Pergamon

Tetrahedron Letters, Vol. 35, No. 37, pp. 6883-6886, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01451-5

TMSO-Triflate-assisted Addition of Enols to Heteroaromatic Imines or Hydroxyaminal Intermediates.

J. L. Moutou, M. Schmitt, C. G. Wermuth and J. J. Bourguignon

Laboratoire de Pharmacochimie Moléculaire associé au CNRS, Centre de Neurochimie du CNRS
5, Rue Blaise Pascal, 67084 STRASBOURG-Cedex (France)

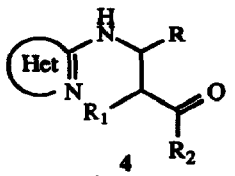
Abstract : TMSOTf-promoted reaction of heteroaromatic imines or hydroxyaminal intermediates with various enolic ketones are reported. This reaction constitutes an original and regioselective mode of alkylation of exocyclic amines of heterocyclic amidines.

Primary heterocyclic amidines **1** are 1,3-dinucleophilic reagents that present two differentiated reactive centres in terms of reactivity : the endocyclic sp^2 nitrogen and the exocyclic amine[1]. Usually, alkylation of primary heterocyclic amidines occurs regioselectively on the endocyclic nitrogen[2], or leads to a mixture of both the endo and exo substituted derivatives[3]. However, in accordance with the HSAB theory[4,5], the reaction of **1** with carbonyl compounds systematically involves the exocyclic nitrogen. Thus reaction of primary heterocyclic amidines **1** with benzaldehyde affords the corresponding highly conjugated Schiff bases **2**[6], whereas when they react with a highly electrophilic aldehyde such as chloral or ethylglyoxylate, they leads to the most stable hydroxyaminal **3** (R = CCl_3[7] and R = CO_2Et).

This paper deals with the electrophilic properties of **2** or **3** (R = CO_2Et[8]) in presence of various enolic compounds. Lewis-acid catalysed addition of Grignard reagents[9] or enols[10] to aromatic imines have been previously described. However, to our knowledge, addition of enols to heteroaromatic imines such as Schiff bases deriving from primary heterocyclic amidines has never been reported.

The Schiff bases **2** or the hydroxyaminals **3** were reacted in presence of trimethylsilyl-triflate (TMSOTf), with various enolisable ketones, or their corresponding silyl enol ethers (entries 1-16), or with 1-TBDMS-oxy-1-ethoxy ethylene as an equivalent of ethyl acetate (entry 17) to yield the secondary amidines **4**. The role of TMSOTf in this reaction is not clearly identified. The Lewis acid probably increases the electrophilicity of the imine **2**, as suggested for aromatic Schiff bases[9,10].

Three methods have been used to prepare compounds **4** (Scheme 1). With *benzaldehyde*, method a [11] (one-pot reaction starting from amidine **1**) or method b (isolation of Schiff base **2**) were used. Using either the enolisable ketone, or the corresponding silyl enol ether afforded similary overall yields in both methods (compare entries 1 and 3, 2 and 4). Thus, when the Schiff base **2** was not available, the convenient one-pot method a using various enolisable compounds can be extended to other heterocycles (entries 10, 12, 15). However no reaction was observed with 5-phenyl thiazole (entry 13), whereas method b afforded the awaited



4

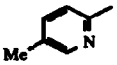
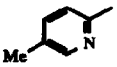
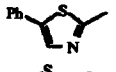
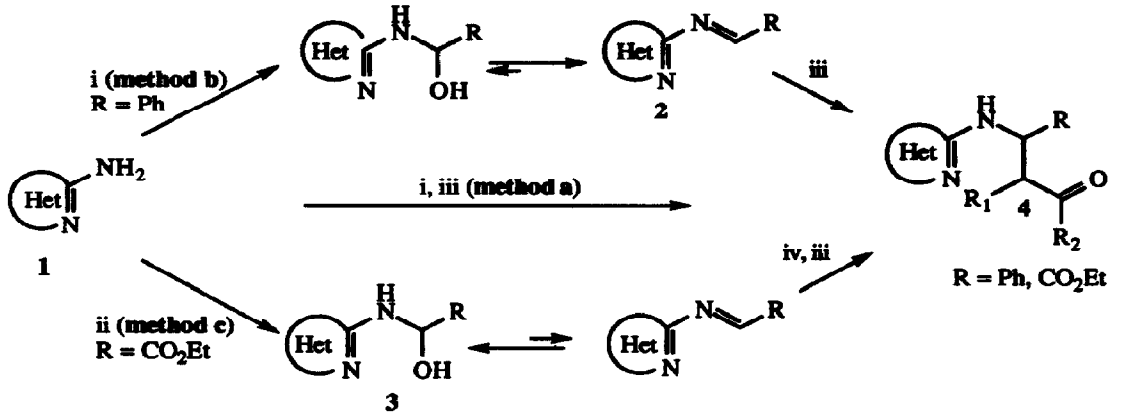
Entry	4	Het	R	R_1	R_2	method	nucleophilic agent	t(hour) 20°C	Yield %	m.p.°C
1	a		Ph	H	Ph	a	CH_2=C(Ph)OTMS	2	43	125
2	a		Ph	H	Ph	a	$PhCOCH_3$	1.5	53	
3	a		Ph	H	Ph	b	CH_2=C(Ph)OTMS	2	65 (43)[1]	
4	a		Ph	H	Ph	b	$PhCOCH_3$	0.5	78 (51)[1]	
5	b		Ph	H	t-Bu	b	t-BuCOCH$_3$	16	34 (22)[1]	107
6	c		Ph	H	p-MeO-Ph	b	p-MeO-PhCOCH$_3$	2.5	75 (49)[1]	111
7	d		Ph	Me	Ph	b	$PhCOCH_2CH_3$	16	84 (55)[1,2]	*
8	e		Ph	Ph	Me	b	$PhCH_2COCH_3$	4	67 (44)[1,2]	**
9	f		CO_2Et	H	Ph	c	CH_2=C(Ph)OTMS	2.5	31	oil
10	g		Ph	H	Ph	a	CH_2=C(Ph)OTMS	6	50	112
11	h		CO_2Et	H	Ph	c	CH_2=C(Ph)OTMS	4	32	oil
12	i		Ph	H	Ph	a	$PhCOCH_3$	16	20	oil
13	j		Ph	H	Ph	a	CH_2=C(Ph)OTMS	3	0[3]	
14	j		Ph	H	Ph	b	CH_2=C(Ph)OTMS	16	29 (20)[1]	160
15	k		Ph	H	Ph	a	CH_2=C(Ph)OTMS	14	56	oil
16	l		CO_2Et	H	Ph	c	CH_2=C(Ph)OTMS	6	0[3]	
17	m		Ph	H	OEt	b	CH_2=C(OEt)OTBDMS	16	18 (12)[1]	oil

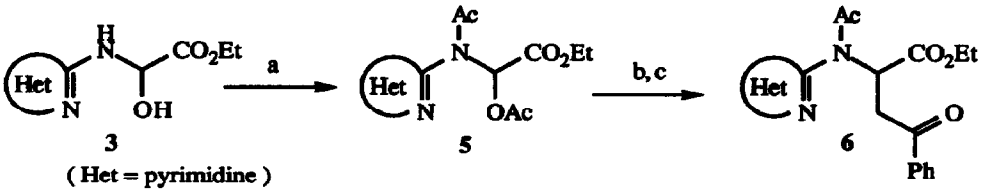
Table 1 : [1] : overall yield starting from amidine 1, [2] : stereochemistry unspecified, [3] : starting material. * : minor compound : oil, major compound : 90°C, ** : minor compound : 159°C, major compound : 155°C.

compound **4j** with a 29 % yield (entry 14). Other enolic ketones were also reacted with **2** yielding the corresponding **4b-e**. It is noteworthy that **4d** and **4e** were obtained as mixtures of diastereomers with a 1:2 ratio.



Scheme 1 : i : PhCHO [6] ; ii : EtO_2CCHO [8] ; iii : TMSOTf, $R_1CH_2COR_2$ or $R_1CH{=}C(OTMS)R_2$, CH_3CN ; iv : TMSCl, Et_3N, CH_2Cl_2.

With *ethyl glyoxylate* (method c [12]), the reaction with enol ethers (entries 9, 11) needed a preliminary activation step of the hydroxyaminal intermediate **3** by means of TMSCl and Et_3N in anhydrous CH_2Cl_2. However with less basic heterocycles such as pyrimidine, no reaction was observed, may be in relation with the poor stability of the corresponding hydroxyaminal **3** (Het = pyrimidine, entry 16). Previous acylation of the latter hydroxyaminal increased both stability and its electrophilicity, and the N,O-diacetylated aminoester **5** led to the corresponding pyrimidine **6** with a 26 % yield (Scheme 2).



Scheme 2 : a : Ac_2O ; b : $CH_2C(Ph)OTMS$; c : TMSOTf

In conclusion, the present work constitutes an original and regioselective mode of alkylation of exocyclic amines of heterocyclic amidines. Particularly the α-heteroarylamino α-substituted esters **4** (R = CO_2Et) and **6** can be efficiently used for the design of novel peptidomimetic compounds [13].

REFERENCES AND NOTES :

1. Deady, L.W. ; Zoltewicz, J. A. ; *J. Am. Chem. Soc.* **1971**, *93*, 54.
2. Hunter, R. F. ; Perken, E. R. ; Short, E. M. ; *J. Chem . soc.* **1959**, 784.
3. Skipper, P. L. ; Tannenbaum, S. R. ; Baldwin, J. E. and Scott, A., *Tetrahedron Lett.* **1977**, *49*, 4269-4272.

4. Pearson, R. G., *J. Am. Chem. Soc.* **1963**, *85*, 3533-3539.
5. Pearson, R. G. and Songstad, J., *J. Am. Chem. Soc.* **1967**, *89*, 1827-1836.
6. El-Shafei, A. K. ; Hassan KH. M. ; El-Kashef H. S. ; *J. Indian Chem. Soc.* **1977**, *56*, 743-745.
7. Böhme, H. ; Ahrens, K. H. ; Hotzel, H. H. ; *Arch.Pharm.* **1974**, 307, 748-755.
8. Typical procedure for the preparation of **3** : Under argon, freshly distillated ethyl glyoxylate (1.1 g, 11 mmol) was added to a stirred solution of 2-aminopyridine (0.94 g, 10 mmol) in anhydrous CH_2Cl_2 (10 ml) which had been precooled to 0 °C. The mixture was allowed to stir at 0 °C for 2 h. Filtration of the precipitate gave a white cristalline material (1.67 g, 85 %). mp 88-89 °C ; IR($CHCl_3$) : 1742cm^{-1} ; ^{1}H-RMN (200MHz, $CDCl_3$) δ : 1.32 (t, J =7.1Hz, 3H), 4.30 (q, J = 7.1Hz, 2H), 5.76 (s broad, 2H), 6.58 (d, J = 8.4Hz, 1H), 6.70 (t, 1H), 7.47 (t, 1H), 8.09 (d, J = 4.3Hz, 1H) ; ^{13}C-RMN (50MHz, DMSO-D_6) δ : 14.2, 60.8, 73.4, 109.5, 113.7, 137.3, 147.5, 157.1, 170.9 .
9. Brook, M. A. and Jahangir, *Synth. Commun.* **1988**, *18*, 893-898.
10. Nogue, D. ; Paugam, R. and Wartski, L., *Tetrahedron Lett.* **1992**, *33*, 1265-1268.
11. General preparation for compounds **4** by method a : **4a.** To a solution of 2-aminopyridine (0.94 g, 10 mmol) in CH_3CN, under argon, benzaldehyde (1.1 g, 10 mmol) was added. The mixture was stirred at 20 °C for 2 h, and acetophenone (1.2 g, 10 mmol) and TMSOTf (4.26ml, 21mmol) were added successively. The mixture was stirred at 20°C for 1.5 h. Then, aqueous concentrated solution of potassium fluoride was added, and the resulting solution was extracted by using CH_2Cl_2. The organic layer was dried (Na_2SO_4), filtred, and the solvent removed under reduce pressure. The resulting residue obtained was chromatographied on silica gel and eluted with ethyl acetate- hexane 1/3 by volume, to afford 1.6 g (53 %) of white powder. mp 125 °C ; IR($CHCl_3$) : 1685cm^{-1} ; ^{1}H-RMN (200MHz, $CDCl_3$) δ : 3.48, 3.67 (ABX system, J_{A-B}=16. 5Hz, J_{A-X} = 5.8Hz, J_{B-X} = 6.7Hz, 2H), 5.46 (m, 1H), 5.75 (d exchangeable with D_2O, J = 7.1Hz, 1H), 6.37 (d, J = 8.4Hz, 1H), 6.54 (dd, 1H, J = 6.9Hz, J = 5.0Hz) ; 7.2-7.6 (m, 9H) ; 7.9-8.0 (m, 2H) ; 8.08 (dd, J = 5.0Hz, J = 1.6Hz, 1H) ; ^{13}C-RMN (50MHz, $CDCl_3$) δ : 45.5, 52.4, 107.4, 113.2, 126.4, 127.2, 128.1, 128.5, 128.6, 133.2, 136.7, 137.3, 142.4, 148.0, 157.7, 197.9 .
12. General preparation for compounds **4** by method c : **4f.** Under argon hydroxyaminal **3**, deriving from 2-aminopyridine (0.6 g, 3.1 mmol), was dissolved in CH_2Cl_2 (30 ml) and cooled to -78 °C. Then trimethylsilyl chloride (0.45 ml, 3.6 mmol) and triethylamine (0.5 ml, 3.6 mmol) were added. The cooling bath was removed and the mixture was stirred at room temperature. After 20 min, TMSOTf (0.73 ml, 3.6 mmol) was added, and 10 min later 1-phenyl-1-(trimethylsilyloxy)ethene was finally added. The mixture was stirred for 2.5 h more, and an aqueous concentrated solution of potassium fluoride was added. The resulting solution was extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), filtrated, and the solvant removed under reduce pressure. The resulting residue was chromatographied on silica gel and eluted with ethyl acetate- hexane 1/2 by volume, to afford 0.29 g (31 %) of an oil. IR($CHCl_3$) : 1742cm^{-1}, 1684cm^{-1} ; ^{1}H-RMN (200MHz, DMSO-d_6) δ : 1.19 (t, J = 7.1Hz, 3H), 3.72 (m, 2H), 4.19 (q, J = 7.1Hz, 2H), 5.17 (m, 1H), 5.49 (d exchangeable with D_2O, J = 7.9,Hz 1H), 6.47 (d, J = 8.4Hz, 1H), 6.56 (ddd, J = 6.9Hz, J = 5.1Hz, J = 0.7Hz, 1H), 7.3-7.6 (m, 4H), 8.06 (dd, 1H, J = 4.9Hz, J = 0.9Hz) ; ^{13}C-RMN (50MHz, $CDCl_3$) δ : 14.0, 40.8, 50.0, 61.3, 109.3, 113.3, 128.0, 128.5, 133.3, 136.2, 137.1, 147.4, 156.9 , 172.6, 197.6 .
13. El-Naggar, A. M. , Zaher, M. R., *Indian J. Chem., Sect. B.* **1977**, 15B(9), 763-865.

(*Received in France* 7 *July* 1994; *accepted* 27 *July* 1994)