The Preparation of 8-(Arylsulfanyl)adenines with Diazonium Salts under Mild, Aerobic Conditions

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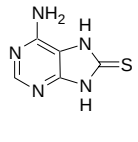
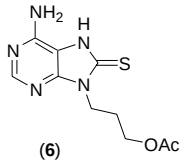
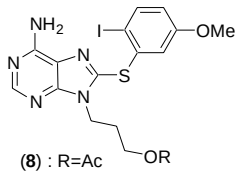
Supporting Information



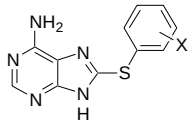
(**3**)



(**6**)



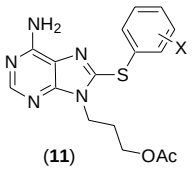
(**8**) : R=Ac
(**9**): R =H



(**5**)

Table 1: Substituent on **5**

Entry	X =
1	4-NO2
2	4-F
3	3-MeO
4	4-Me



(**11**)

Table 4: Substituent on **11**

Entry	X =
1	4-Br
2	4-NO2
3	4-F
4	4-CO2Et
5	5-MeO-2-I
6	2,4-di-F
7	4-MeO
8	4-Me
9	H
10	3-MeO

MATERIALS AND METHODS

The final compounds were purified by preparative TLC (silica gel 60 Å; EtOAc/hexane or MeOH/CH_2Cl_2), flash chromatography (silica gel 60 Å, EtOAc/hexane or MeOH/CH_2Cl_2). The ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a 400 MHz spectrometer. Analytical HPLC chromatograms were obtained using a C18 column (5 microns; 4.6 mm x 150 mm). A gradient was applied between solvent A (0.1% TFA in H_2O) and solvent B (0.5% TFA in CH_3CN) increasing the proportion of A linearly from 5% (t=0) to 100% (t=7.00 min), with a constant flow rate of 1 mL/min. The samples were diluted to typically 0.1 mg/mL in MeOH and the injection volumes were typically 10 µl. The column was not heated, and UV detection was effected at 254 nm.

GENERAL PROCEDURE FOR THE PREPARATION OF DIAZONIUM TETRAFLUOROBORATES

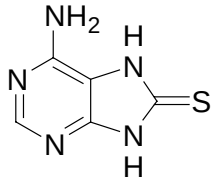
The 4-nitro- and 4-bromo-benzenediazonium tetrafluoroborate were purchased. The 2-iodo-5-methoxy-benzenediazonium tetrafluoroborate was prepared according to the published procedure.[1] The other diazonium salts were prepared as follows:

A mixture of the aniline (20 mmol) and water (10–25 mL) was treated with conc. HCl (10 mL), whereupon the aniline either dissolved or turned into a slurry. The mixture was cooled to –10 – 0 ºC (external acetone bath at –20 ºC, cooled occasionally with dry ice) and treated dropwise with $NaNO_2$ 5M (4 mL), maintaining the internal temperature under 5 ºC. After 10 min, aq. HBF_4 48% (5 mL) was added. The diazonium tetrafluoroborate precipitated or crystallized out of solution, and was isolated by filtration, dissolved in a minimum volume of acetone, precipitated with diethyl ether, and filtered. The

dissolution/precipitation/filtration was repeated, the salt was air-dried on the filter, and used without further purification.

PROCEDURES AND CHARACTERIZATION FOR COMPOUNDS 3, 6, 8, AND 9

6-Amino-7,9-dihydro-purine-8-thione (3)



This compounds was prepared by a modification of the published procedure.[2] A mixture of 4,5,6-triaminopyrimidine sulfate (50 g, 223 mmol), NaOH (19.7 g, 493 mmol) and water (500 mL) was heated to 80 ºC until all the solids dissolved. The solution was cooled to 0–5 ºC and the pH was adjusted to 7.0 with HCl 1N, whereupon the free base crystallized as white needles (19.8 g, 71%).

4,5,6-triaminopyrimidine (50 g, 400 mmol) and thiourea (106 g, 1.39 mol, 3.5 equiv.) were finely ground together in a mortar and transferred to a round-bottom flask. The flask was immersed in a pre-heated oil bath (T_{bath} = 180 ºC), with magnetic stirring. The internal temperature gradually rose to 145 ºC, with gas evolution, whereupon the mixture became a fluid melt. Upon reaching 160 ºC, the mixture solidified. It was kept at that temperature for 1 h. While the material was still warm, water (800 mL) was added, and the material was triturated and stirred overnight, filtered. The fine powder was rinsed with additional water (800 mL) and acetone (400 mL). Drying gave the pure thione **3** as a pale brown powder (50 g, 75%).

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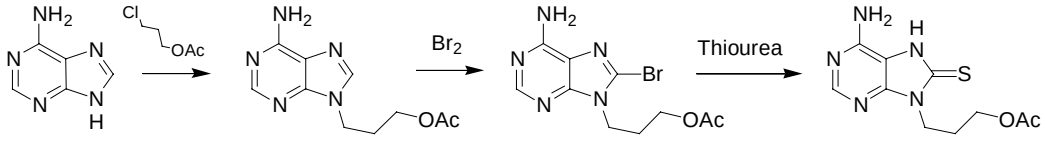
[1] (a) Ma, C.; Liu, X.; Li, X.; Flippen-Anderson, J.; Yu, S.; Cook, J. M. *J. Org. Chem.;* **2001**, *66*, 4525 (b) Flynn, B. L.; Verdier-Pinard, P.; Hamel, E. *Org. Lett.;* **2001**, *3*, 651-654.

[2] Robins, R. K. *J. Am. Chem. Soc.* **1958**, *80*, 6671.

t_R = 1.99 min. ^{1}H-NMR (DMSO-d_6) δ 13.04 (s, 1H), 12.05 (s, 1H), 8.07 (s, 1H), 6.75 (s, 2H). ^{13}C-NMR (DMSO-d_6) δ 167.0, 153.1, 150.33, 147.8, 108.5.

Acetic acid 3-(6-amino-8-thioxo-7,8-dihydro-purin-9-yl)-propyl ester (6)



Acetic acid 3-(6-amino-8-bromo-purin-9-yl)-propyl ester

A mixture of adenine (200 g, 1.48 mol), Cs_2CO_3 (721 g, 2.22 mol, 1.5 equiv.), AcO-$(CH_2)_3$-Cl (273 mL, 2.22 mol, 1.5 equiv.) and DMF (2.0 L) was stirred at 70 ºC for 12 h, at which point the reaction was complete as judged by anal. HPLC of both the supernatant and the solid residues. The DMF was evaporated *in vacuo* and the residue was added to a mixture of AcOH (120 mL, 2.22 mol, 1.5 equiv.) water (300 mL) and ice (100 g). The solid was filtered, washed with 100 mL ice-cold water, and dried under high vacuum on a rotary evaporator to give 307 g (yield 88.0%, HPLC purity: 88.2%) of acetic acid 3-(6-amino-purin-9-yl)-propyl ester as a white powder, still containing cesium salts.

The 9-alkyl adenine (307 g, "1.3 mol") was dissolved in a mixture of AcOH buffer[3] (1.8 L), MeOH (200 mL), and CH_2Cl_2 (500 mL). Bromine (95 mL, 1.84 mol, 1.4 equiv.) was added over 10 min, and the purple reaction mixture was stirred for 1h. Additional DCM (500 mL) was added, and the reaction was quenched with sat. aq. $Na_2S_2O_3$ until the reaction turned from purple to yellow, controlling that the pH remained at approximately 5. The organic layer was washed with brine (200 mL), and concentrated to about 200 mL. The slurry was filtered, and washed with cold CH_2Cl_2 (2 x 30 mL) to give the title compound as a pale yellow powder (123 g, 30 % over 2 steps).

[3] The acetic acid buffer was made with AcONa (262 g, 3.2 mol), AcOH (192 mL, 3.2 mol) and H_2O (1.6 L).

t_R = 3.91 min. ^{1}H-NMR (DMSO-d_6) δ 8.14 (s, 1H), 7.50–7.40 (s, 2H), 4.22 (t, J = 6.7 Hz, 2H), 3.98 (t, J = 6.0 Hz, 2H), 2.09 (quint, J = 6.3 Hz, 2H), 1.90 (s, 3H). ^{13}C-NMR (DMSO-d_6) δ 170.6, 155.0, 153.0, 151.3, 126.9, 119.5, 61.8, 41.7, 28.1, 21.0.

Acetic acid 3-(6-amino-8-thioxo-7,8-dihydro-purin-9-yl)-propyl ester

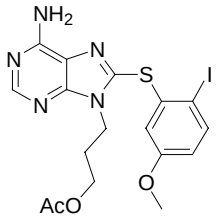
A mixture of 8-bromo-adenine (20 g, 64 mmol), thiourea (24.3 g, 320 mmol, 5 equiv.) and n-butanol (200 mL) was heated to reflux for 3h. After cooling, the reaction mixture was diluted with EtOAc (400 mL) and MeOH (100 mL), washed with brine (3 × 100 mL), and evaporated to give the title compound as a pale yellow powder (15.0 g, 88%).

Note that it is critical for the next step to remove the excess thiourea, and this is best done during the work-up by washing with brine – not water, otherwise the desired product is lost to the aqueous phase.

t_R = 4.14 min. ^{1}H-NMR (DMSO-d_6) δ 12.32 (s, 1H), 8.14 (s, 1H), 6.98–6.74 (s, 2H), 4.20 (t, J = 6.7 Hz, 2H), 3.99 (t, J = 6.1 Hz, 2H), 2.08 (quint, J = 6.4 Hz, 2H), 1.91 (s, 3H). ^{13}C-NMR (DMSO-d_6) δ 170.7, 167.0, 153.0, 149.6, 148.0, 107.3, 62.1, 40.6, 27.0, 21.0.

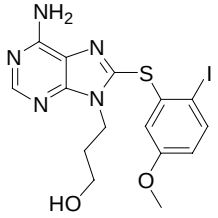
Acetic acid 3-[6-amino-8-(2-iodo-5-methoxy-phenylsulfanyl)-purin-9-yl]-propyl ester (8)

The title compound was prepared according to the general procedure described in the article.



t_R = 5.60 min. ^{1}H-NMR ($CDCl_3$) δ 8.32 (s, 1H), 7.68 (d, *J* = 8.7 Hz, 1H), 6.63 (d, *J* = 2.3 Hz, 1H), 6.63–6.54 (br. s, 2H), 6.54 (dd, *J* = 8.7 & 2.3 Hz, 1H), 4.34 (t, *J* = 7.0 Hz, 2H), 4.06 (t, *J* = 5.7 Hz, 2H), 3.63 (s, 3H), 2.13 (quint., *J* = 6.3 Hz, 2H), 2.01 (s, 3H). ^{13}C-NMR ($CDCl_3$) δ 170.8, 160.5, 155.2, 153.5, 151.5, 144.5, 140.4, 138.3, 120.4, 116.3, 115.1, 87.2, 61. 5, 55.5, 41.3, 28.6, 30.9. HRMS *m/z* calc. for $C_{17}H_{18}IN_5O_3S$ (M+1): 500.0248, found: 500.0242. Anal. calc for $C_{17}H_{17}IN_5O_3S$: C 40.59, H 3.63, N 14.03, found C 40.77, H 3.62, N 14.07.

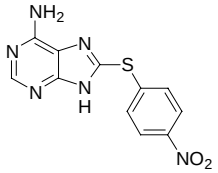
3-[6-Amino-8-(2-iodo-5-methoxy-phenylsulfanyl)-purin-9-yl]-propan-1-ol (9)



t_R = 5.04 min. ^{1}H-NMR (DMSO-d_6) δ 8.19 (s, 1H), 7.78 (d, *J* = 8.7 Hz, 1H), 7.55–7.45 (br. s, 2H), 6.70 (dd, *J* = 8.7, 2.8 Hz, 1H), 6.47 (d, *J* = 2.8 Hz, 1H), 4.62 (t, *J* = 5.1 Hz, 1H), 4.21 (t, *J* = 7.3 Hz, 2H), 3.61 (s, 3H), 3.39 (q, *J* = 6.1 Hz, 2H), 1.85 (quint., *J* = 6.3 Hz, 2H). ^{13}C-NMR (DMSO-d_6) δ 160.4, 156.0, 153.8, 151.3, 143.1, 140.8, 139.5, 120.2, 115.9, 115.2, 87.6, 58.6, 55.8, 41.6, 33.0.

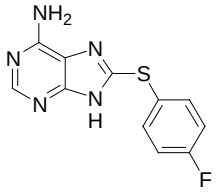
HPLC AND ^{1}H-NMR DATA FOR COMPOUNDS IN TABLE 1

8-(4-Nitro-phenylsulfanyl)-9H-purin-6-ylamine (Table 1, entry 1)



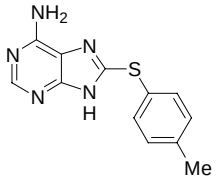
t_R = 4.29 min. ^{1}H-NMR (CD_3OD:$CDCl_3$ 1:1) δ 8.17 (d, *J* = 9.0 Hz, 2H), 8.17 (s, 1H), 7.53 (d, *J* = 9.0 Hz, 2H).

8-(4-Fluoro-phenylsulfanyl)-9H-purin-6-ylamine (Table 1, entry 2)



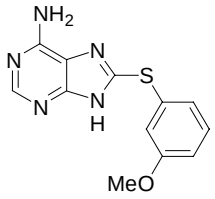
t_R = 4.27 min. ^{1}H-NMR (CD_3OD) δ 8.10 (s, 1H), 7.62–7.57 (m, 2H), 7.14 (t, *J* = 8.6 Hz, 2H).

8-p-Tolylsulfanyl-9H-purin-6-ylamine (Table 1, entry 3)



t_R = 4.65 min. ^{1}H-NMR (CD_3OD) δ 8.09 (s, 1H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.14 (d, *J* = 8.1 Hz, 2H).

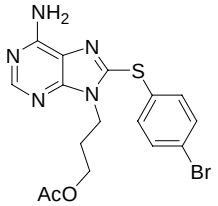
8-(3-Methoxy-phenylsulfanyl)-9H-purin-6-ylamine (Table 1, entry 4)



t_R = 4.32 min. ^{1}H-NMR (CD_3OD) δ 8.10 (s, 1H), 7.30 (t, *J* = 8.0 Hz, 1H), 7.11–7.07 (m, 1H), 6.92 (dd, *J* = 8.2, 1.9 Hz, 1H), 3.77 (s, 3H).

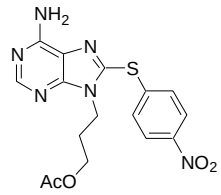
HPLC, ^{1}H -NMR AND HRMS DATA FOR COMPOUNDS IN TABLE 4

Acetic acid 3-[6-amino-8-(4-bromo-phenylsulfanyl)-purin-9-yl]-propyl ester (Table 4, entry 1)



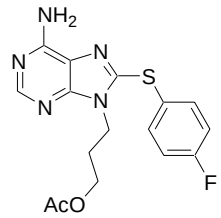
t_R = 5.63 min. ^{1}H-NMR ($CDCl_3$) δ 8.32 (s, 1H), 7.48 (d, *J* = 8.5 Hz, 2H), 7.30 (t, *J* = 8.7 Hz, 2H), 5.75 (s, 2H), 4.31 (q, *J* = 7.1 Hz, 2H), 4.07 (t, *J* = 6.0 Hz, 2H), 2.13 (quint, *J* = 6.7 Hz, 2H), 2.02 (s, 3H). HRMS *m/z* calc. for $C_{16}H_{17}BrN_5O_2S$ (M+1): 422.0281, found: 422.0273.

Acetic acid 3-[6-amino-8-(4-nitro-phenylsulfanyl)-purin-9-yl]-propyl ester (Table 4, entry 2)



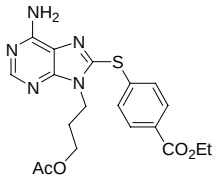
t_R = 5.15 min. ^{1}H-NMR ($CDCl_3$) δ 8.34 (s, 1H), 8.14 (dd, *J* = 7.0, 2.0 Hz, 2H), 7.43 (dd, *J* = 7.0, 2.0 Hz, 2H),6.17 (s, 2H), 4.34 (t, *J* = 7.0 Hz, 2H), 4.05 (t, *J* = 6.1 Hz, 2H), 2.15 (quint., *J* = 6.7 Hz, 2H), 2.03 (s, 3H). ^{13}C-NMR (DMSO-d_6) δ 170.6, 156.2, 154.1, 151.5, 146.5, 143.5, 140.4, 128.3, 125.0, 120.4, 61.8, 41.2, 28.6, 21.0. HRMS *m/z* calc. for $C_{16}H_{17}N_6O_4S$ (M+1): 389.1026, found: 389.1015.

Acetic acid 3-[6-amino-8-(4-fluoro-phenylsulfanyl)-purin-9-yl]-propyl ester (Table 4, entry 3)



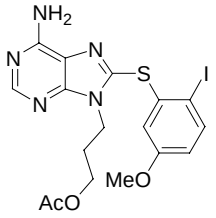
t_R = 5.19 min. ^{1}H-NMR ($CDCl_3$) δ 8.26 (s, 1H), 7.46–7.43 (m, 2H), 7.01 (t, *J* = 8.5 Hz, 2H), 6.30 (s, 2H), 4.29 (q, *J* = 7.1 Hz, 2H), 4.06 (t, *J* = 6.0 Hz, 2H), 2.11 (quint, *J* = 7.0 Hz, 2H), 2.00 (s, 3H). HRMS *m/z* calc. for $C_{16}H_{17}FN_5O_2S$ (M+1): 362.1081, found: 362.1079.

4-[9-(3-Acetoxy-propyl)-6-amino-9H-purin-8-ylsulfanyl]-benzoic acid ethyl ester (Table 4, entry 4)



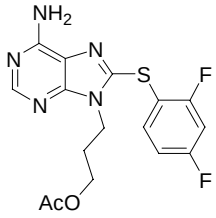
t_R = 6.22 min. ^{1}H-NMR ($CDCl_3$) δ 8.35 (s, 1H), 7.98 (d, *J* = 8.3 Hz, 1H), 7.36 (d, J = 8.3 Hz, 2H), 6.15 (s, 2H), 4.37 (q, *J* = 7.1 Hz, 2H), 4.32 (t, *J* = 7.1 Hz, 2H), 4.06 (t, *J* = 5.9 Hz, 2H), 2.13 (quint, *J* = 6.7 Hz, 2H), 2.01 (s, 3H), 1.39 (t, *J* = 7.1 Hz, 3H). HRMS *m/z* calc. for $C_{19}H_{22}N_5O_4S$ (M+1): 416.1387, found: 416.1383.

Acetic acid 3-[6-amino-8-(2-iodo-5-methoxy-phenylsulfanyl)-purin-9-yl]-propyl ester (Table 4, entry 5)



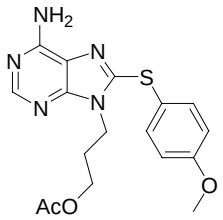
See compound **8**, page S6.

Acetic acid 3-[6-amino-8-(2,4-difluoro-phenylsulfanyl)-purin-9-yl]-propyl ester (Table 4, entry 6)



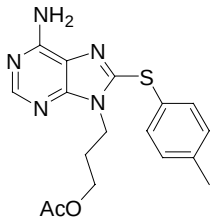
t_R = 5.25 min. ^{1}H-NMR ($CDCl_3$) δ 8.31 (s, 1H), 7.28 (q, *J* = 7.7 Hz, 1H), 6.95 (t, *J* = 8.7 Hz, 2H), 5.74 (s, 2H), 4.39 (q, *J* = 7.1 Hz, 2H), 4.13 (t, *J* = 6.0 Hz, 2H), 2.21 (quint, *J* = 6.5 Hz, 2H), 2.06 (s, 3H). HRMS *m/z* calc. for $C_{16}H_{16}F_2N_5O_2S$ (M+1): 380.0987, found: 380.0986.

Acetic acid 3-[6-amino-8-(4-methoxy-phenylsulfanyl)-purin-9-yl]-propyl ester (Table 4, entry 7)



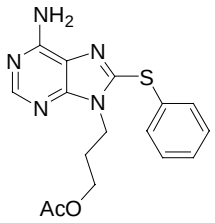
t_R = 5.19 min. ^{1}H-NMR ($CDCl_3$) δ 8.29 (s, 1H), 7.47 (d, *J* = 8.5 Hz, 2H), 6.90 (d, *J* = 8.6 Hz, 2H), 6.20 (s, 2H), 4.32 (t, *J* = 7.1 Hz, 2H), 4.10 (t, *J* = 6.0 Hz), 3.78 (s, 3H), 2.16 (quint., *J* = 6.8 Hz, 2H), 2.13 (s, 3H). HRMS *m/z* calc. for $C_{17}H_{20}N_5O_3S$ (M+1): 374.1281, found: 374.1276.

Acetic acid 3-(6-amino-8-p-tolylsulfanyl-purin-9-yl)-propyl ester (Table 4, entry 8)



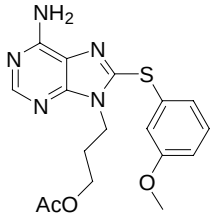
t_R = 5.36 min. ^{1}H-NMR ($CDCl_3$) 8.25 (s, 1H), 7.28 (d, *J* = 8.2 Hz, 2H), 7.07 (d, *J* = 8.1 Hz, 2H), 6.79 (s, 2H), 4.27 (t, *J* = 7.2 Hz, 2H), 4.03 (t, *J* = 6.0 Hz), 2.26 (s, 3H), 2.07 (quint., *J* = 6.6 Hz, 2H), 1.99 (s, 3H). HRMS *m/z* calc. for $C_{17}H_{20}N_5O_2S$ (M+1): 358.1332, found: 358.1333.

Acetic acid 3-(6-amino-8-phenylsulfanyl-purin-9-yl)-propyl ester (Table 4, entry 9)



t_R = 5.09 min. ^{1}H-NMR ($CDCl_3$) δ 8.30 (s, 1H), 7.40 (dd, *J* = 8.2 & 1.9 Hz, 2H), 7.38–7.30 (m, 3H), 6.30 (s, 2H), 4.29 (q, *J* = 7.1 Hz, 2H), 4.06 (t, *J* = 6.0 Hz, 2H), 2.09 (quint, *J* = 6.8 Hz, 2H), 2.00 (s, 3H). HRMS *m/z* calc. for $C_{16}H_{18}N_5O_2S$ (M+1): 344.1176, found: 344.1173.

Acetic acid 3-[6-amino-8-(3-methoxy-phenylsulfanyl)-purin-9-yl]-propyl ester (Table 4, entry 10)



t_R = 5.17 min. ^{1}H-NMR ($CDCl_3$) δ 8.26 (s, 1H), 7.13 (t, *J* = 8.4 Hz, 1H), 6.96 (s, 2H), 6.87–6.85 (m, 1H), 6.78–6.72 (m, 1H), 4.26 (t, *J* = 7.0 Hz, 2H), 4.01 (t, *J* = 6.0 Hz), 3.68 (s, 3H), 2.04 (quint., *J* = 6.8 Hz, 2H), 1.96 (s, 3H). HRMS *m/z* calc. for $C_{17}H_{19}N_5NaO_3S$ (M+Na): 396.1101, found:396.1101.

ANALYSIS OF SECOND- VERSUS THIRD-ORDER KINETICS

For a reaction A + B → C:

If the reaction is first order in each reactant (overall second order): $d[A]/dt = -k[A][B]$.

Since A and B disappear at the same rate, at all times: [A] = [B].

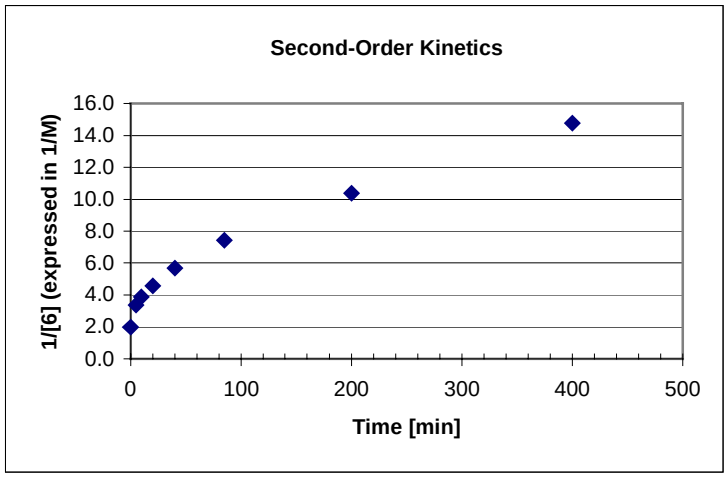
And therefore: $d[A]/[A]^2 = -k\,dt$

For which the solution is: $[A]^{-1} = [A_0]^{-1} + kt$

Wherein $[A_0]$ is the concentration of A at t = 0.

Hence a plot of $[A]^{-1}$ versus time is linear, with a slope equal to k.

However, in the case in point where A is the thione **6**, a plot of $[\mathbf{6}]^{-1}$ is not linear:



Similarly, if the reaction is overall <u>third order</u>, by definition $d[A]/[A]^3 = -k\,dt$.

For which the solution is $[A]^{-2} = [A_0]^{-2} + 2kt$.

This time, the plot is closer to linearity, with a slope $2k = 8.7 \pm 1.5\ min^{-1}M^{-2}$ ($r^2 = 0.998$).