Efficient alkylation of N,N′-disubstituted formamidines using Mitsunobu's reagents

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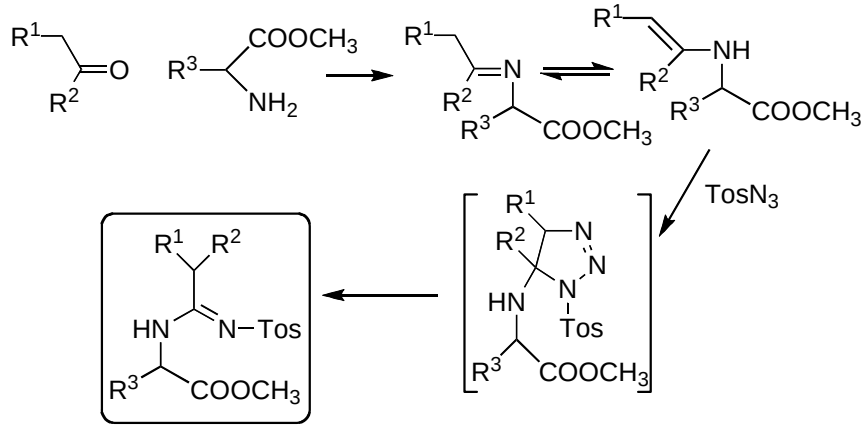
Abstract

A new synthetic protocol for the alkylation of N,N′-disubstituted formamidines under Mitsunobu conditions is reported. The asymmetrical substitution of amidine substrates allowed investigation of the reaction trends.

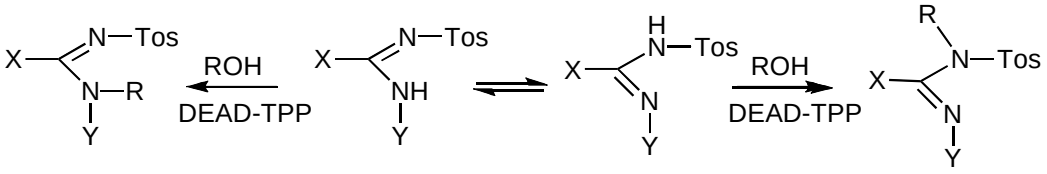
Keywords: N,N′-Disubstituted amidines, Mitsunobu reaction, alkylation, benzyl alcohol

Introduction

Amidines are versatile starting materials in several synthetic contexts, mainly in the preparation of heterocyclic compounds.[1] Our group recently reported a simple and versatile synthetic method to produce *N,N′*-disubstituted amidines through heterocyclic transformation.[2] Particularly, several amidines were synthesized arising from tosyl azide and amino acid ester enamines.[2]

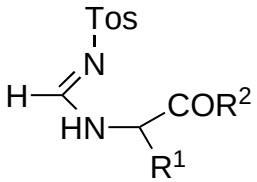


With the aim of studying the synthetic potential of these amidines, we investigated the possibility of N-alkylation. Conventional conditions such as weak or strong bases are ineffective. A survey of the literature revealed that the symmetrically substituted *N,N′*-acetamidines were efficiently alkylated under Mitsunobu conditions,[4] and that this method also appeared to be suitable for the alkylation of *N*-monosubstituted arylsulfonamides.[3a,b] We recently reported that β-hydroxy-*N,N′*-disubstituted amidines undergo intramolecular cyclization under Mitsunobu conditions.[2b] In this case, the NH involved in the Mitsunobu reaction was that of the tosylamide. This example demonstrated the ability for both amidine nitrogen atoms to react. These results induced us to investigate the trend of Mitsunobu reactions, starting from amidines bearing different substituents at the two nitrogen atoms, in order to evaluate which one was favoured in the alkylation process.

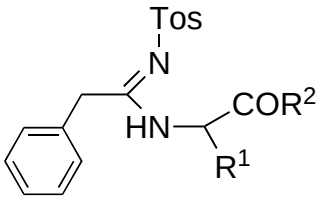


Results and Discussion

The starting materials were the *N*-tosyl-formamidines **1a-d** and the *N*-tosyl-2-benzyl-amidines **2a-d**[2c] using benzyl alcohol as the alkylation agent.



1a-d



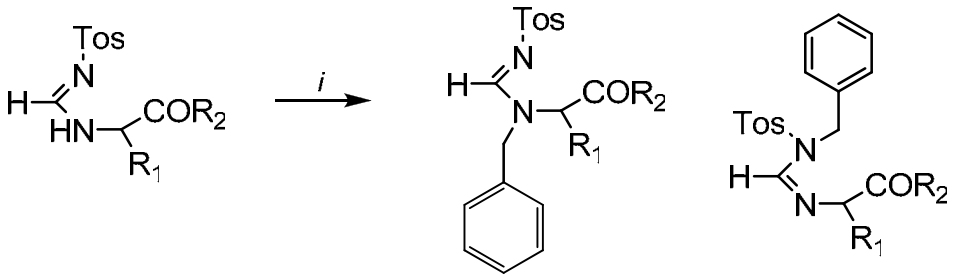
2a-d

a $R^1 = CH(CH_3)_2$, $R^2 = OCH_3$
b $R^1 = CH_3$, $R^2 = OCH_3$
c $R^1 = H$, $R^2 = OCH_3$
d R^1,$R^2 = CH(CH_2)_2SCO$

A Mitsunobu protocol was applied in standard conditions using diethyl azodicarboxylate (DEAD) and triphenylphosphine (TPP) at room temperature and in an inert atmosphere. Unfortunately, the 2-benzyl-substituted amidines **2a-d** did not react in these conditions, while more extreme conditions led to degradation. Indeed, it is known that the Mitsunobu reaction is limited by steric hindrance.[5] Instead, *N*-tosyl-formamidine **1a** reacted with benzyl alcohol in

standard Mitsunobu conditions yielding products **3a** and **4a** in a molecular ratio of 14:1, which were easily separated and identified by spectroscopic methods (Scheme 1).

Both compounds showed a singlet at 8.55 ppm and 8.27 ppm associated with the formamidine CH and an AB spin system associated with the benzyl methylene at 4.69 ppm and 4.80 ppm. The structures of **3a** and **4a** were assigned by NOESY experiments. Regarding compound **3a**, a strong interaction was observed between the benzyl methylene (AB spin system 4.69 ppm) and the doublet (3.49 ppm) related to the CH proton on the isopropyl group.



1a-d **3a-d** **4a-d**

	Yield (%)	
	3	**4**
a $R_1 = CH(CH_3)_2$, $R_2 = OCH_3$	69	5
b $R_1 = CH_3$, $R_2 = OCH_3$	45	
c $R_1 = H$, $R_2 = OCH_3$	35	
d $R_1,R_2 = CH(CH_2)_2SCO$	47	

Scheme 1. Reagents and conditions: amidine 1 mmol, benzylalcohol 1.1 mmol, triphenylphosphine 1.1 mmol, DEAD 1.1mmol, THF, r.t., 2h.

Compound **4a** displayed only spatial proximity between the benzyl methylene (AB spin system 4.80 ppm) and the alpha-aromatic CH of the tosyl group (7.48 ppm).

With the aim of further studying the reaction trends in detail, we extended the Mitsunobu protocol to the *N*-tosyl-formamidines **1b-d**. All the tested substrates showed comparable reactivity, but only one product was isolated. The structure of the derivatives **3c-d**, initially deduced from spectroscopic data, was unambiguously assigned by two-dimensional experiments. Analytical data leads to the conclusion that, as for **3a**, compounds **3c** and **3d** have the benzyl substituent linked to the *N*-amino ester function. The interpretation of the spectroscopic data of the amidine derivative **3b** was rather difficult. ^{1}H NMR in $CDCl_3$ showed the presence of a 1:1 ratio mixture of two products. Two different signal sets were observed and initially assigned through a COSY analysis of two products, hereafter referred to as **A** and **B**. Product **A** showed at 4.13 ppm a quartet associated to CH coupled with CH_3 and at 4.77 ppm, an AB spin system

related to benzylic CH_2. On the other hand, product **B** showed at 4.72 ppm a quartet associated to CH, and at 4.59 ppm an AB spin system associated to the benzylic methylene. In a NOESY experiment, a strong interaction between benzyl methylene at 4.77 ppm and CH quartet at 4.13 ppm was observed for product **A**, while for product **B** the overlapping of CH and CH_2 signals made the two-dimensional spatial interaction analysis unusable.

On the other hand, HPLC analysis of this mixture showed a characteristic profile, with a considerable interconversion region between the two resolved peaks (plateau) being observed at room temperature. At 0 °C, the two peaks were completely separated and at 40 °C a single peak was detected. This well-known behaviour[6] demonstrated that the mixture actually consisted of **3b** as *E*/*Z* isomers.

In conclusion, we have developed a general and powerful method for the alkylation of asymmetric *N,N′*-disubstituted-formamidines. In all cases, the NH involved in the alkylation reaction was the starting amino ester and in only one case was it obtained as a by-product arising from NH-tosyl alkylation.

Experimental Section

General Procedures. Mps were determined using a Büchi 510 (capillary) apparatus. NMR spectra were obtained with Bruker Advance 300, Bruker Advance 500 and Varian Gemini 200 spectrometers in $CDCl_3$ solution, unless otherwise stated. *J* values are given in Hz. $[\alpha]_D$ Values were measured with a Perkin Elmer 343 polarimeter. Low-resolution MS spectra were recorded with a Thermo-Finnigan LCQ ADVANTAGE AP electrospray/ion trap-equipped instrument using a syringe pump device for the direct injection of sample solutions. HPLC was performed with HP 1050, DAD, pump Merck-Hitachi L 7100, injector Rhedyne loop 20µl, C18 column, 1ml/min, and H_2O/MeOH (1:1).

Alkylation of formamidines. General procedure

Formamidine **1a-d** (5 mmol) and benzyl alcohol (7.5 mmol) were dissolved in anhydrous THF (20 ml) under N_2 at room temperature. Triphenylphosphine (5.5 mmol) and DEAD (5.5 mmol) were added and the mixture was stirred for 12 hours until disappearance of the starting materials (TLC ethyl acetate-cyclohexane 2:3). The solution was evaporated at reduced pressure, taken up in CH_2Cl_2 and washed with 20 mL of cold water, dried with Na_2SO_4 and then evaporated. Toluene (20 mL) was added and evaporated at reduced pressure to remove the remaining benzyl alcohol. The crude material was purified by chromatography with ethyl acetate-cyclohexane (2:3).

Methyl 2-(*N*-benzyl-*N′*-tosylformimidamido)-3-methylbutanoate (3a). Yield 69%, Mp 85 °C (from diethylether). $[\alpha]_D$ = -25.8 (*c* 1.00, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): ppm 0.83 (d, *J* = 6.80, 3H, CH_3), 0.95 (d, *J* = 6.5, 3H, CH_3), 2.27-2.39 (m, 1H, CH), 2.44 (s, 3H, CH_3), 3.49 (d, *J* = 10.7, 1H, CH), 3.52 (s, 3H, OCH_3), 4.69 (AB $_{\text{spin system}}$ *J* = 14.6, 2H, CH_2), 7.14-7.83 (m, 9H,

ArH), 8.55 (s, 1H, CH). ^{13}C NMR (50 MHz, $CDCl_3$) ppm 18.2(CH_3), 18.6(CH_3), 28.9(CH_3), 51.1(CH_2), 51.7(CH_3), 69.2(CH), 125.9(CH), 127.4(CH), 127.9(CH), 128.0(CH), 128.6(CH), 133.9(C), 138.5(C), 141.8(C), 159.0(CH), 169.4(C). ESI-MS: *m/z* 403 [M+H]. Anal. Calcd. for $C_{21}H_{26}N_2O_4S$: C, 62.66; H, 6.51; N, 6.96% Found C, 62.38; H, 6.64; N, 6.73%

Methyl 2-[(*N*-benzyl-4-methylphenylsulfonamido)methyleneamino]-3-methylbutanoate (4a). Yield 5%, oil, $[\alpha]_D$ = -16.9 (*c* 1.00, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): ppm 0.75 (d, *J* = 6.6, 3H, CH_3), 0.80 (d, *J* = 6.5, 3H, CH_3), 2.14-2.24 (m, 1H, CH), 2.42 (s, 3H, CH_3), 3.65 (d, *J* = 6.2,1H, CH), 3.69 (s, 3H, OCH_3), 4.80 (AB $_{\text{spin system}}$ *J* = 14.8, 2H, CH_2), 7.19-7.62 (m, 9H, ArH), 8.27 (s, 1H, CH). ^{13}C NMR (50 MHz, $CDCl_3$) ppm 19.3(CH_3), 19.7(CH_3), 30.0(CH_3), 52.2(CH_2), 52.7(CH_3), 70.3(CH), 126.9(CH), 128.5(CH), 128.9(CH), 129.1(CH), 129.7(CH), 135.0(C), 139.6(C), 142.9(C), 160.1(CH), 170.5(C). ESI-MS: *m/z* 403 [M+H]. Anal. Calcd. for $C_{21}H_{26}N_2O_4S$: C, 62.66; H, 6.51; N, 6.96% Found C, 62.41; H, 6.80; N, 6.59%

Methyl 2-(*N*-benzyl-*N´*-tosylformimidamido) propanoate (3b). Yield 45%, (mixture *E/Z* ratio 1:1): Oil, $[\alpha]_D$ = -14.9 (*c* 1.00, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): ppm 1.36 and 1.53 (2d, *J* = 7.3 and 7.4, 3+3H, CH_3), 2.39 and 2.41 (2s, 3+3H, $2CH_3$), 3.47 and 3.59 (2s, 3+3H, CH_3), 4.13 and 4.72 (2q, *J*= 7.3 and 6.3, 1+1H, CH), 4.59 and 4.72 (2 AB $_{\text{spin system}}$ *J* =14.3 and 15.0, 2+2H, CH_2), 7.14-7.79 (m, 9+9 H, ArH), 8.31 and 8.47 (2s, 1+1H, CH). ^{13}C NMR (125 MHz, $CDCl_3$) ppm 14.3 and 17.0($2CH_3$), 21.5(CH_3), 50.6 and 54.6(CH_2), 52.3(CH_3), 54.9 and 58.6(CH), 126.5(CH), 128.0(CH), 128.3(CH), 129.1(CH), 129.3(CH), 134.6 and 134.8(C), 139.1 and 139.2(C) 142.6(C),159.3 and 159.4(CH), 170.3 and 170.7(C). ESI-MS: *m/z* 397[M+Na]. Anal. Calcd. for $C_{19}H_{22}N_2O_4S$: C,60.94; H, 5.92; N, 7.48% Found C, 60.70; H, 6.11; N, 7.32%

Methyl 2-*N*-benzyl-*N´*-tosylformimidamido) acetate (3c). Yield 35%, Mp 99 °C (from diethyl ether). ^{1}H NMR (200 MHz, $CDCl_3$): ppm 2.39 (s, 3H, CH_3), 3.62 (s, 3H, CH_3), 4.04 (s, 2H, CH_2), 4.59 (s, 2H, CH_2), 7.16-7.76 (m, 9H, ArH), 8.46 (s, 1H, CH). ^{13}C NMR (50 MHz, $CDCl_3$) ppm 21.7(CH_3), 46.7(CH_2), 52.6(CH_3), 57.1(CH_2), 126.7(CH), 128.4(CH), 129.1(CH), 129.4(CH), 129.5(CH), 133.7(C), 139.2, 142.9, 160.1(CH), 167.9. ESI-MS: *m/z* 383[M+Na], 359 [M-H]. Anal. Calcd. for $C_{18}H_{20}N_2O_4S$: C, 59.98; H, 5.59; N, 7.77% Found C, 59.71; H, 5.78; N, 7.59%

***N*-benzyl-*N*-2-oxo-tetrahydrothiophen-3-yl)-*N´*-tosylformimidamide (3d).** Yield 47%, oil. ^{1}H NMR (200 MHz, $CDCl_3$): ppm 2.13-2.52 (m, 2H, CH_2), 2.40 (s, 3H, CH_3), 3.16-3.29 (m, 2H, CH_2), 4.72-4.93 (m, 1H, CH), 7.18-7.82 (m, 9H, ArH), 8.38 (s, 1H, CH). ^{13}C NMR (50 MHz, $CDCl_3$) ppm 21.7 (CH_3), 27.5(CH_2), 32.1(CH_2), 55.5, 65.9(CH), 126.7(CH), 128.0(CH), 128.3(CH), 129.0(CH), 129.6(CH), 134.7(C), 142.9(C), 156.8(C), 160.3(CH), 201.6(C). ESI-MS: *m/z* 389 [M+H]. Anal. Calcd. for $C_{19}H_{20}N_2O_3S_3$: C, 58.74; H, 5.19; N,7.21% Found C, 58.58; H, 5.37; N, 7.13%

Acknowledgements

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