33), 154 (13), 153 (11), 134 (11), 127 (27), 104 (13), 78 (34), 63 (7), 51 (30). Found, %: C 63.32; H 3.86; N 18.64. $C_{12}H_9N_3O_2$ (227.22). Calculated, %: C 63.43; H 3.99; N 18.49.

(*E/Z*)-*N*-(1-Nitro-2-naphthylidene)-3-methylaniline (3bk). Solid, yield 58%. ^{1}H NMR ($CDCl_3$): 8.60 (s, 1H, C**H**=N), 8.36 & 8.05 (2xd, *J* = 8.8 Hz, 2H, H-Ar), 8.00—7.93 (m, 1H, H-Ar), 7.89—7.82 (m, 1H, H-Ar), 7.75—7.63 (m, 2H, H-Ar), 7.38—7.04 (m, 4H, H-Ar), 2.41 ppm (s, 3H, CH_3). MS, *m/z* (% rel. int.): 290 ($M^{+\bullet}$, 80), 273 (100), 258 (10), 245 (20), 242 (23), 230 (25), 215 (19), 202 (49), 184 (5), 169 (14), 154 (11), 141 (8), 140 (7), 126 (11), 114 (10), 106 (12), 91 (27), 79 (5), 65 (15). Found, %: C 73.61; H 4.62; N 9.11. $C_{18}H_{14}N_2O_2$ (290.32). Calculated, %: C 74.47; H 4.86; N 9.65.

(*E/Z*)-*N*-(1-Nitro-2-naphthylideno)-4-methylaniline (3bl). Solid, yield 71%. ^{1}H NMR ($CDCl_3$): 8.60 (s, 1H, C**H**=N), 8.37 & 8.04 (2xd, *J* = 8.6 Hz, 2H, H-Ar), 8.00—6.89 (m, 8H, H-Ar), 2.39 ppm (s, 3H, CH_3). MS, *m/z* (% rel. int.): 290 ($M^{+\bullet}$, 10), 273 (10), 259 (5), 258 (6), 245 (5), 243 (4), 230 (5), 215 (5), 202 (11), 195 (4), 194 (4), 169 (3), 149 (8), 107 (94), 106 (100), 92 (7), 91 (25), 79 (18), 77 (20), 65 (7), 63 (4), 53 (4), 51 (5), 39 (5). HR-MS calculated for $C_{18}H_{14}N_2O_2$: 290.1055, found: 290.1057.

(*E/Z*)-*N*-(1-Nitro-2-naphthylidene)-4-bromoaniline (3bm). Solid, yield 75%. ^{1}H NMR ($CDCl_3$): 8.56 (s, 1H, C**H**=N), 8.33 & 8.05 (2xd, *J* = 8.7 Hz, 2H, H-Ar), 8.00—7.80 (m, 2H, H-Ar), 7.74—7.62 (m, 2H, H-Ar), 7.53 & 7.15 ppm (AA'XX', 4H, H-Ar). MS, *m/z* (% rel. int.): 356 (28) & 354 (28) [isotopic $M^{+\bullet}$], 339 (54), 337 (54), 326 (5), 325 (8), 324 (17), 323 (7), 322 (13), 309 (3), 308 (3), 258 (7), 245 (4), 244 (5), 243 (7), 231 (19), 230 (100), 229 (19), 228 (25), 227 (24), 217 (7), 216 (12), 215 (9), 203 (14), 202 (75), 201 (30), 200 (19), 189 (6), 185 (5), 184 (6), 183 (5), 169 (18), 157 (17), 155 (17), 154 (18), 153 (8), 142 (4), 141 (12), 140 (15), 127 (15), 126 (26), 115 (13), 114 (21), 113 (7), 107 (6), 101 (19), 100 (21), 88 (14), 87 (8), 76 (17), 75 (19), 63 (8), 58 (11), 51 (5), 50 (7), 44 (6), 43 (29), 39 (5). HR-MS calculated for $C_{17}H_{11}N_2BrO_2$: 354.0004, found: 354.0002.

(*E/Z*)-*N*-(1-Nitro-2-naphthylidene)-4-chloroaniline (3bn). Solid, yield 55%. ^{1}H NMR ($CDCl_3$): 8.57 (s, 1H, CH=N), 8.36 & 8.07 (2xd, *J* = 8.5 Hz, 2H, H-Ar), 8.02—7.95 (m, 1H, H-Ar), 7.90-7.84 (m, 1H, H-Ar), 7.74—7.66 (m, 2H, H-Ar), 7.45—7.36 & 7.28—7.19 ppm (AA'XX', 4H, H-Ar). MS, *m/z* (% rel. int.): 312 (22) & 310 (63) [isotopic $M^{+\bullet}$], 296 (7), 295 (34), 294 (21), 293 (100), 280 (5), 278 (10), 265 (9), 263 (9), 258 (8), 251 (5), 236 (7), 231 (12), 230 (64), 229 (17), 228 (30), 227 (22), 216 (8), 203 (14), 202 (75), 201 (30), 200 (11), 184 (8), 170 (5), 169 (15), 154 (20), 153 (8), 141 (9), 140 (12), 139 (8), 129 (5), 128 (7), 127 (18), 126 (32), 114 (13), 113 (9), 111 (25), 100 (10), 75 (15), 63 (4), 51 (4). HR-MS calculated for $C_{17}H_{11}N_2ClO_2$: 310.0509, found: 310.0506.

(*E/Z*)-*N*-(1-Nitro-2-naphthylidene)-4-cyanoaniline (3bo). Solid, yield 84%. ^{1}H NMR ($CDCl_3$): 8.53 (s, 1H, CH=N), 8.32 & 8.08 (2xd, *J* = 8.7 Hz, 2H, H-Ar), 8.02—7.66 (m, 6H, H-Ar), 7.34–7.25 ppm (part of AA′XX′, 2H, H-Ar). MS, *m/z* (% rel. int.): 301 ($M^{+\bullet}$, 32), 284 (100), 253 (20), 242 (9), 228 (14), 227 (27), 201 (12), 184 (11), 169 (7), 154 (18), 140 (7), 126 (14), 114 (5), 102 (15), 75 (5). Found, %: C 71.06; H 3.17; N 13.56. $C_{18}H_{11}N_3O_2$ (301.30). Calculated, %: C 71.75; H 3.68; N 13.95.

(*E/Z*)-*N*-(1-Nitro-2-naphthylidene)-2,4-difluoroaniline (3bp). Semi-crystalline, unstable, yield *ca* 32%, it was used for the next steps; for crude product ^{1}H NMR and MS spectra were recorded. ^{1}H NMR ($CDCl_3$): 8.67 (s, 1H, CH=N), 8.38 & 8.07 (2xd, *J* = 8.7 Hz, 2H, H-Ar), 8.01—7.95 (m, 1H, H-Ar), 7.91—7.84 (m, 1H, H-Ar), 7.75—7.65 (m, 2H, H-Ar), 7.30—7.16 (m, 1H, H-Ar), 7.02-6.88 ppm (m, 2H, H-Ar). MS, *m/z* (% rel. int.): 312 ($M^{+\bullet}$, 53), 296 (24), 295 (100), 280 (11), 267 (16), 265 (21), 264 (29), 263 (9), 259 (14), 253 (14), 245 (13), 239 (52), 238 (73), 220 (12), 219 (40), 189 (5), 184 (10), 171 (7), 169 (8), 156 (5), 155 (5), 154 (20), 141 (12), 140 (12), 128 (11), 127 (12), 126 (23), 115 (8), 113 (12), 97 (6), 85 (9), 71 (13), 69 (10), 63 (7), 57 (17), 55 (8), 43 (12), 41 (8).

(*E/Z*)-*N*-(1-Nitro-2-naphthylidene)tritylamine (3br). Solid, yield 42%. ^{1}H NMR ($CDCl_3$): 8.29 & 8.05 (2xd, *J* = 8.6 Hz, 2H, H-Ar), 8.21 & 7.99 (2xs, 1H, CH=N, *E/Z* isomers), 7.98—7.50 (m, 4H, H-Ar), 7.39-7.20 ppm (m, 15H, 3×Ph). MS, *m/z* (% rel. int.): 365 (<1, M-Ph), 347 (<1), 319 (<1), 257 (3), 244 (20), 243 (100), 228 (5), 215 (4), 165 (30), 77 (3). Found, %: C 80.02; H 4.65; N 6.08. $C_{30}H_{22}N_2O_2$ (442.52). Calculated, %: C 81.43; H 5.01; N 6.33.

(*E/Z*)-N-(2-Nitro-3-thienylidene)tritylamine (3cr). Solid, yield 61%. ^{1}H NMR ($CDCl_3$): 8.58 (s, 1H, CH=N), 7.86 & 7.46 (2xd, *J* = 5.6 Hz, 2H, H-4,5), 7.39—7.20 ppm (m, 15H, 3×Ph). MS, *m/z* (% rel. int.): 398 ($M^{+\bullet}$, <1), 321 (<1), 288 (<1), 274 (<1), 243 (100), 228 (8), 165 (48), 77 (2). Found, %: C 72.71; H 4.48; N 6.11. $C_{24}H_{18}N_2O_2S$ (398.48). Calculated, %: C 72.34; H 4.55; N 7.03.

Catalytic Hydrogenation of Schiff Bases 3.

The Schiff base **3** dissolved in ethanol (*ca* 5 ml for 100 mg) was hydrogenated in a Parr apparatus using *ca* 20 mg of catalyst (10% Pd/C): **3aa**, **3ab**, **3ac**, **3ai**, **3bk**, **3br** — 20 psi, 2.5 h; **3af**, **3aj** — 20 psi, 1.5 h; **3ag** — 15 psi, 3 h; **3bo** — 30 psi, 2 h; **3bl**, **3bn**, **3bm**, **3bp** — 40 psi, 4 h. The reactions were monitored by TLC ($CHCl_3$). After the reduction, the catalyst was filtered off and washed with methanol. The solvent was evaporated to give the desired products **4**. These crude products were used for the next steps.

For the crude imine **4aa** ^{1}H NMR and LSIMS (+) spectra were recorded. ^{1}H NMR ($CDCl_3$): 8.56 (s, 1H, C**H**=N), 7.63-6.86 (m, 5H, H-Ar), 6.69-6.41 (m, 4H, H-Ar), 4.98 (broad s, 2H, NH_2). LSIMS (+), *m/z* (% rel. int.): 197 (M+1, 11).

Transformation of Imines 4 to Fused Pyrimidines.

The above crude imines **4** (*ca* 100 mg) were suspended in triethyl orthoformate (5 ml) and the mixture was to refluxed until the reaction was completed (*ca* 15—20 h; TLC monitoring, $CHCl_3$). The excess of the orthoester was removed under reduced pressure and the residue (crude imidates **5**) was dissolved in dried liquid ammonia (2 ml; in a sealed tube). The reaction mixture

was heated for 8—12 h at 80—90 °C (the critical temperature for NH_3, 132 °C under pressure 111.5 atm, not alowing to reach). Then the sealed tube was cooled to –50 °C, opened, and the ammonia was evaporated to give crude products **7a**, **7b**. They were purified by column chromatography (eluent: from $CHCl_3$ to $CHCl_3$/MeOH—20:1). Yields are given in Table 1.

Quinazoline (7a). M.p. 45-46°C (*n*-hexane), lit.[18] m.p. 47—48°C. ^{1}H NMR ($CDCl_3$): 9.41 (s, 1H, H-2), 9.34 (s, 1H, H-4), 8.10-8.03 (m, 1H, H-8), 7.99—7.88 (m, 2H, H-Ar), 7.67 ppm (ddd, J = 8.3, 6.8, 1.3 Hz, 1H, H-Ar). ^{13}C NMR ($CDCl_3$): 160.2, 155.2, 149.9, 134.1, 128.3, 127.9, 127.1, 125.0 ppm. MS, *m/z* (% rel. int.): 130 ($M^{+\bullet}$, 100), 103 (60), 76 (28), 50 (14).

Benzo[*h*]quinazoline (7b). M.p. 101—102°C (*n*-hexane), lit.[19] m.p. 102—103°C. ^{1}H NMR ($CDCl_3$): 9.47 (s, 1H, H-2), 9.35 (s, 1H, H-4), 9.30—9.22 (m, 1H, H-Ar), 7.96—7.70 (m, 3H, H-Ar), 7.90 & 7.72 ppm (2xd, J = 8.9 Hz, 2H, H-5,6). ^{13}C NMR ($CDCl_3$): 158.2, 155.4, 150.3, 135.2, 130.3, 129.2, 128.1, 127.7, 127.6, 124.7, 123.2, 122.8 ppm. MS, *m/z* (% rel. int.): 180 ($M^{+\bullet}$, 100), 153 (27), 126 (47), 118 (3), 90 (4), 76 (5), 63 (12).

***N*-(*ortho*-Tolyl)formamide (9a).** Semi-crystalline, *ca* 95% purity. ^{1}H NMR ($CDCl_3$): 8.73—8.10 (m, *ca* 3H, NHCHO & its tautomers, *E/Z*; 1H of H-Ar), 7.58—7.05 (m, *ca* 3H, H-Ar), 2.30 ppm (s, 3H, CH_3). MS, *m/z* (% rel. int.): 135 ($M^{+\bullet}$, 30), 121 (100), 107 (13), 106 (35), 93 (45), 77 (7), 75 (7), 66 (23), 51 (6), 39 (10).

***N*-(2-Chlorophenyl)formamide (9b).** Semi-crystalline, *ca* 90% purity. ^{1}H NMR ($CDCl_3$): 9.12—8.41 (m, 2H, CHO & its tautomers, *E/Z*; 1H of H-Ar), 7.90—6.88 ppm (m, *ca* 4H, H-Ar & NH). MS, *m/z* (% rel. int.): 157 (12) & 155 (38) [isotopic $M^{+\bullet}$], 129 (24), 127 (72), 120 (100), 106 (5), 100 (11), 99 (12), 92 (33), 91 (16), 73 (7), 65 (29), 52 (8), 39 (14).

***N*-(4-Cyanophenyl)formamide (9c).** M. p. 186—190 °C ($CHCl_3$), lit. [20] m. p. 189—190 °C. ^{1}H NMR ($CDCl_3$): 8.45 (s, 1H, CHO), 7.80—7.60 ppm (AA′XX′, 4H, H-Ar), NH — undetected. MS, *m/z* (% rel. int.): 147 (M+1, 7), 146 ($M^{+\bullet}$, 63), 119 (12), 118 (100), 117 (7), 91 (51), 90 (13), 64 (12), 63 (9).

Acknowledgements. This work was supported (in part) by the State Committee for Scientific Research, Grant 2 P303 087 07.

REFERENCES

1. D. J. Brown, in *The Chemistry of Heterocyclic Compounds, The Pyrimidines*, Ed. E. C. Taylor, Wiley & Sons, New York, Chichester, Brisbane, Toronto, Singapore, 52, 1994.
2. a) W. L. F. Armarego, in *The Chemistry of Heterocyclic Compounds, Fused Pyrimidines, Part I: Quinazolines*, Ed. D. J. Brown, Interscience Publishers, New York, London, Sydney, 1967, 24/1. b) J. H. Lister, in *The Chemistry of Heterocyclic Compounds, Fused Pyrimidines, Part II: Purines*, Ed. D. J. Brown, Wiley, Interscience, New York, London, Sydney, Toronto, 1971, 24/2. c) D. J. Brown, *The Chemistry of Heterocyclic Compounds, Fused Pyrimidines*, Part III: *Pteridines*, Ed. E. C. Taylor, Wiley & Sons, New York, Chichester, Brisbane, Toronto, Singapore, 1988, 24/3. d) T. J. Delia, *The Chemistry of Heterocyclic Compounds*, *Fused Pyrimidines*, Part IV: Miscellaneous Fused Pyrimidines, Ed. E. C. Taylor, Wiley & Sons, Inc., New York, Chichester, Brisbane, Toronto, Singapore, 1992, 24/4.
3. a) A. Bischler, *Ber.*, **24**, 506 (1891). b) W. L. F. Armarego, C. J. Smith, *J. Chem. Soc.* (*C*), 234 (1966).
4. a) A. Riedel, Ger. Pat. 174941 (1905). b) M. T. Bogert, E. M. McColm, *J. Am. Chem. Soc.*, 49, 2650 (1927). c) W. L. F. Armarego, *J. Chem. Soc.*, 561 (1962).
5. S. Niementowski, *J. prakt. Chem.* (*N. F.*), **51**, N 2, 564 (1895). b) Ref. 2a), pp. 74–78.
6. D. Chakravarti, R. N. Chakravarti, L. A. Cohen, B. Dasgupta, S. Datta, H. K. Miller, *Tetrahedron*, 16, 224 (1961). b) S. C. Pakrashi, J. Bhattacharyya, L. F. Johnson, H. Budzikiewicz, *Tetrahedron*, 19, 1011 (1963). c) G. G. Munoz, R. Madronero, *Chem. Ber.*, 9, 2182 (1962).
7. S. Ostrowski, *Synlett*, 253 (1995).
8. S. Ostrowski, *J. Chem. Res.* (*S*), 14 (1998); (M) 0180-0187.
9. S. Ostrowski, *Molecules*, 4, 287 (1999).

10. M. Makosza, *Synthesis*, 103 (1991), b) M. Makosza, K. Wojciechowski, *Liebigs Ann. Chem.*, 1805 (1997).
11. S. Ostrowski, A. M. Wolniewicz, in Abstracts of *5th Polish Symposium on Organic Chemistry*, Konstancin-Jeziorna, Poland, 1998, 63.
12. L. P. Hammet, *J. Am. Chem. Soc.*, **59**, 96 (1937). b) J. Shorter, *Chem. in Britain*, 5, 269 (1969). c) H. C. Brown, Y. Okamoto, *J. Am. Chem. Soc.*, **80**, 4979 (1958).
13. M. Mąkosza, Z. Owczarczyk, *J. Org. Chem.*, **54**, 5094 (1989).
14. M. Mąkosza, M. Białecki, *J. Org. Chem.*, **63**, 4878 (1998).
15. a) E. E. Gilbert, *Synthesis*, 372 (1971). b) P. Sensi, G. G. Gallo, *Gazz. Chim. Ital.*, **85**, 235 (1955).
16. R. W. Layer, *Chem. Rev.*, **63**, 489 (1963).
17. B. E. Love, J. Ren, *J. Org. Chem.*, **58**, 5556 (1993).
18. W. L. F. Armarego, J. L. C. Smith, *J. Chem. Soc.*, 5360 (1965).
19. T. Koyama, T. Hirota, F. Yagi, S. Ohmori, M. Yamata, *Chem. Pharm. Bull.*, **23**, 3151 (1975).
20. J.-Y. Huot, D. Serve, S. Desjardins, J. Lessard, *Can. J. Chem.*, **66**, 35 (1988).

Institute of Organic Chemistry,
Polish Academy of Sciences,
ul. Kasprzaka 44/52, PL-01-224 Warszawa,
Poland
e-mail: stan@icho.edu.pl

Received 25.02.2000