1-Substituted Xanthines

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A convenient general procedure for the preparation of 1-alkyl-, 1-aryl-, and 1-aminoxanthines from an easily prepared imidazole precursor is described.

Xanthines exhibit a variety of biological effects due to their activity as adenosine receptor antagonists and phosphodiesterase inhibitors.[1,2] Many derivatives, in particular 1,3-dialkylxanthines, have been made with the goal of discovering compounds with significant biochemical selectivity.

Methods for the synthesis of 1-substituted xanthines have been very limited.[3] Recently a general method for the preparation of 1-alkylxanthines was reported.[4] The strategy in that approach was selective alkylation of a pyrimidine derivative, which was then elaborated, in several steps, to the 1-alkylxanthine. Herein we report an alternative synthesis of 1-substituted xanthines from a readily prepared imidazole derivative. The method is based on a traditional procedure used mainly for the synthesis of 2-thioxanthines.[5]

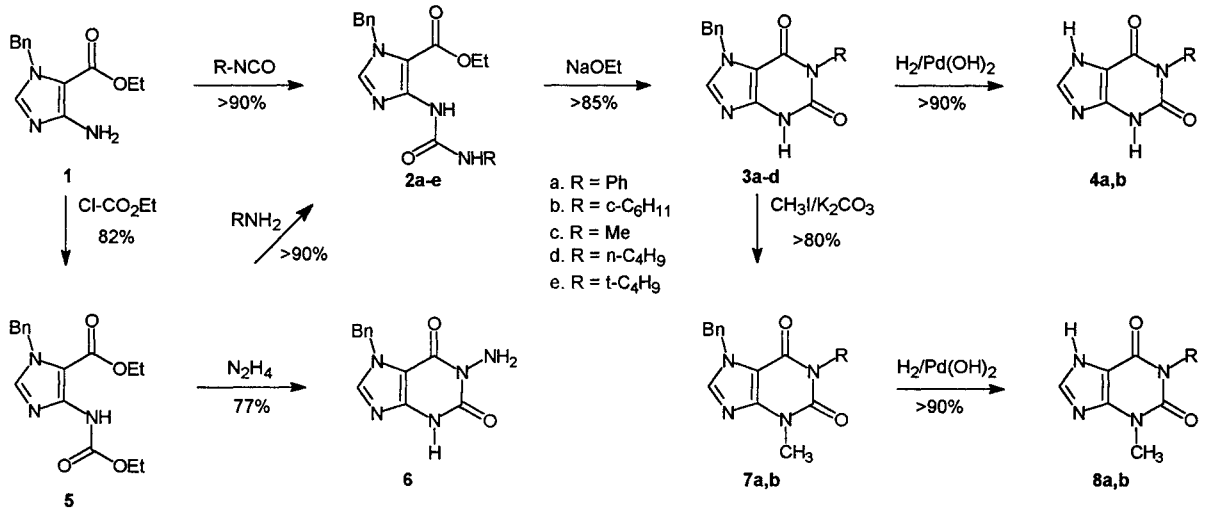
The starting material required for this synthesis, ethyl 4-amino-1-benzylimidazole-5-carboxylate (**1**), was readily prepared on a large scale from commercially available *N*-benzylglycine ethyl ester by modification of a method used previously to prepare 1-arylimidazoles.[6] Reaction of compound **1** with phenyl, cyclohexyl, and methyl isocyanate proceeded readily at elevated temperature to give the ureas **2a–c** in excellent yield (Scheme 1).[7] No reaction was observed with *tert*-butyl isocyanate, however. Treatment of ureas **2** with sodium ethoxide in ethanol resulted in ring closure to give xanthines **3** in near quantitative yield. The structure of these xanthines was confirmed by proton and carbon NMR, IR spectroscopy, and elemental analysis. It is worth noting that, in contrast to this facile intramolecular reaction, the carboxylate group of the imidazole **1** is inert to nucleophiles, failing to react even with hydrazine at high temperature and in the presence of a Lewis acid catalyst.

Catalytic hydrogenolysis over 20% palladium hydroxide on carbon was used to remove the benzyl group from xanthines **3a, b** yielding the previously unreported 1-substituted xanthines **4a, b**.[8] One limitation of this protecting group is that unsaturated functional groups in the substituent may be reduced under the conditions used for its removal.

Since aminoimidazole **1** did not react with sterically hindered *tert*-butyl isocyanate, an alternative approach to the intermediate ureas was explored. Carbamate **5** was prepared in good yield by reaction of **1** with ethyl chloroformate. Treatment of **5** with butylamine and *tert*-butylamine gave ureas **2d** and **2e** respectively. While ring closure occurred smoothly on treatment of **2d** with sodium ethoxide, no reaction was observed when **2e** was similarly treated. Thus it seems that tertiary alkyl substituents cannot be introduced at N-1 by this method.

Carbamate **5** also reacts with hydrazine, and in this case the aminoxanthine **6** is the only product, the presumed intermediate urea not being observed. Other methods for making 1-aminoxanthines are only effective if there is a substituent at N-3.[9,10]

Finally it is worth noting that the intermediates **3** can be used for the preparation of 1,3-disubstituted xanthines. Thus methylation of **3a** and **b** yielded the trisubstituted xanthines **7a** and **b**, respectively. Debenzylation gave 1,3-disubstituted xanthines **8a, b**, isomeric with compounds which would be available by the Traube synthesis where



Scheme 1

Table 1. *N*-Substituted *N'*-(1-Benzyl-5-ethoxycarbonylimidazol-4-yl)ureas **2**

Compound	R	Method	Yield (%)	mp (°C) (solvent)	^{1}H NMR (DMSO-d_6) δ				
					Bn	OEt	H-2	NHCONH	R
2a	Ph	A	97	159–160 (aq. EtOH)	5.47 (s), 7.0–7.5[a]	1.15 (t), 4.19 (q)	8.18 (s)	8.21 (s), 10.67 (s)	7.0–7.5[a]
2b	c-C_6H_{11}	A	92	137–139 (aq. EtOH)	5.43 (s), 7.1–7.4	1.13 (t), 4.17 (q)	8.09 (s)	7.87 (s), 8.51 (d)	1.26 (m, 5H), 1.62 (m, 3H), 1.83 (m, 2H), 3.59 (m, 1H)
2c	Me	A	89	167–169 (aq. EtOH)	5.44 (s), 7.1–7.4	1.13 (t), 4.17 (q)	8.09 (s)	7.91 (s), 8.31 (q)	2.76 (d, 3H)
2d	n-C_4H_9	B	95	112–114 (c-C_6H_{12})	5.44 (s), 7.1–7.4	1.13 (t), 4.17 (q)	8.09 (s)	7.89 (s), 8.47 (t)	0.88 (t, 3H), 1.33 (m, 2H), 1.44 (m, 2H), 3.22 (q, 2H)
2e	*t*-C_4H_9	B	91	108–110 (c-C_6H_{12})	5.43 (s), 7.1–7.4	1.13 (t), 4.16 (q)	8.08 (s)	7.76 (s), 8.52 (s)	1.32 (s, 9H)

[a] Signals for the two phenyl groups in **2a** overlap and integrate for 10H.

Table 2. Xanthines Prepared.

Compound	R	Method	Yield (%)	mp (°C) (solvent)	^{1}H NMR (DMSO-d_6) δ				
					7-Bn	3-Me	H-8	NH (br)	R
3a	Ph	C	98	271–273 (aq. EtOH)	5.42 (s), 7.2–7.5[a]		8.23 (s)	12.03	7.2–7.5[a]
3b	c-C_6H_{11}	C	85	204–206 (aq. EtOH)	5.43 (s), 7.2–7.4		8.12 (s)	11.73	1.20 (m, 3H), 1.54 (m, 3H), 1.74 (m, 2H), 2.34 (m, 2H), 4.65 (m, 1H)
3c	Me	C	89	274–276 (EtOH)	5.44 (s), 7.2–7.4		8.16 (s)	11.91	3.14 (s, 3H)
3d	n-C_4H_9	C	97	162–164 (aq. EtOH)	5.45 (s), 7.2–7.4		8.16 (s)	11.95	0.90 (t, 3H), 1.27 (m, 2H), 1.49 (m, 2H), 3.80 (q, 2H)
4a	Ph	E	95	dec. > 350 (EtOH)			8.00 (s)	12.13, 13.12	7.2–7.5 (m, 5H)
4b	c-C_6H_{11}	E	91	dec. > 320 (aq. EtOH)			7.91 (s)	11.67, 13.32	1.20 (m, 3H), 1.54 (m, 3H), 1.76 (m, 2H), 2.36 (m, 2H), 4.68 (m, 1H)
7a	Ph	D	88	156–157 (aq. EtOH)	5.45 (s), 7.2–7.5[a]	3.43 (s)	8.33 (s)		7.2–7.5[a]
7b	c-C_6H_{11}	D	83	113–115 (aq. PrOH)	5.45 (s), 7.2–7.4	3.37 (s)	8.21 (s)		1.20 (m, 3H), 1.54 (m, 3H), 1.75 (m, 2H), 2.36 (m, 2H), 4.71 (m, 1H)
8a	Ph	E	97	291–293 (water)		3-45 (s)	8.08 (s)	13.60	7.2–7.5 (m, 5H)
8b	c-C_6H_{11}	E	94	244–245 (aq. EtOH)		3.39 (s)	8.00 (s)	13.51	1.20 (m, 3H), 1.54 (m, 3H), 1.77 (m, 2H), 2.38 (m, 2H), 4.75 (m, 1H)

[a] Signals for the two phenyl groups in **3a** and **7a** overlap and integrate for 10H.

Table 3. ^{13}C NMR and IR Data for Imidazoles

Compound	^{13}C NMR δ									IR ν(C=O) cm^{-1}
	OEt	CH_2Ph	CH_2*Ph*	C-5	C-2	C-4	NHCOXR	CO_2Et	R	
1	14.2, 58.5	49.3	126.5, 127.3, 128.4, 138.1	99.7	140.8	156.5		160.4		1685
2a	13.9, 60.3	49.9	126.5, 127.5, 128.5, 137.0	104.0	139.6	146.7	150.8	159.6	118.9, 122.7, 128.8, 138.6	1657, 1702
2b	14.2, 60.7	50.3	126.8, 127.9, 128.9, 137.3	103.0	139.9	148.0	153.0	160.0	24.3, 25.4, 32.9, 48.1	1670
2c	13.8, 60.1	49.9	126.4, 127.5, 128.4, 137.1	102.6	139.5	147.9	153.9	160.0	26.1	1678
2d	13.8, 60.1	49.9	126.4, 127.5, 128.4, 137.0	102.5	139.5	147.9	153.2	160.0	13.5, 19.4, 31.5, 39.9	1675
2e	13.9, 60.2	49.8	126.5, 127.6, 128.6, 137.1	102.3	139.6	148.0	152.0	160.0	28.8, 50.0	1680, 1721
5	13.8, 60.2	49.6	126.7, 127.5, 128.5, 137.4	112.2	139.5	142.9	153.7	159.5	14.4, 59.9	1663, 1743

Table 4. ^{13}C NMR and IR Data for Xanthines

Compound	^{13}C NMR δ									IR
	3-Me	CH_2Ph	$CH_2\mathit{Ph}$	C-5	C-8	C-4	C-2	C-6	1-R	ν (C=O) cm^{-1}
3a		48.8	127.6, 127.8, 128.6, 136.8	106.0	142.9	148.2	150.9	155.0	127.8, 128.6, 129.3, 135.7	1674, 1723
3b		48.8	127.5, 127.9, 128.7, 137.0	105.8	142.8	147.5	150.9	155.5	25.0, 26.0, 28.3, 52.2	1659, 1706
3c		48.7	127.4, 127.7, 128.5, 137.0	105.6	142.6	147.5	150.9	155.1	26.7	1670, 1718
3d		48.7	127.4, 127.7, 128.5, 136.9	105.6	142.6	147.6	150.7	154.9	13.5, 19.5, 29.5, 39.3	1657, 1703
4a				106.7	140.9	147.6	151.1	155.1	127.8, 128.7, 129.3, 136.1	1642, 1734
4b				106.4	140.7	146.9	151.0	155.4	25.0, 26.0, 28.3, 52.0	1653, 1717
6		48.7	127.5, 127.7, 128.6, 137.5	105.4	142.1	150.7	151.9	152.9		1654, 1725
7a	29.7	49.3	127.6, 127.8, 128.6, 136.7	106.5	143.0	149.3	151.2	154.6	127.9, 128.7 129.2, 136.0	1656, 1716
7b	29.2	48.8	127.4, 127.8, 128.5, 136.9	105.8	142.5	148.3	150.6	154.6	25.0, 25.9, 28.2, 52.5	1648, 1695
8a	29.7			106.7	140.7	148.4	151.1	154.3	127.9, 128.7 129.2, 136.4	1674, 1729
8b	29.5			106.4	140.5	147.8	150.9	154.6	25.0, 26.0, 28.3, 52.8	1641, 1704

the more bulky group appears at N-3.[11] The scope of this application has not yet been explored in detail.

In summary, the method described here is useful for the introduction of primary and secondary alkyl, aryl, and amino groups at N-1 of the xanthine ring. In addition, extension of this method may provide access to some 1,3-disubstituted xanthines which are not otherwise readily available.

Mps were determined on a Laboratory Devices Mel-Temp apparatus and are uncorrected. Proton and carbon NMR spectra were recorded in DMSO-d_6 on a Varian VXR-300 spectrometer. Chemical shifts are reported in ppm downfield from TMS. Microanalyses were performed by Desert Analytics, Tucson, Arizona. Compound **1**, **2a–e**, **3a–d**, **4a, b**, **5**, **6**, **7a, b** and **8a, b** gave C,H,N analysis $\pm$ 0.27%; except **3b**, C + 0.38%.

Ethyl 4-Amino-1-benzylimidazole-5-carboxylate (1):
Cyanamide (40.0 g, 0.95 mol) was dissolved in triethyl orthoformate (300 mL) and the solution was heated under reflux for 2 h before removing EtOH by distillation. Fractional distillation of the residue gave ethyl *N*-cyanoimidate (81.9 g, 88%), bp 55–57 °C/5 mmHg. To a solution of this imidate (25.0 g, 0.25 mol) in Et_2O (25 mL) was slowly added *N*-benzylglycine ethyl ester (50.0 g, 0.26 mol). The solution was stirred at r.t. for 1 h, the Et_2O was evaporated in vacuo, and the residue was added to a solution of sodium ethoxide (0.27 mol) in EtOH (175 mL). The mixture was stirred for 0.5 h at r.t. then cooled in an ice-bath. The precipitate was collected by filtration, washed with cold aq EtOH, and dried to yield **1** 42.7 g (67.2%). Recrystallization from EtOH gave an analytical sample, mp 110–112 °C.

^1H NMR: δ = 1.25 (t, 3H, CH_3), 4.10 (q, 2H, OCH_2), 5.31 (s, 2H, NCH_2), 5.70 (s, 2H, NH_2), 7.08–7.33 (m, 5H, Ph), 7.70 (s, 1H, H-2).

Ethyl *N*-(1-Benzyl-5-ethoxycarbonylimidazol-4-yl)carbamate (5):
To a solution of ethyl carboxylate **1** (2.1 g, 8.5 mmol) in CH_2Cl_2 (50 mL) was added ethyl chloroformate (1.0 mL, 11 mmol) and 0.5 M aq NaOH (50 mL). After stirring the mixture for 3 h at r.t., more ethyl chloroformate (1.0 mL, 11 mmol) was added. After 3 h the organic layer was separated and concentrated, the residue was dissolved in EtOH (50 mL), and aq NH_3 (5 mL) was added. After 2 h the solution was concentrated in vacuo, and the residue was subjected to flash chromatography (silica; $CHCl_3$). The major product (2.2 g, 82%) was recrystallized from Et_2O, mp 108–110 °C.

^1H NMR: 1.13 (t, 3H, CH_3), 1.17 (t, 3H, CH_3), 4.03 (q, 2H, OCH_2), 4.09 (q, 2H, OCH_2), 5.45 (s, 2H, NCH_2), 7.10–7.35 (m, 5H, Ph), 7.98 (s, 1H, H-2), 9.05 (s, 1H, NH).

General Procedures for the Preparation of Ureas 2:

Method A:

The appropriate isocyanate (11 mmol) was added to a suspension of ethyl carboxylate **1** (2.4 g, 10 mmol) in xylene (75 mL) and the mixture was heated under reflux for 18 h. More isocyanate (11 mmol) was added, and heating was continued for a further 24 h. After evaporating the solvent in vacuo, the residue was purified by flash chromatography (silica; 1–5% EtOH in $CHCl_3$) to yield ureas **2a–c** (Table 1).

Method B:

The appropriate amine (10 mmol) was added to a solution of the carbamate **5** (2 mmol) in xylene (20 mL). The solution was heated under reflux for 18 h then concentrated. The residue was purified by flash chromatography (silica; 1:1, EtOAc–cyclohexane) to yield ureas **2d, e** (Table 1).

Xanthines; General Procedures:

Method C:

The appropriate urea **2** (6 mmol) was added to a solution of sodium ethoxide (12 mmol) in EtOH (90 mL) and the solution was heated under reflux for 3 h. The EtOH was evaporated in vacuo, the residue was dissolved in water (200 mL), and the solution was acidified with 10% aq HCl. The precipitate was collected by filtration, washed with water, and recrystallized to yield xanthines **3a–d** (Table 2).

Method D:

The xanthine **4** was dissolved in DMF (10 mL per mmol), and K_2CO_3 (1 g per mmol) was added. After stirring at r.t. for 0.5 h, iodomethane (1.1 mmol per mmol) was added and stirring was

continued for 0.5 h. The mixture was partitioned between water and CH_2Cl_2, and the organic phase was washed with water, dried ($MgSO_4$), and concentrated. The residue was crystallized to yield xanthines **7a, b** (Table 2).

Method E:

To a solution of the appropriate 7-benzylxanthine in glacial AcOH was added 20% palladium hydroxide on carbon (0.4 g per mmol), and the mixture was shaken under hydrogen (40 psi) for 24 h. The catalyst was removed by filtration, the filtrate was concentrated in vacuo, and the residue was crystallized to yield xanthines **4a, b** and **8a, b** (Table 2).

1-Amino-7-benzylxanthine (6):

To a solution of the carbamate **5** (0.5 g, 1.6 mmol) in toluene (20 mL) was added anhydr. hydrazine (4 mL). The mixture was heated under reflux for 2 h, then cooled and concentrated. The crystalline product (0.3 g, 77%) was separated by filtration and recrystallized from EtOH, mp 236–238 °C.

^{1}H NMR: δ = 5.25 (s, 2H, NH_2), 5.45 (s, 2H, CH_2), 7.25–7.35 (m, 5H, Ph), 8.20 (s, 1H, H-8), 12.1 (br, 1H, H-3).

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