Unusual Ring Closure Reaction of Amides with Pyrimidines: Novel Stereoselective Synthesis of Hexahydroimidazo[1,2-*c*]pyrimidines

Alberto Acero-Alarcón,[a] Trinidad Armero-Alarte,[a] Joan M. Jorda-Gregori,[a] Cristina Rojas-Argudo,[a] Elena Zaballos-García,[a] Juan Server-Carrió,[b] Fatima Z. Ahjyaje,[a] José Sepulveda-Arques*[a]

[a] Departamento de Química Orgánica, Facultad de Farmacia, Universidad Valencia, Burjassot, Valencia, Spain
Fax +34(96)3864939; E-mail jose.sepulveda@uv.es
[b] Departamento de Química Inorgánica, Facultad de Farmacia, Universidad de Valencia, Burjassot, Valencia, Spain
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Abstract: Hexahydromidazo[1,2-*c*]pyrimidines **6** were prepared by the reaction of tosylpyrimidines **2** with bromoacetamides **3** in one step. The stereoselectivity of the reaction has been confirmed by X-ray analysis. Imidazo[1,2-*a*]pyrimidines **5** were obtained on heating hexahydroimidazo[1,2-*c*]pyrimidines **6** with trifluoroacetic anhydride.

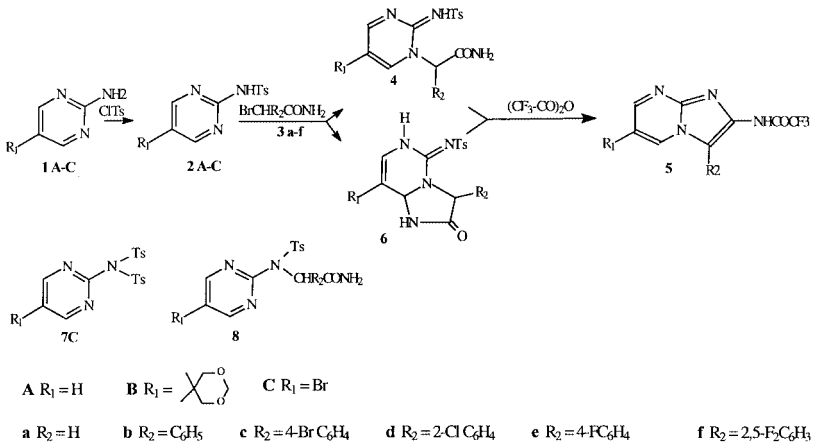
Key words: imidazopyrimidines, Michael addition, unsaturated imines, stereoselective conjugated addition, ring closure, heterocycles, amides

During the preparation of a series of imidazo[1,2-*a*]pyrimidines **5** for a study of pharmacological activity, we found that the reaction of 2-aminopyrimidine **(1A)** with *p*-toluenesulfonyl chloride and further alkylation of the sulfonamidopyrimidine **2A** formed with the bromoacetamides **3a–f**[1] afforded the alkylated products **4Aa–f**. Heating **4Aa–f** with trifluoroacetic anhydride afforded the expected imidazo[1,2-*a*]pyrimidines **5Aa–c,f**. Similar results occur with the 5-substituted 2-aminopyrimidines **1B,C** as starting materials when the bromoacetamide **3a** was used for alkylation. However, when the 2-aminopyrimidines **1B,C**, were tosylated and the derivatives **2B,C** were alkylated with **3b–f**, the hexahydroimidazo[1,2-*c*] pyrimidines **6**, (R_1 = **B,C**; R_2 = **b–f**) were isolated as the major products along with minor amounts of the corresponding alkylated derivatives **4**. Hexahydroimidazo[1,2-*c*]pyrimidines **6** were converted to the imidazo[1,2-*a*]pyrimidines **5** by refluxing with trifluoroacetic anhydride similar to the reaction of the alkylated products **4**. (Scheme).

The procedure used for the preparation of the imidazo [1,2-*a*]pyrimidines **5** was based on the literature using 2-aminopyridines as starting material.[2] In the first step the tosylation of the 2-aminopyrimidines **1A,B** afforded the sulfonamidopyrimidines **2A,B** as solid compounds in very high yields. The ^{1}H NMR and ^{13}C NMR data are shown in Tables 1 and 2. The tosylation of **1C** was a slower reaction and when it was heated to completion, the ditosylated derivative **7C** was obtained (14%) along with **2C** (76%).

The tosylation of 2-aminopyrimidines having electron-withdrawing substituents at C-5 was not successful. 2-Amino-5-formylpyrimidine did not react even under forced conditions and 2-amino-5-ethoxycarbonylpyrimidine gave only small amounts (8%) of the corresponding tosylated derivative.

In the reaction of **2A** with bromoacetamides **3a–f** and **2B,C**, alkylation occurred on the endocyclic nitrogen in the reaction with the bromoacetamide **(3a)** affording the derivatives **4**. The products **4**, showed in the ^{1}H NMR spectra typical AMX patterns (three doublets of doublets) where R_1 = H (**4Aa–f**) and an AB pattern where $R_1 \neq$ H (**4Ba**, **4Ca**) for pyrimidine ring hydrogen atoms, because of the asymmetry of the molecule. The chemical shift of H-4 was always at lower field than H-6 (Tables 3 and 4). An NOE effect (26%) on the H-6 signal appeared for **4Aa**

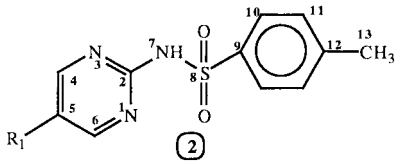


Scheme

Table 1 ^{1}H NMR (DMSO-d_6/TMS) Data of Sulfonamidopyrimidines **2**[a], δ, *J* (Hz)

Product	$H_{4(6)}$	H_5	H_{10}	H_{11}	$J_{5,4(6)}$	$J_{10,11}$	H_{13}	NH
2A[b]	8.64	6.95	7.98	7.26	4.75	8.03	2.38	9.85
2B	8.50		7.87	7.35		8.03	2.34	
2C	8.63		7.87	7.33		7.95	2.29	11.95

[a]



[b] Recorded in $CDCl_3$/TMS.

Table 2 ^{13}C NMR (DMSO-d_6/TMS) Data of Sulfonamidopyrimidines **2**[a], δ

Product	C_2	$C_{4(6)}$	C_5	C_9	C_{10}	C_{11}	C_{12}	C_{13}
2A[b]	156.9	158.6	115.7	136.7	128.4	129.2	144.1	21.6
2B	155.2	154.3	124.3	135.2	125.8	127.3	141.5	20.6
2C	155.8	159.0	112.9	137.2	127.9	129.7	143.9	21.3

[a] For numbering of the structure, see Table 1.
[b] Recorded in $CDCl_3$/TMS.

when NCH_2CONH_2 was irradiated. Chemical shifts for quaternary carbons (C-9 and C-12) of the toluenesulfonyl groups were closer than for the original tosylated derivatives **2A–C** as a result of a different electronic effect of the $=NSO_2$ substituent.

In the reaction of **2A** and **2C** with bromoacetamide **(3a)**, in addition to compounds **4Aa** and **4Ca**, a small amount of compounds **8Aa** (7%) and **8Ca** (8%) derived from alkylation on the exocyclic nitrogen were obtained.The ^{1}H NMR agreed with the symmetry of the molecule and only one doublet for H-4 and H-6 of the pyrimidine ring appeared in spectra. (Tables 5 and 6). Here again the chemical shifts of the quaternary carbons of the *p*-toluenesulfonyl group had quite different values.

On the other hand the reaction of **2B,C** with bromoacetamides **3b–f**, afforded the hexahydroimidazo[1,2-*c*]pyrimidines **6** instead of the expected alkylated products **4**, as a result of an intramolecular Michael addition of the amide group to the α-β unsaturated imino system. Structures of compounds **6** were elucidated by ^{1}H and ^{13}C NMR (Tables 7 and 8). A singlet for H-8a at δ = 6.2 is in agreement with a low coupling constant because of the dihedral angle between hydrogens at C-8a and C-7 (79.3º). On the other hand the olefinic hydrogen H-7 appeared as a doublet coupled with the NH which exchanges slowly on the NMR time-scale due to hydrogen bonding with the SO_2 group

Table 3 ^{1}H NMR (DMSO-d_6/TMS) Data of 2-[2-(4-Methylphenylsulfonylimino)-1,2-dihydro-1-pyrimidinyl]acetamides **4**[a], δ, *J* (Hz)

Product	H_4	H_5	H_6	H_{10}	H_{11}	H_{14}	$J_{4,5}$	$J_{4,6}$	$J_{5,6}$	$J_{10,11}$	H_{13}	NH_2
4Aa	8.60	6.83	8.35	7.69	7.24	4.74	4.39	2.19	6.58	8.23	2.33	7.84, 7.45
4Ab	8.56	6.70	7.42	7.77	7.28	6.75	4.38	2.20	6.58	7.68	2.34	8.19, 7.77
4Ac	8.56	6.70	7.80	7.77	7.27	6.67	4.38	2.19	6.94	8.04	2.34	8.19, 7.84
4Ad	8.57	6.68	7.48	7.76	7.28	6.90	4.38	2.19	6.58	8.05	2.33	8.34, 7.93
4Ae	8.56	6.71	7.79	7.78	7.27	6.69	4.40	2.20	6.60	8.03	2.33	8.19, 7.79
4Af	8.59	6.72	7.96	7.74	7.28	6.95	4.02	2.19	6.58	8.05	2.33	8.31, 7.96
4Ba	8.60		8.44	7.69	7.24	4.78		2.56		8.23	2.33	7.84, 7.44
4Ca	8.93		8.93	7.86	7.42	4.86				7.33	2.34	7.87, 7.66

[a]

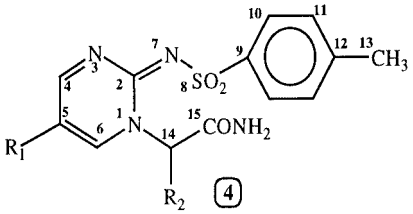


Table 4 ^{13}C NMR (DMSO-d_6/TMS) Data of 2-[2-(4-methylphenylsulfonylimino)-1,2-dihydro-1-pyrimidinyl]acetamides **4**,[a] δ

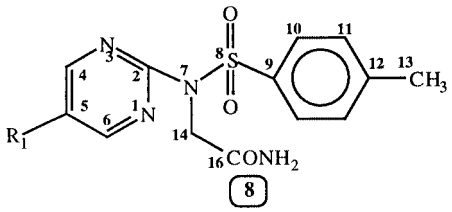
Product	C_1	C_4	C_5	C_6	C_9	C_{10}	C_{11}	C_{12}	C_{13}	C_{14}	C_{15}
4Aa	154.6	164.5	108.0	151.8	141.2	126.7	128.8	141.2	21.1	54.6	167.2
4Ab	154.4	164.0	108.1	148.5	141.0	127.0	128.9	141.2	21.1	65.1	167.9
4Ac	154.4	164.1	108.2	148.6	141.0	127.1	128.9	141.3	21.2	64.7	167.7
4Ad	154.2	164.2	108.3	147.9	140.9	127.0	128.9	141.3	21.1	63.4	167.4
4Ae	154.5	164.1	108.2	148.5	141.1	127.1	129.0	141.3	21.2	64.7	168.0
4Af	154.0	164.5	108.3	148.6	140.8	127.0	128.9	141.4	21.1	59.2	166.7
4Ba	154.4	162.4	118.8	149.7	140.9	127.0	128.8	141.2	21.1	54.7	167.2
4Ca	152.9	164.7	100.6	151.6	140.7	126.9	128.9	141.4	21.1	54.8	166.8

[a] For numbering of the structure, see Table 3.

Table 5 ^{1}H NMR (DMSO-d_6/TMS) Data of 2-[4-Methylphenyl-(2-pyrimidinyl)sulfonamido]acetamides **8**[a], δ, *J* (Hz)

Product	$H_{4(6)}$	H_5	H_{10}	H_{11}	H_{14}	$J_{4(6),5}$	$J_{10,11}$	H_{13}	NH_2
8Aa	8.49	7.06	8.00	7.35	4.76	4.73	8.40	2.36	7,59, 7.11
8Ca	8.68		7.98	7.36	4.74		8.05	2.37	7.60, 7.14

[a]



8

(as it can be deduced from an X-Ray study on **6Ac** which shows a distance of 1.76 Aº between H (61) and O (11).

Heterocosy spectra on **6Bd** and **6Be** showed a correlation between H-8a (δ = 6.19 and 6.02) and the aliphatic carbon signal at δ = 66.6 and 65.8, in agreement with the proposed structure. The hexahydroimidazo[1,2-*c*]pyrimidines **6** with the $=NSO_2C_6H_4Me$ substituent at C-5, presented very close values for the chemical shifts of the quaternary carbons of the toluenesulfonyl group.

The imidazo[1,2-*a*]pyrimidines **5** were obtained when either the alkylated products **4**, or the hexahydroimidazo[1,2-*c*]pyrimidines **6**, were heated at reflux with trifluoroacetic anhydride in dichloromethane as a solvent. The yields were lower when R_2 = H and also when R_1 = 5,5-dimethyl-1,3-dioxan-2-yl. In this latter case the low yield

Table 6 ^{13}C NMR (DMSO-d_6/TMS) Data of 2-[4-Methylphenyl(2-pyrimidinyl)sulfonamidoacetamides **8**[a], δ

Product	C_2	$C_{4(6)}$	C_5	C_9	C_{10}	C_{11}	C_{12}	C_{13}	C_{14}	C_{15}
8Aa	157.7	158.0	116.2	137.8	128.8	129.2	143.8	21.3	48.1	169.5
8Ca	156.2	158.2	112.9	137.2	128.8	129.2	144.0	21.2	48.4	169.0

[a] For numbering of the structure, see Table 5.

Table 7 ^{1}H NMR (DMSO-d_6/TMS) Data of Hexahydroimidazo[1,2-*c*]pyrimidines **6**[a], δ, *J* (Hz)

Product	H_3	H_7	H_8	H_{8a}	H_{12}	H_{13}	$J_{12,13}$	H_{15}	2 NH
6Ac	5.03	6.40	5.07	6.04	7.60	7.27	8.02	2.35	9.28, 9.17
6Bb	5.16	6.49		6.02	7.60	7.28	8.03	2.34	9.44, 9.23
6Bc	5.16	6.48		6.03	7.61	7.28	8.03	2.34	9.45, 9.30
6Bd	5.50	6.49		6.19	7.52	7.26	8.05	2.34	9.43, 9.37
6Be	5.17	6.48		6.02	7.62	7.28	8.03	2.34	9.43, 9.25
6Cb	5.23	6.72		6.18	7.58	7.26	8.05	2.33	9.53
6Cc	5.23	6.70		6.16	7.56	7.27	8.03	2.35	9.53, 9.51
6Cd	5.59	6.71		6.29	7.50	7.25	8.03	2.34	9.62, 9,52

[a]

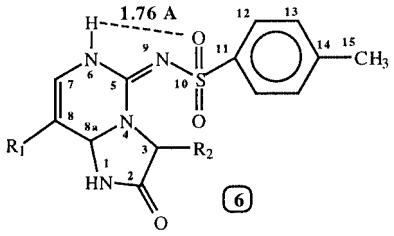


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Table 8 ^{13}C NMR (DMSO-d_6/TMS) Data of Hexahydroimidazo[1,2-*c*]pyrimidines **6**[a], δ

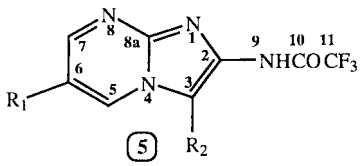
Product	C_2	C_3	C_5	C_7	C_8	C_{8a}	C_{11}	C_{12}	C_{13}	C_{14}	C_{15}
6Ac	169.1	61.8	148.5	125.1	100.1	65.6	140.7	125.9	129.4	142.1	21.1
6Bb	170.2	62.2	148.0	122.2	108.9	65.8	140.7	125.8	129.4	142.1	21.1
6Bc	169.8	61.7	148.0	122.1	109.1	65.9	140.6	125.9	129.4	142.2	21.2
6Bd	169.2	60.6	148.2	122.0	109.8	66.6	140.8	125.7	129.3	142.1	21.1
6Be	170.2	61.6	148.1	122.2	109.0	65.8	140.7	125.9	129.5	142.2	21.1
6Cb	170.1	63.6	147.7	125.4	94.6	68.5	140.6	126.0	129.6	142.4	21.2
6Cc	169.6	63.0	147.7	125.4	94.6	68.3	140.5	125.9	129.5	142.3	21.2
6Cd	169.1	61.7	147.8	125.3	95.1	68.8	140.7	125.7	129.4	142.2	21.2

[a] For numbering of the structure, see Table 7.

Table 9 ^{1}H NMR (DMSO-d_6/TMS) Data of Imidazo[1,2-*a*]pyrimidines **5**[a], δ, *J* (Hz)

Product	H_3	H_5	H_6	H_7	$J_{5,6}$	$J_{5,7}$	$J_{6,7}$	NH
5Aa	8.21	9.01	7.11	8.54	6.94	1.83	4.38	10.48
5Ab		8.44	6.76	8.28	6.95	1.83	4.03	10.74
5Ac		8.41	6.72	8.22	6.95	1.83	4.38	10.63
5Af		8.75	7.19	8.68	7.04	2.20	5.13	11.11
5Ba	8.13	8.51		8.86		1.83		
5Bb		8.70		8.70				9.48
5Bd		8.37		8.73		2.42		11.99
5Ca	8.16	9.34		8.58		2.19		10.14

[a]



was stored in THF at room temperature for a week in the presence of catalytic amounts of diisopropylethylamine (DIPEA), the corresponding product **6Ac** was obtained (20%). On the other hand when **6Be** was stirred with catalytic amounts of *p*-toluenesulfonic acid, the corresponding open ring alkylated product **4Be** was detected by ^{13}C NMR spectroscopy (partial hydrolysis of the ketal function was observed). These experiments and the reported fact that imidazo[1,2-*a*]pyrimidines **5** can be obtained either from alkylated pyrimidines **4** or from imidazo[1,2-*c*]pyrimidines **6**, indicate that both compounds can be interconverted and that the proportion in which they are obtained from the sulfonamidopyrimidines **2** depends on the substituents of the reactants and also on the reaction conditions.

Compounds **6Bb–e** and **6Cb–d**, where $R_2 \neq H$, can exist in diastereoisomeric forms due to the stereogenic centres at C-3 and C-8a. However, the ^{1}H and ^{13}C NMR spectra of compounds **6** show only one set of signals indicating that the ring closure reaction is diastereoselective. In ex-

Table 10 ^{13}C NMR (DMSO-d_6/TMS) Data of Imidazo[1,2-*a*]pyrimidines **5**[a], δ, *J* (Hz)

Product	C_2	C_3	C_5	C_6	C_7	C_{8a}	C_{10}	$^2J_{C,F}$	C_{12}	$^1J_{C,F}$
5Aa	140.7	100.5	133.5	108.7	149.5	144.8	154.6	37.8	115.2	283.5
5Ab	126.8	117.2	133.0	110.2	151.3	145.4	155.0	37.8	115.5	283.5
5Ac	126.3	116.0	133.2	110.3	151.6	145.6	156.0	37.8	116.1	289.8
5Af	137.8	118.2	133.9	110.2	151.8	145.9	155.1	37.8	116.0	283.5
5Ba	144.2	97.8	132.8	120.2	148.3	145.0	155.6	37.8	116.0	289.8
5Bb	126.6	117.7	130.3	121.3	149.8	145.1	156.0	37.8	116.0	289.8
5Bd	126.1	113.8	130.7	121.1	149.7	145.3	155.0	37.8	115.9	289.8
5Ca	141.4	101.6	135.1	104.1	150.6	143.4	154.6	37.8	115.8	289.8

[a] For numbering of the structure, see Table 9.

is due to partial hydrolysis of the ketal group. Table 9 and 10 show the NMR data of some examples of compounds **5**, prepared from **4** or **6** as starting materials.

The formation of the hexahydroimidazo[1,2-*c*]pyrimidines **6** appears to be the first example of a Michael addition of a carboxamide on an α,β-unsaturated imino system and it constitutes a novel method of synthesis of these compounds.

In the literature there are examples of conjugated additions of organomagnesium compounds to α,β-unsaturated imines.[3] In our reaction the nucleophile is probably the $CONH^-$ formed in basic solution of diisopropylethylamine in dimethylformamide. The electron-withdrawing $=NSO_2C_6H_4Me$ substituent at C-2 favours the nucleophilic attack.

The formation of the hexahydroimidazo[1,2-*c*]pyrimidines **6** as major products only in the case of pyrimidines with substituents at C-5 and R_2 different from H can be due to steric factors that induce a favourable conformation for the ring closure. However, they can be also obtained from C-5 unsubstituted sulfonamidopyrimidines **2A**. In fact when the alkylated product **4Ac**, obtained from **2Ac**, periments with **6Be** and **6Bd** an NOE effect was not observed on the H-8a signal when H-3 was irradiated in agreement with a *trans*-disposition of both hydrogens.

The X-ray crystallographic analysis of a single crystal of **6Ac** (from ethyl acetate/dichloromethane) confirmed unequivocally the structure and also the stereochemistry. The analysis revealed the presence of four molecules in the cell: two of the (*R*,*R*)-enantiomer that are chemically equivalent, and two molecules of the (*S*,*S*)-enantiomer generated by the inversion centre. The Figure shows one of these molecules with the numbering scheme used in the crystal study. Table 11 gives the selected bond lengths, angles and torsion angles. The *trans*-disposition of the hydrogen atoms attached to C(91) and C(31) confirms that the conjugated Michael addition is diastereoselective with the nucleophilic attack of the amido nitrogen occurring preferentially on the opposite face to the aryl substituent (R_2) at C-3.

In summary we have presented a new synthesis of hexahydroimidazo[1,2-c]pyrimidines **6** in good yields

Table 11 Selected X-Ray Bond Lengths, Bond Angles and Torsional Angles for **6Ac**

S(1)-O(11)	1.920(9)	C(21)–N(11)–C(91)	115.4(7)	O(21)-C(21)-N(11)-C(91)	173.6(8)
S(1)-N(71)	1.594(8)	C(31)–N(41)–C(91)	112.9(6)	C(21)-N(11)-C(91)-C/(81)	129.5(8)
O(21)-C(21)	1.214(8)	C(51)–N(41)–C(91)	121.7(6)	C(21)-C(31)-C(101)-C(111)	92.0(9)
N(11)-C(21)	1.330(9)	C(51)–N(61)–C(71)	119.4(6)	C(21)-C(31)-C(101)-C(151)	–88.1(9)
N(11)-C(91)	1.446(8)	N(11)–C(21)-C(31)	108.1(7)	C(31)-C(21)-N(11)-C(91)	–5.9(9)
N(41)-C(31)	1.454(9)	N(41)–C(31)-C(21)	101.3(6)	C(51)-N(41)-C(91)-C(81)	35.8(9)
N(41)-C(51)	1.345(7)	N(41)–C(51)-N(61)	116.6(6)	C(51)-N(61)-C(71)-C(81)	23.8(12)
N(41)-C(91)	1.472(9)	N(61)–C(71)-C(81)	121.9(8)	N(11)-C(21)-C(31)-N(41)	–2.3(8)
N(61)-C(51)	1.356(9)	C(71)–C(81)-C(91)	116.9(8)	N(11)-C(21)-C(31)-C(101)	122.9(7)
N(61)-C(71)	1.398(8)	N(11)–C(91)-N(41)	100.7(6)	N(11)-C(91)-N(41)-C(31)	–12.5(8)
N(71)-C(51)	1.314(9)	N(41)–C(91)-C(81)	109.4(6)	N(11)-C(91)-N(41)-C(51)	159.5(6)
C(21)-C(31)	1.541(9)	N(41)–C(31)-H(31)	110.0	N(11)-C(91)-C(81)-C(71)	–146.8(8)
C(71)-C(81)	1.312(8)	C(21)–C(31)-H(31)	115.8	N(41)-C(31)-C(101)-C(111)	151.4(8)
C(81)-C(91)	1.492(8)	C(101)–C(31)-H(31)	100.9	N(41)-C(31)-C(101)-C(151)	28.6(10)
		N(11)–C(91)-H(91)	111.4	N(41)-C(51)-N(61)-C(71)	–21.9(10)
		N(41)–C(91)-H(91)	117.6	N(41)-C(91)-N(11)-C(21)	11.2(9)
		C(81)–C(91)-H(91)	101.6	N(61)-C(51)-N(41)-C(31)	161.8(6)
				N(61)-C(51)-N(41)-C(91)	–9.3(10)
				N(61)-C(71)-C(81)-C(91)	6.4(12)
				N(71)-C(51)-N(41)-C(31)	–18.5(10)
				N(71)-C(51)-N(41)-C(91)	170.4(7)
				N(71)-C(51)-N(61)-C(71)	158.5(8)

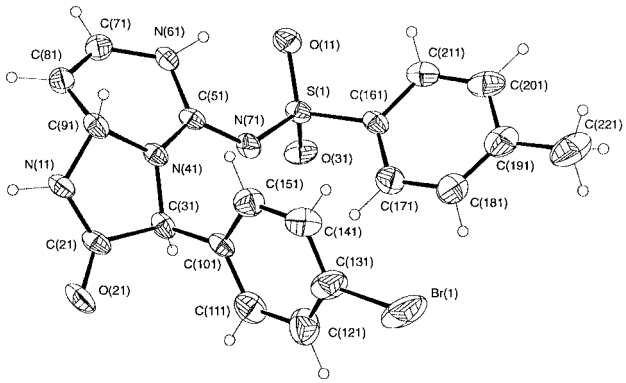


Figure X-Ray Crystallographic Structure of **6Ac**

(70–80%) by alkylation of sulfonamidopyrimidines **2** with α-arylbromoacetamides. This reaction is the first example of an intramolecular conjugated Michael addition of an amide to an α,β-unsaturated imino system and constitutes a novel and stereoselective procedure for the preparation of these compounds.

Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-250 in DMSO-d_6, unless otherwise indicated. HRMS were obtained for all compounds using a VG Autospec TRIO 1000 intrument. The ionization mode used in mass spectra was electron impact (EI) at 70 eV or fast atom bombardment (FAB). All new compounds were characterized spectroscopically by ^{1}H and ^{13}C NMR spectra and HRMS.

5-(5,5-Dimethyl-1,3-dioxan-2-yl)-2-pyrimidinamine (1B)

2,2-Dimethylpropane-1,3-diol (3.75 g, 36 mmol) was added to 2-amino-5-pyrimidinecarboxaldehyde[4] (4 g, 32 mmol) and *p*-toluenesulfonic acid (1,15 g, 6 mmol) in toluene (130 mL). The mixture was heated at reflux temperature for 16 h in a Dean–Stark apparatus. The solvent was removed and the residue extracted with EtOAc, then washed with aq NaOH solution and the solvent was evaporated. Addition of Et_2O afforded the crystalline product **1B** (4.6 g, 68%, mp 186–187 ºC.

HRMS: *m*/*z* found M^+, 209.1163. $C_{10}H_{15}N_3O_3$ requires M, 209.1164.

^{1}H NMR: δ = 0.81 (s, 3 H), 1.28 (s, 3 H), 3.62 (d, *J* = 11 Hz, 2 H), 3.75 (d, *J* = 11 Hz, 2 H), 5.30 (br, 2 H), 5.33 (s, 1 H), 8.41 (s, 2 H).

^{13}C NMR: δ = 21.8, 22.9, 30.1, 77.5, 98.9, 122.3, 156.8, 163.2.

Sulfonamidopyrimidines 2 A,B; General Procedure

p-Toluenesulfonyl chloride (30 mmol) in pyridine (6 m L) was slowly added to the corresponding 2-aminopyrimidine **1A,B** (20 mmol) in pyridine (8 mL) at 0 ºC. The mixture was stirred for 2 h and allowed to reach r.t., then it was poured into H_2O (100 mL) and the solid was filtered off and recrystallized from $CHCl_3$.

2A

Yield: 88%; mp 204–206 ºC.

HRMS: *m*/z found M^+, 249.0568. $C_{11}H_{11}N_3O_2S$ requires M, 249.0571.

2B

Yield: 75%; mp 274–276 ºC.

HRMS: *m*/*z* found $(M + 1)^+$, 364.1336 (FAB). $C_{17}H_{22}N_3O_4S$ requires M + 1, 364.1331 (M + 1).

Sulfonamidopyrimidine 2C

p-Toluenesulfonyl chloride (60 mmol) in pyridine (20 mL) was slowly added to **1C** (20 mmol) in pyridine (20 mL). The mixture was heated at 80 ºC for 16 h and then was poured into H_2O (100 mL). The solid was washed with H_2O, hexane and CH_2Cl_2 and recrystallized from EtOH affording **2C** (76%); mp 254–256 ºC. The CH_2Cl_2 filtrate contained the product **7C.**

HRMS: *m*/*z* found 327.9758 $(M + 1)^+$, (FAB). $C_{11}H_{10}BrN_3O_2S$ requires (M + 1), 327.9755.

7C

Yield. 18%; mp 243–245 ºC.

HRMS: *m/z* found $(M + 1)^+$, 481.9836 (FAB). $C_{18}H_{17}BrN_3O_4S_2$ requires (M + 1), 481.9844 (M + 1).

^{1}H NMR: δ = 3.3 (s, 6 H), 7.50 (d, *J* = 8 Hz, 4 H), 7.95 (d, *J* = 8 Hz, 4 H), 9.20 (s, 2 H).

^{13}C NMR: δ = 21.4, 121.0, 128.9, 129.9, 136.2, 145.9, 154.1, 161.0.

Alkylation of Sulfonamidoyrimidines 2 A–C with Bromoacetamides 3 a–f; General Procedure

Diisopropylethylamine (0.65 mL, 3.6 mmol) was slowly added to the corresponding sulfonamidopyrimidines **2** (3 mmol) in DMF (12 mL) under argon over 40 min. The corresponding bromoacetamide **3** (3.6 mmol) was added to the mixture and stirred for 16 h at r.t. The crude mixture was poured into H_2O (200 mL) affording the alkylated derivatives **4** or the Michael addition products **6** besides small amounts of **8**.

4Aa
Yield: 85%; mp 213–215 ºC.

HRMS: *m/z* found $(M + 1)^+$, 307.0865 (FAB). $C_{13}H_{15}N_4O_3S$ requires (M + 1), 307.0865.

8Aa
Yield: 7%; mp 220–222 ºC.

HRMS: *m/z* found $(M + 1)^+$, 307.0858 (FAB). $C_{13}H_{15}N_4O_3S$ requires (M + 1), 307.0865.

4Ab
Yield: 89%; mp 196–198 ºC.

HRMS: *m/z* found M^+, 382.1097. $C_{19}H_{18}N_4O_3S$ requires M, 382.1100.

4Ac
Yield: 70%; mp 187–189 ºC.

HRMS: *m/z* found M^+, 460.0201. $C_{19}H_{17}BrN_4O_3S$ requires M, 460.0205.

4Ad
Yield: 91%; mp 254–257 ºC.

HRMS: *m/z* found $(M + 1)^+$, 417.0783 (FAB). $C_{19}H_{18}ClN_4O_3S$ requires (M + 1), 417.0788.

4Ae
Yield: 67%; mp 214–216°C.

HRMS: *m/z* found M^+, 400.1008. $C_{19}H_{17}FN_4O_3S$ requires M, 400.1005.

4Af
Yield: 80%; mp 226–228 ºC.

HRMS: *m/z* found M^+, 418.0909. $C_{19}H_{16}F_2N_4O_3S$ requires M, 418.0911.

6Bb
Yield: 69%; mp 228–230 ºC.

HRMS: *m/z* found M^+, 495.1706. $C_{25}H_{27}N_4O_5S$ requires M, 495.1702.

6Bc
Yield: 74%; mp 248–250 ºC.

HRMS: *m/z* found M^+, 574.0864. $C_{25}H_{27}BrN_4O_5S$ requires M, 574.0886.

6Bd
Yield: 75%; mp 249–251 ºC.

HRMS: *m/z* found $(M - 1)^+$, 529.1310. $C_{25}H_{26}ClN_4O_5S$ requires (M – 1), 529.1312.

6Be
Yield: 80%; mp 250–252 ºC.

HRMS: *m/z* found $(M - 1)^+$, 513.1621. $C_{25}H_{26}FN_4O_5S$ requires (M – 1), 513.1608.

4Ca
Yield: 87%; mp 215–217 ºC.

HRMS: *m/z* found M^+:383.9874. $C_{13}H_{13}BrN_4O_3S$ requires M 383.9892),

8Ca
Yield: 8%.

HRMS: *m/z* found M^+, 383.9879. $C_{13}H_{13}BrN_4O_3S$ requires M, 383.9892.

Isolation of Compounds **4Ba** and **6Cb–d**

When the reaction product did not precipitate, the aqueous phase was extracted with EtOAc (3 × 50 mL), the combined extracts were dried (Na_2SO_4) and the solvent evaporated. The residue was chromatographed on silica using CH_2Cl_2/THF (9:1) or CH_2Cl_2/EtOAc (7:3) to afford compounds **4Ba** and **6Cb–d.** Compounds **6Cb–d,** were obtained as gums which could not be induced to crystallise.

4Ba
Yield: 65%; mp 191–193 ºC.

HRMS: *m/z* found M+, 420.1449. $C_{19}H_{24}N_4O_5S$ requires M, 420.1467.

6Cb
Yield: 71%.

HRMS: *m/z* found M^+, 492.0101. $C_{19}H_{17}BrN_4O_5S$ requires M, 492.0103.

6Cc
Yield: 75%.

HRMS: *m/z* found M^+, 569.9203. $C_{19}H_{16}Br_2N_4O_5S$ requires M, 569.9208.

6Cd
Yield: 80%.

HRMS: *m/z* found M^+, 529.9709. $C_{19}H_{16}BrClN_4O_5S$ requires M, 529.9713.

Conversion of 4Ac to 6Ac

When the alkylated product **4Ac** was stored in THF solution at room temperature for a week in the presence of catalytic amounts of diisopropylethylamine, the corresponding product **6Ac** was obtained; yield: 20%; mp 196–198 ºC.

HRMS: *m/z* found M^+, 460.0201. $C_{19}H_{17}BrN_4O_3S$ requires M, 460.0205.

Imidazo[1,2-*a*]pyrimidines 5; General Procedure

The alkylated derivatives **4Aa, 4Ab, 4Ac, 4Af, 4Ba, 4Ca** and the hexahydroimidazo[1,2-*c*]pyrimidines **6Bb, 6Bd** (2 mmol) were heated at reflux with trifluoroacetic acid (15 mL, 50 mmol) in CH_2Cl_2 (35 mL) under argon for 4 h.. The solvent was evaporated and the residue extracted with EtOAc. The organic phase washed with aq $NaHCO_3$ solution, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography using CH_2Cl_2/EtOAc (3:1) affording imidazo[1,2-*a*]pyrimidines **5.**

5Aa
Yield: 40%; mp 255–257 ºC.

HRMS: *m/z* found M^+, 230.0413; $C_8H_5F_3N_4O$ requires M, 230.0415.

5Ab
Yield: 75%; mp 235–237 ºC.

HRMS: *m/z* found M^+, 306.0734. $C_{14}H_9F_3N_4O$ requires M, 306.0728.

5Ac
Yield: 80%; mp 233–235 ºC.

HRMS: *m*/*z* found M^+, 383.9834. $C_{14}H_8BrF_3N_4O$ requires M, 383.9834.

5Af
Yield: 78%; mp 211-213 C.

HRMS: *m*/*z* found M^+, 342.0545. $C_{14}H_7F_5N_4O$ rrequires M, 342.0540.

5Ba
Yield: 36%; mp 265–267 ºC.

HRMS: *m*/*z* found M^+, 344.1099. $C_{14}H_{15}F_3N_4O_3$ requires M, 344.1096.

5Bb
Yield: 32%; mp 270–272 ºC.

HRMS: *m*/*z* found M^+, 420.1407. $C_{20}H_{19}N_4O_3F_3$ requires M, 420.1409.

5Bd
Yield: 40%; mp 172–174 ºC.

HRMS: *m*/*z* found $(M + 1)^+$, 455.1093 (FAB). $C_{20}H_{19}ClF_3N_4O_3$ requires (M + 1), 455.1098.

5Ca
Yield: 42%; mp 299–301 ºC.

HRMS: *m*/*z* Found M^+, 307.9521. $C_8H_4BrF_3N_4O$ requires M, 307.9521.

X-ray Crystal Data
$C_{19}H_{17}N_4O_3SBr$ (**6Ac)**: M = 461.34, triclinic Pl, α = 9.303(1), b = 11.962(2), c = 18.417(2) Å, α = 83.30(1), β = 78.44(1), γ = 78.04(1)°, U = 1958.3(4) Å^3, D_c = 1.57 g cm^{-3}, Z = 4, MoK_α (λ = 0.7107 Å), μ = 22.3 cm^{-1}. From the 6861 independent reflections 3446 were considered observed with the $I>2\sigma(I)$ criterion. The structure was solved by direct methods using the program SIR92.[5] All non-hydrogen atoms were anisotropically refined by least-squares on F using the XRAY76 System[6] (505 refined parameters). Hydrogens bonded to C atoms were placed at calculated positions and Fourier difference maps detected the hydrogens on the N atoms, all these were included as fixed contributors with a common isotropic temperature factor. In the final stages an empirical weighting scheme was chosen as to give no trends in $<\omega\Delta^2F>$ *vs* $<F_o>$ and *vs* $<\sin\theta/\lambda>$ using the program PESOS,[7] giving final R = 0.069 and R_w = 0.072 values.

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