Synthesis of Series of 1- and 3-Differently Substituted Xanthines from Imidazoles

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A new and general method is described for the synthesis, in three steps and in good overall yields, of tetrasubstituted xanthines from an easily prepared imidazole precursor. The method is especially useful for the preparation in standardized conditions of series of xanthines combining a broad variety of primary or secondary alkyl, benzyl or aryl groups at *N*1 and of alkyl or arylmethyl groups at *N*3, that are not readily available by other methods.

Key words imidazole; xanthine; series; reductive amination; substituents combination

Xanthine derivatives play an important role in several biological processes, including the inhibition of both calcium-independent and calcium-dependent phosphodiesterases,[1,2] and the antagonism of adenosine receptors (ARs).[3,4] Since the characterization and cloning of the different subtypes of ARs,[5—7] a large number of compounds with the xanthine framework have been synthesized in search of improved activity and selectivity.[8—10]

In connection with a search for novel antagonists of A_{2B} receptors, it was required a method for the preparation of some series of tetrasubstituted xanthines, each with a fixed set of substituents at *N*7 and *C*8 and a broad variety of substituents at *N*1 and *N*3. Though appropiated methods for the preparation of tri- and tetrasubstituted xanthines are known,[11,12] they have in common that start from a mono- or disubstituted aminopyrimidine precursor, so substitutents at *N*1 and/or *N*3 of the final xanthine have to be introduced in the early steps of the synthesis. This means the synthesis has to be repeated almost from the very beginning for each combination of substitutents at *N*1 and *N*3, making the procedure poorly attractive for the mentioned purpose.

Our attention was turned at this point to a strategy, seldom used and thus not well investigated, that has been reported to produce very simple 1-monosubstituted xanthines in varying yields.[13—16] We have now developed the procedure described herein that, starting from an aminoimidazole precursor, affords differently tetrasubstituted xanthines, having a methyl group (for example) at *N*7, a benzyl group at *C*8, a primary alkyl group at *N*3 and an alkyl or aryl group at *N*1, and thus substantially widening the scope of the partially similar procedure of Bridson[16] for the preparation of 1-monosubstituted xantines.

Ethyl 4-amino-2-benzyl-1-methylimidazole-5-carboxylate (**1**),[13] a precursor that can readily be prepared on a large scale, was easily converted into secondary amines **2a—d** at room temperature by one-pot reductive amination: treatment of **1** with two equivalents of the appropriate aldehyde, AcOH and $NaBH_3CN$ in methanol afforded yields ≥80% with simple aliphatic and aromatic aldehydes, and a 67% yield of **2d** when applied to the sterically hindered pivalaldehyde (Chart 1).

Reaction of compounds **2a—c** with one equivalent of an alkyl isocyanate in the presence of one equivalent of triethylamine in refluxing dry toluene led to the corresponding alkylureas, **3a—g**, in good-to-excellent yields; the reaction was completed within 72 h, and only traces of *N*,*N*′-dialkyureas were observed when the crude reaction products were examined by thin layer chromatography. Compound **2d** (Chart 1), however, failed to react even at high temperatures and pressures and in the presence of a large excess of the isocyanate. Treatment of ureas **3a—g** with KOH in refluxing ethanol resulted in ring closure, giving high post-isolation yields of 3-substituted 1-alkylxanthines **4a—g** (Chart 2).

When in an attempt to extend this method to the synthesis of 1-arylxanthines compounds **2a—c** (Chart 1) were treated

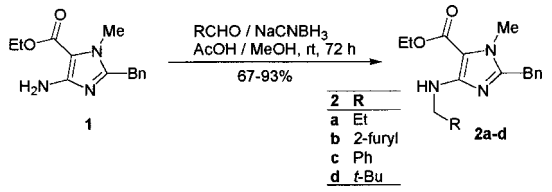

Chart 1

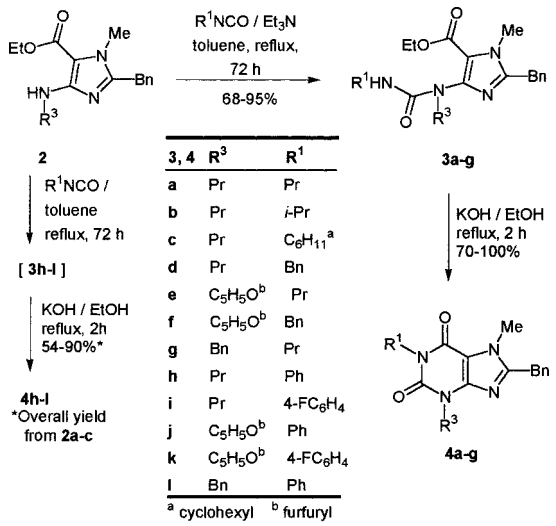

Chart 2

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Table 1. Yields, Physical, IR, ^{1}H-NMR and MS Data for Amines **2a—d**

Compound	Yield (%)	mp (°C)	IR (film) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$) δ (mult., n^a, J)	MS (70 eV) *m/z* (%)
2a	90	Oil	3392 (NH), 1654 (C=O)	0.98 (t, 3H, 7.3), 1.33 (t, 3H, 7.1), 1.33 (sex, 2H, 7.3), 3.41 (q, 2H, 6.6), 3.55 (s, 3H), 4.05 (s, 2H), 4.27 (q, 2H, 7.1), 5.59 (s, 1H), 7.13—7.34 (m, 5H)	301 (M^+, 27), 226 (100)
2b	80	Oil	3375 (NH), 1651 (C=O)	1.32 (t, 3H, 7.1), 3.58 (s, 3H), 4.06 (s, 2H), 4.27 (q, 2H, 7.1), 4.65 (d, 2H, 6.6), 5.81 (s, 1H), 6.24 (d, 1H, 3.0), 6.31 (dd, 1H, 1.8, 3.0), 7.29 (d, 1H, 1.8),7.19—7.35 (m, 5H)	339 (M^+, 100)
2c	93	Oil	3390 (NH), 1653 (C=O)	1.32 (t, 3H, 7.1), 3.58 (s, 3H), 4.05 (s, 2H), 4.68 (q, 2H, 7.1), 4.68 (d, 2H, 8.0), 5.88 (s, 1H),7.13—7.42 (m, 10H)	349 (M^+, 100)
2d	67	Oil	3386 (NH), 1651 (C=O)	1.06 (s, 9H), 1.34 (t, 3H, 7.1), 3.27 (d, 2H, 6.1), 3.56 (s, 3H), 4.05 (s, 2H), 4.28 (q, 2H, 7.1), 5.75 (s, 1H), 7.12—7.42 (m, 5H)	329 (M^+, 15), 226 (100)

a) *n*, number of protons.

Table 2. Yields, Physical, IR, ^{1}H-NMR and MS Data for Alkylureas **3a—g**

Compound	Yield (%)	mp (°C)	IR (KBr) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$) δ (mult., $n^{a)}$, J)	MS (70 eV) *m/z* (%)
3a	95	117—120	3324 (NH), 1701 (C=O), 1640 (C=O)	0.84 (t, 3H, 7.5), 0.89 (t, 3H, 7.3), 1.17 (t, 3H, 7.1), 1.33 (sex, 2H, 7.3), 1.56 (sex, 2H, 7.5), 3.14 (q, 2H, 6.6), 3.64 (t, 3H, 7.5), 3.74 (s, 3H), 4.14 (s, 2H), 4.28 (q, 2H, 7.1), 4.70 (s, 1H), 7.15—7.35 (m, 5H)	386 (M^+, 34), 272 (100)
3b	68	127—130	3322 (NH), 1705 (C=O), 1636 (C=O)	0.88 (t, 3H, 7.5), 1.06 (d, 3H, 6.5), 1.14 (d, 3H, 6.5), 1.32 (t, 3H, 7.1), 1.57 (sex, 2H, 7.5), 3.61 (t, 2H, 7.5), 3.74 (s, 3H), 3.93 (quint, 1H, 6.5), 4.14 (s, 2H), 4.27 (q, 2H, 7.1), 4.46 (s, 1H), 7.15—7.34 (m, 5H)	386 (M^+, 34), 272 (100)
3c	58	126—129	3321 (NH), 1706 (C=O), 1635 (C=O)	0.87 (t, 3H, 7.5), 0.96—1.24 (m, 4H), 1.31 (t, 3H, 7.1), 1.36—1.62 (m, 2H), 1.57 (sex, 2H, 7.5), 1.67—1.94 (m, 4H), 3.49—3.55 (m, 1H), 3.61 (t, 2H, 7.5), 3.73 (s, 3H), 4.13 (s, 2H), 4.26 (q, 2H, 7.1), 4.53 (s, 1H), 7.14—7.33 (m, 5H)	426 (M^+, 23), 272 (100)
3d	91	135—138	3319 (NH), 1700 (C=O), 1643 (C=O)	0.90 (t, 3H, 7.5), 1.29 (t, 3H, 7.1), 1.58 (sex, 2H, 7.5), 3.66 (t, 2H, 7.5), 3.70 (s, 3H), 4.10 (s, 2H), 4.24 (q, 2H, 7.1), 4.39 (d, 2H, 5.6), 4.98 (t, 1H, 5.6), 7.09—7.30 (m, 10H)	434 (M^+, 39), 272 (100)
3e	90	112—114	3324 (NH), 1708 (C=O), 1642 (C=O)	0.84 (t, 3H, 7.4), 1.28 (t, 3H, 7.1), 1.45 (sex, 2H, 6.9), 3.15 (q, 2H, 6.8), 3.69 (s, 3H), 4.10 (s, 2H), 4.20 (q, 2H, 7.1), 4.86 (s, 1H), 4.89 (s, 2H), 6.19 (d, 1H, 3.2), 6.23 (dd, 1H, 1.6, 3.2), 7.11 (d, 1H, 1.6), 7.21—7.31 (m, 5H)	424 (M^+, 14), 81 (100)
3f	68	136—138	3340 (NH), 1706 (C=O), 1640 (C=O)	1.26 (t, 3H, 7.1), 3.66 (s, 3H), 4.07 (s, 2H), 4.18 (q, 2H, 7.1), 4.42 (d, 2H, 5.5), 4.93 (s, 2H), 5.15 (d, 1H, 5.3), 6.20 (d, 1H, 3.0), 6.23 (dd, 1H, 1.8, 3.0), 7.05 (d, 1H, 1.8), 7.22—7.31 (m, 10H)	472 (M^+, 28), 292 (100)
3g	80	87—88	3331 (NH), 1704 (C=O), 1640 (C=O)	0.83 (t, 3H, 7.4), 1.13 (t, 3H, 7.1), 1.47 (sex, 2H, 7.2), 3.16 (t, 2H, 7.1), 3.64 (s, 3H), 4.07 (s, 2H), 4.19 (q, 2H, 7.1), 4.60 (s, 1H), 4.91 (s, 2H), 7.00—7.31 (m, 10H).	434 (M^+, 8), 91 (100)

a) *n*, number of protons.

with one equivalent of an aryl isocyanate and triethylamine under reaction conditions similar to those specified above, *N*,*N*′-diarylureas were isolated as the major products, and only traces of the desired arylureas **3h—l** were detected. However, **3h—l** were successfully obtained by reacting amines **2** with one equivalent of the appropriate aryl isocyanate in refluxing dry toluene without any triethylamine. Flash column chromatography of the crude product gave arylureas **3h—l** that were not entirely free from *N*,*N*′-diarylureas, and treatment of these mixtures with KOH in refluxing ethanol then gave xanthines **4h—l** in fair overall yields (54—90%) from amines **2** (Chart 2).

The structures of the new compounds were elucidated by their IR, ^{1}H-, ^{13}C-NMR and electron impact-mass spectra (EI-MS) data, which are summarized in Tables 1—6.

In conclusion, an efficient and general synthetic procedure affording tetrasubstituted xanthines in good overall yields has been developed. It is especially appropriate for the synthesis under standardized conditions of series of xanthines combining a broad variety of primary or secondary alkyl, benzyl or aryl groups at *N*1 and of alkyl or arylmethyl groups at *N*3, that are not readily available by other methods.

Experimental

Melting points were determined on a Reichert Kofler thermopan and are uncorrected. The IR spectra of samples prepared in KBr discs (solids) or as films between NaCl plates (oils) were recorded on a Perkin Elmer FTIR 1640 spectrometer. ^{1}H- and ^{13}C-NMR spectra were recorded in a Bruker AMX-300 spectrometer at 300 and 75 MHz, respectively, with tetramethylsilane (TMS) as internal standard. Mass spectra were recorded on a Kratos MS-59 spectrometer. Silica gel (400 mesh) for flash chromatography (FC)

Table 3. Yields, Physical, IR, ^{1}H-NMR and MS Data for 1,3-Disubstituted Xanthines **4a—l**

Compound	Yield (%)	mp (°C)	IR (KBr) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$)[a] δ (mult., n[b]), J)	MS (70 eV) *m/z* (%)
4a	100	103—106	1701 (C=O), 1654 (C=O)	0.95 (t, 3H, 7.5), 0.98 (t, 3H, 7.4), 1.67 (sex, 2H, 7.5), 1.81 (sex, 2H, 7.4), 3.79 (s, 3H), 3.95 (t, 2H, 7.5), 4.08 (t, 2H, 7.4), 4.15 (s, 2H), 7.16—7.34 (m, 5H)	298 (M^+, 100)
4b	85	>240	1699 (C=O), 1652 (C=O)	0.90 (t, 3H, 7.1), 1.54 (sex, 2H, 6.9), 1.90 (d, 6H, 6.6), 3.78 (s, 3H), 3.81—3.95 (m, 1H), 3.89 (t, 2H, 7.1), 4.18 (s, 2H), 7.22—7.34 (m, 5H)	340 (M^+, 100)
4c	70	212—213	1699 (C=O), 1636 (C=O)	0.90 (t, 3H, 7.4), 0.95—1.24 (m, 4H), 1.31—1.43 (m, 2H), 1.55 (sex, 2H, 7.4), 1.61—1.85 (m, 4H), 3.50—3.55 (m, 1H), 3.64 (t, 2H, 7.4), 3.78 (s, 3H), 4.19 (s, 2H), 7.21—7.49 (m, 5H)	380 (M^+, 6), 56 (100)
4d	64	82—85	1699 (C=O), 1652 (C=O)	0.98 (t, 3H, 7.4), 1.81 (sex, 2H, 7.4), 3.78 (s, 3H), 4.08 (t, 2H, 7.4), 4.15 (s, 2H), 5.18 (s, 2H), 7.15—7.49 (m, 10H)	388 (M^+, 100)
4e	100	93—95	1695 (C=O), 1658 (C=O)	0.93 (t, 3H, 7.5), 1.65 (sex, 2H, 7.5), 3.79 (s, 3H), 3.94 (t, 2H, 7.5), 4.17 (s, 2H), 5.29 (s, 2H), 6.30 (dd, 1H, 1.9, 3.1), 6.42 (d, 1H, 3.1), 7.18—7.34 (m, 6H)	378 (M^+, 56), 81 (100)
4f	97	126—128	1700 (C=O), 1654 (C=O)	3.78 (s, 3H), 4.17 (s, 2H), 5.17 (s, 2H), 5.29 (s, 2H), 6.30 (dd, 1H, 1.9, 3.1), 6.41 (d, 1H, 3.1), 7.17—7.48 (m, 11H)	426 (M^+, 18), 81 (100)
4g	100	>330	1699 (C=O), 1651 (C=O)	0.93 (t, 3H, 7.5), 1.65 (sex, 2H, 7.5), 3.80 (s, 3H), 3.93 (t, 4H, 7,5), 4.15 (s, 2H), 5.28 (s, 2H), 7.18—7.54 (m, 10H)	388 (M^+, 67), 91 (100)
4h	90[c]	154—156	1713 (C=O), 1654 (C=O)	1.00 (t, 3H, 7.4), 1.86 (sex, 2H, 7.4), 3.78 (s, 3H), 4.12 (t, 2H, 7.4), 4.19 (s, 2H), 7.10—7.51 (m, 10H)	374 (M^+, 100)
4i	85[c]	205—208	1709 (C=O), 1654 (C=O)	1.00 (t, 3H, 7.4), 1.85 (sex, 2H, 7.4), 3.78 (s, 3H), 4.11 (t, 2H, 7.4), 4.19 (s, 2H), 7.05—7.36 (m, 9H)	392 (M^+, 23), 111 (100)
4j	54[d]	214—216	1713 (C=O), 1664 (C=O)	3.78 (s, 3H), 4.21 (s, 2H), 5.33 (s, 2H), 6.32 (dd, 1H, 1.9, 3.2), 6.45 (d, 1H, 3.2), 7.21—7.50 (m, 11H)	412 (M^+, 100)
4k	76[d]	205—207	1715 (C=O), 1662 (C=O)	3.78 (s, 3H), 4.21 (s, 2H), 5.32 (s, 2H), 6.32 (dd, 1H, 1.7, 3.1), 6.44 (d, 1H, 3.1), 7.02—7.40 (m, 10H)	430 (M^+, 45), 81 (100)
4l	88[e]	170—173	1708 (C=O), 1659 (C=O)	3.79 (s, 3H), 4.20 (s, 2H), 5.31 (s, 2H), 7.20—7.62 (m, 15H)	422 (M^+, 100)

a) ^{1}H-NMR data for compounds **4b** and **4c** were obtained using CD_3OD as solvent. *b*) *n*, number of protons. *c*) Overall yield from **2a**. *d*) Overall yield from **2b**. *e*) Overall yield from **2c**.

Table 4. ^{13}C-NMR Shift Values for Amines **2a—d** ($CDCl_3$)

Compound	EtOCO	N–Me	CH_2Ph	C-5	C-2	C-4	CH_2R
2a	15.0, 59.6, 161.8	33.1	34.1, 127.1, 128.5, 129.1, 136.1	102.0	149.6	157.0	11.8, 23.8, 44.9
2b	15.0, 59.8, 167.1	33.1	34.1, 127.2, 128.6, 129.1, 136.6	102.7	149.2	153.8	40.4, 106.9, 110.6, 142.2, 161.7
2c	15.0, 59.7, 161.8	33.1	34.0, 127.2, 128.6, 129.1, 136.6	102.3	149.6	156.6	47.2, 127.4, 128.8, 129.3, 140.6
2d	15.5, 59.7, 162.1	33.1	34.0, 127.2, 128.5, 129.1, 136.5	101.7	149.4	153.2	27.6, 35.8, 54.7

Table 5. ^{13}C-NMR Shift Values for Alkylureas **3a—g** ($CDCl_3$)

Compound	EtOCO	N–Me	CH_2Ph	C-5	C-4	C-2	R^3	R^1NHCO
3a	14.6, 61.1, 160.3	33.5	34.1, 127.5, 128.6, 129.4, 136.0	117.4	145.7	149.7	11.8, 22.4, 51.1	11.8, 23.7, 42.8, 157.1
3b	14.6, 61.2, 160.3	33.4	34.2, 127.5, 128.6, 129.4, 136.1	117.4	145.5	149.6	11.8, 22.6, 51.1	23.7, 23.9, 42.7, 155.0
3c	14.7, 61.2, 160.3	33.4	34.1, 127.5, 128.6, 129.3, 136.1	117.0	145.8	149.6	11.8, 22.5, 51.1	25.3, 25.4, 26.1, 34.2, 34.4, 51.1, 156.4
3d	14.6, 61.2, 160.2	33.4	34.2, 127.5, 128.6, 129.4, 135.9	117.3	145.3	149.7	11.8, 22.4, 51.3	45.1, 127.4, 127.9, 128.8, 140.1, 157.1
3e	14.6, 61.2, 160.1	33.4	34.1, 127.5, 128.6, 129.3, 136.0	117.6	144.6	149.6	45.2, 108.7, 110.6, 142.2, 152.5	11.7, 23.7, 42.9, 156.8
3f	14.5, 61.3, 160.7	33.4	34.1, 127.5, 128.6, 129.3, 135.9	117.4	145.1	149.7	45.2, 108.8, 110.6, 142.3, 152.3	45.2, 127.4, 128.0, 128.8, 139.8, 157.3
3g	14.6, 61.2, 169.3	33.4	34.1, 127.5, 128.9, 129.3, 135.9	117.3	145.3	149.6	52.6, 127.3, 128.4, 128.5, 138.8	11.8, 23.7, 43.0, 157.2

Table 6. ^{13}C-NMR Shift Values for 1,3-Disubstituted Xanthines **4a—l** ($CDCl_3$)[a)]

Compound	N–Me	CH_2Ph	C-5	C-4	C-8	C-2	C-6	R^3	R^1
4a	32.3	33.8, 127.6, 128.6, 129.4, 135.5	108.2	148.1	151.5	152.4	155.7	11.6, 21.8, 45.2	11.8, 21.7, 43.2
4b	33.2	33.9, 129.2, 129.7, 129.8, 137.5	108.9	148.4	148.7	159.2	159.8	11.8, 22.9, 49.8	23.3, 23.6, 43.64
4c	33.4	33.9, 127.8, 129.3, 129.8, 137.6	108.2	148.7	148.9	158.2	159.2	11.7, 22.4, 49.8	25.8, 26.7, 27.1, 34.2, 34.3
4d	32.4	33.9, 127.6, 128.6, 129.4, 135.5	108.3	148.3	151.7	152.7	155.6	11.6, 21.8, 45.4	44.7, 127.8, 128.8, 129.2, 138.0
4e	32.4	33.9, 127.6, 128.7, 129.3, 135.5	108.3	147.7	151.3	152.5	155.6	39.7, 109.7, 110.8, 142.7, 150.3	11.7, 21.7, 13.3
4f	32.4	33.9, 127.7, 128.7, 129.3, 135.4	108.3	147.8	151.5	152.8	155.5	39.8, 109.7, 110.8, 142.7, 150.1	44.8, 127.8, 128.7, 129.4, 137.8
4g	32.3	33.8, 127.6, 128.7, 129.3, 135.6	108.6	148.2	151.6	152.5	155.6	46.8, 128.1, 128.8, 129.3, 137.1	11.7, 21.7, 43.3
4h	32.4	33.9, 127.7, 128.7, 129.4, 135.4	108.3	150.1	151.8	153.1	155.7	11.6, 21.8, 45.5	128.9, 129.1, 129.7, 136.0
4i	32.4	33.9, 127.7, 128.7, 129.4, 135.4	107.8	148.9	151.7	153.2	155.7	11.6, 21.8, 45.6	116.7 (d, J=22 Hz), 130.9 (d, J=9 Hz)
4j	32.4	33.9, 127.7, 128.7, 129.4, 135.5	108.5	148.4	151.4	153.1	155.6	39.9, 110.2, 110.9, 142.7, 150.0	128.9, 129.2, 129.7, 135.8
4k	32.4	33.9, 127.7, 128.7, 129.4, 135.4	108.4	148.4	151.3	153.3	155.6	39.9, 110.2, 110.9, 142.8, 149.9	116.7 (d, J=23 Hz), 130.9 (d, J=8 Hz)
4l	32.4	33.9, 127.7, 128.8, 129.4, 135.5	108.7	148.6	151.6	153.0	155.4	47.7, 128.2, 128.8, 129.2, 137.0	129.0, 129.1, 129.8, 135.9

a) ^{13}C-NMR data for compounds **4b** and **4c** were obtained using CD_3OD as solvent.

was from Merck. Reagents and solvents were of commercial grade (Aldrich Chemical Co.).

General Procedure for the Preparation of Amines 2a—d The appropriate aldehyde (2 mmol) was added to a solution of imidazole **1** (1 mmol) and AcOH (0.15 ml, 2 mmol) in dry MeOH (10 ml), and this mixture was stirred for 1 h at room temperature. $NaCNBH_3$ was added and stirring was continued for a further 24 h. After evaporation of the solvent *in vacuo*, the residue was purified by flash column chromatography (10—40% EtOAc in hexane), affording the desired amine **2**.

General Procedure for the Preparation of Alkylureas 3a—g A mixture of the corresponding amine **2** (1 mmol), Et_3N (0.14 ml, 1 mmol) and the appropriate isocyanate (1 mmol) in dry toluene (10 ml) was heated under reflux for 18 h. More isocyanate (1 mmol) was then added, and heating was continued for a further 48 h. After evaporation of the solvent *in vacuo*, the residue was purified by flash column chromatography (30—60% EtOAc in hexane), affording the desired alkylurea **3**.

General Procedure for the Preparation of 3-Substituted 1-Alkylxanthines 4a—g 1N KOH (2 ml) was added to a solution of the corresponding alkylurea **3** (1 mmol) in EtOH (5 ml), and the mixture was heated under reflux for 2 h and then neutralized with 0.5N HCl. The solvent was evaporated *in vacuo*, and the residue was purified by flash column chromatography (0—10% hexane in EtOAc), yielding the desired xanthine **4a—g**.

General Procedure for the Preparation of 3-Substituted 1-Arylxanthines 4h—l A mixture of the corresponding amine **2** (1 mmol) and the appropriate aryl isocyanate (1 mmol) in dry toluene (10 ml) was heated under reflux for 72 h. After evaporation of the solvent *in vacuo*, the residue was purified by flash column chromatography (10% EtOAc in hexane), affording an arylurea **3** mixed with traces of an *N*,*N'*-diarylurea. This mixture was dissolved in EtOH (5 ml), and after addition of 1N KOH (2 ml) was heated under reflux for 2 h and neutralized with 0.5N HCl. The solvent was evaporated *in vacuo*, and the residue was purified by flash column chromatography (10—30% EtOAc in hexane), giving the desired xanthine **4h—l**.

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