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Two-Step Three-Component Process for One-Pot Synthesis of 8-Alkylmercaptocaffeine Derivatives

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M. N. Soltani Rad* and S. Maghsoudi

A highly efficient, odourless and two-step three-component process for one-pot synthesis of some 8-alkylmercaptocaffeine derivatives has been described. The catalyst-free three-component reaction of alkyl bromides, thiourea, and 8-bromocaffeine gave 8-alkylmercaptocaffeine products in excellent to quantitative yields. In addition, the impact of parameters on sample reaction is discussed.

Introduction

Undoubtedly methylxanthines are one of the most interesting classes of compounds that people around the world are exposed in their everyday life.[1] Methylxanthine alkaloids involving caffeine, theophylline, theobromine and their related metabolite i.e. paraxanthine are naturally found in berries, seeds and leaves of many plants like coffee, cocoa and tea (Fig. 1).[2] Methylxanthines are unique molecules since the immense of their pharmaceutical activities.[3] This is due to the fact that xanthine-based scaffolds are well-recognized by plenty of enzymes or receptors in human and animal cells.[4] Methylxanthines and their derivatives have received much attention over the years for their magnificent chemotherapeutic properties as bronchodilator (antiasthmatic, expectorant), antiemetic, cardiotonic, coronary vasodilator, diuretic, analgesic, anti-migraine, anti-rhinitis, analeptic, antispasmodic, psychotonic, CNS stimulant and so on.[5] Moreover, methylxanthines are known as antagonizing agents for phosphodiesterase enzymes[6] and adenosine receptors.[7] Among methylxanthines, most chemical modifications were achieved on theophylline and theobromine.[8] Since the presence of nucleophilic nitrogens (i.e.: N7 and N1 in theophylline and theobromine, respectively) they readily prone to react with diverse carbon electrophiles; whereas, the caffeine has neither the intense nucleophilic nor electrophilic sites to react with active chemical species (Fig. 1). In particular, the caffeine can be affected merely from C(8) site through the reaction with certain electrophilies like positive halogens and so on.[9]

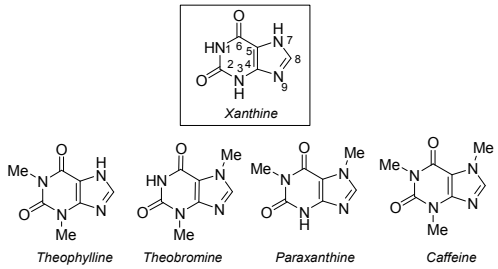

Fig. 1 The structures of xanthine and natural methylxanthines.

The structural activity relationship (SAR) studies of natural methylxanthines and their synthetic derivatives have revealed that the site of alkylation almost determines the pharmaceutical and the biological behavior trend of the corresponding methylxanthine.[10] As an instance, the C(8) alkylation/substitution of caffeine has often led to the new analogues with potential anti-rhinitis or antagonistic property for adenosine receptors as well as phosphodiesterase enzymes; whereas, the N(1)–alkylation of theobromine shifts the property to vasodilatory activity (Fig. 2).[11]

Since the discovery of 6-mercaptopurine (6-MP) as an immunosuppressive medication for treating acute lymphocytic leukemia[12] and also 8-methylmercaptoxanthine as a main metabolite of oncogene (i.e.: 3-hydroxyxanthine),[13] efforts have been made to incorporate the mercapto moiety into scaffolds of diverse methylxanthines to access new bioactive derivatives. In this connection, 8-thiosubstituted methylxanthines especially 8-mercaptocaffeine derivatives have found particular attention since their noticeable pharmaceutical profiles. Up to now, few numbers of these derivatives have been developed. Petzer and coworkers reported the synthesis of 8-[(alkyl) sulfanyl] caffeine derivatives **1** as potent MAO-B inhibitors through C-8 substitution of caffeine with thioether moieties.[14,15] Krutovskikh et al. reported the synthesis of 8-β-dialkylaminoethylmercaptocaffeine analogous **2** with radio-protective property.[16] Caffeine-8-thioglycolic acid derivatives **3** were synthesized by Zlatkov and coworkers with brain antihypoxic activity.[17] In addition, several 8-mercapto-caffeine derivatives

Medicinal Chemistry Research Laboratory, Department of Chemistry, Shiraz University of Technology, Shiraz 71555-313, Iran; soltani@sutech.ac.ir

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and/or related scaffolds **4-8** with certain biological activities have been established.[18-22] The structures of compounds **1-8** and their corresponding therapeutic activities are shown in Fig. 3.

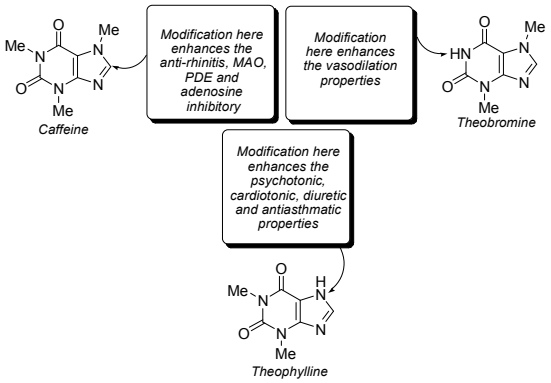

Fig. 2 The modifications (alkylation or substitution) to scaffolds of methylxanthines lead to diverse pharmaceutical properties.

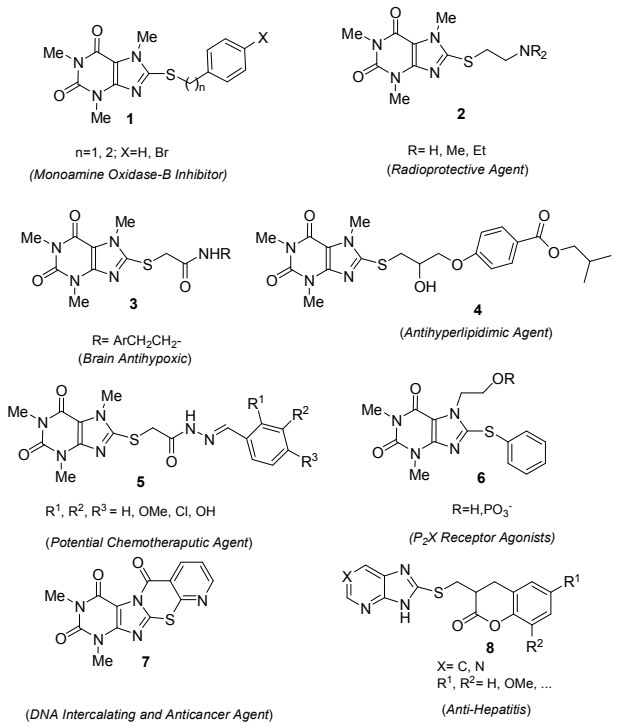

Fig. 3 The structures and therapeutic activities of 8-alkylmercaptocaffeine and their related derivatives.

To access 8-alkylmercaptocaffeine derivatives, diverse approaches have been reported so for comprising (*i*) reaction of 8-mercaptocaffeine [CAS No: 56223-58-6] with alkyl halides in the presence of an efficient base,[16,23] (*ii*) direct thiolation reaction of mercaptans with 8-chlorocaffeine (8-CC) or 8-bromocaffeine (8-BC) in basic media [14,15,24] and more recently, (*iii*) copper-catalyzed direct thiolation of isocaffeine via disulfides utilized AgOAc as an additive under O_2 atmosphere.[25] Despite the usefulness of the above approaches for synthesis of some 8-alkylmercaptocaffeine derivatives, the drawbacks still have remained. As instances, the reaction of 8-mercaptocaffeine with alkyl halides[16,23] requires strong bases such as EtONa which often leads to the low yields of products. The low yield of products is attributed to narrow nucleophilic power of 8-mercaptocaffeine. The weak nucleophilic potency of 8-mercaptocaffeine is owing to the fact that charge density on –SH moiety is distributed between sulfur and adjacent N7 and N9 atoms through the possible tautomerization effect.[23] Therefore, the application scope of S-alkylation reaction for 8-mercaptocaffeine via alkyl halides is very limited. The direct thiolation reaction of mercaptans with 8-chlorocaffeine (8-CC) or 8-bromocaffeine (8-BC) in basic media also associates with two main drawbacks involving the extreme of unpleasant and disgusting odours of used mercaptans, and sensitivity of mercaptans toward oxidizing agents like atmospheric oxygen which readily converts the thiols into disulfides at basic pH (pH>7). Moreover, an approach developed by Zhu and coworkers[25] for straightforward thiolation of isocaffeine requires less available and presynthesized disulfieds, the use of an expensive additive and performing the reaction under an O_2 atmosphere which is not simple and easy to handle.

Thiourea is a safe, cheap and widely available organosulfur compound which has been extensively used for generation of thiols from alkyl halides.[26,27] The major advantages associated with the use of thiourea is the *in situ* generation of thiols. The *in situ* generated thiols subsequently can be used to react with set of diverse carbon electrophiles in one-pot reaction condition to access a plenty of thio-compounds. This advantage prevents the requirement of extra procedure for separation and purification of thiols and thus diminishes the intense of the odd smell of thiols and largely reduces the oxidative homocoupling of thiols to disulfides.[28-30]

Regarding to remarkable therapeutic activity of 8-alkylmercaptocaffeine derivatives and also in continuation of our long-standing interest on synthesis of new methylxanthine derivatives;[8,31] hereby, we would like to report highly efficient, catalyst-free, odourless and three-component process for one-pot synthesis of some 8-alkylmercaptocaffeine (Scheme 1).

In this synthesis, the reaction of thiourea with alkyl bromides in refluxing EtOH followed by addition of aqueous NaOH at room temperature provided the corresponding 8-alkylmercaptocaffeine derivatives **12a-q** in excellent yields.

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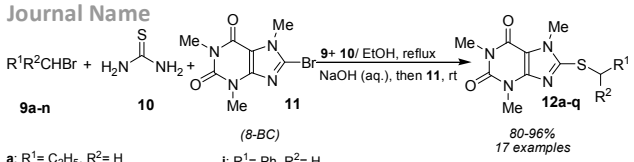


a: R^1= C_2H_5, R^2= H
b: R^1= *n*-C_3H_7, R^2= H
c: R^1= *n*-C_4H_9, R^2= H,
d: R^1= *n*-C_5H_{11}, R^2= H
e: R^1= *n*-C_6H_{13}, R^2= H
f: R^1= *n*-C_7H_{15}, R^2= H
g: R^1= *n*-C_9H_{19}, R^2= H
h: R^1= $CH_2CH(Me)CH_3$, R^2= H
i: R^1= 4-Me-C_6H_4 R^2= H
j: R^1= Ph, R^2= H
k: R^1= $PhCH_2$, R^2= H
l: R^1= $PhCH_2CH_2$, R^2= H
m: R^1= β-naphtyl, R^2= H
n: R^1= Ph, R^2= Ph
o: R^1= CH_2CH_2(benzimidazol-1-yl), R^2= H
p:$(CH_2)_3CH_2$(2-methyl-4-nitroimidazol-1-yl), R^2= H
q: CH_2(phthalimid-N-yl), R^2= H

Scheme 1 Synthesis of 8-alkylmercaptocaffeine through one-pot, three-component reaction using thiourea, alkyl bromide and 8-BC.

Results and discussion

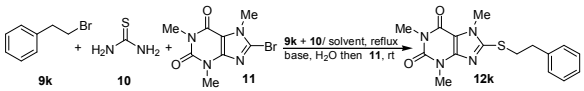
To start synthesizing the title compounds, we first considered the synthesis of **12k** as a sample compound as this potent inhibitor of MAO-B was previously synthesized by Petzer et al.[14,15] We initially attempted to synthesize **12k** through the reaction of 8-mercaptocaffeine with phenethyl bromide in refluxing absolute ethanol. However, no reaction was carried out after refluxing for 48 h. Additionally, utilizing organic and inorganic bases to improve the reaction yield were only acquired the moderate yield of **12k**. As an instance, the use of fresh EtONa in absolute ethanol only afforded **12k** in 45% yield after prolonging the reaction time up to 72 h. As mentioned earlier, the low yield of product obtained by direct reaction of 8-mercaptocaffeine with alkyl halides is caused by weak nucleophilic nature of 8-mercaptocaffeine.

8-Bromo- (8-BC) or 8-chlorocaffeine (8-CC) are known as interesting compounds for introduction of 8-caffeinyl moiety to diverse nucleophiles.[14,15,17,24,32] As matter of fact, the linkage of C(8) with three electron withdrawing elements in 8-BC or 8-CC extensively enhances the positive charge density on C(8) which dispose to be attacked by varied nucleophiles through S_NAr-type reaction. Thus, to obtain the higher yield of **12k**, an alternative approach was applied in which 2-phenylethanethiol (CAS NO: 4410-99-5) was directly reacts with 8-BC in the presence of an efficient base (NaOH) in EtOH at reflux condition due to procedure reported by Petzer et al.[14,15] and Long.[24] Although a good yield of **12k** (>78%) were obtained using current approach, this procedure suffer from the extreme of unpleasant odours of the used mercaptan.

Regarding to numerous benefits of one-pot multicomponent reactions (MCR),[33] we applied this strategy to overcome the addressed issues. To this end, the one-pot two-step three component reaction of thiourea as a sulfur source agent with alkyl halides followed by addition of 8-BC seems to be an attractive and effectual strategy to access 8-alkylmercaptocaffeine derivatives.

To find out the optimized reaction conditions, we screened the influence of parameters like solvent and base. In this connection, the optimization was begun with studying the influence of various aprotic, protic and other solvents on the sample reaction in the presence of aqueous NaOH as a base (Table 1). As shown in Table 1, through the examined solvents, ethanol (Table 1, entry 10) afforded the best result and hence it was solvent of choice for all next reactions. In general, the use of protic solvents (Table 1, entries 10-13) gained the better results compared to aprotic solvents while in contrary, water (Table 1, entry 9) was insufficient to process the reaction. In addition to ethanol, methanol also afforded an excellent yield of **12k**; however, since its toxicity, the use of ethanol was preferred. Utilizing polar aprotic solvents (Table 1, entries 1-7) acquired low to moderate yields of **12k** in different times. Whereas, toluene and a room temperature ionic liquid (i.e.: bmim[Br]) were failed to improve the reaction (Table 1, entries 8 and 14).

Table 1 Effect of various solvents and bases on reaction of phenethyl bromide, thiourea and 8-BC[a]



Entry	Solvent	Base[b]	Time (h)	Yield[c] (%)
1	DMF[d]	NaOH	34	42
2	THF	NaOH	40	38
3	DMSO[d]	NaOH	37	40
4	MeCN	NaOH	42	32
5	NMP[d]	NaOH	44	38
6	HMPA[d]	NaOH	48	32
7	Me_2CO	NaOH	48	29
8	PhMe	NaOH	72	NR[e]
9	H_2O	NaOH	72	25
10	EtOH	NaOH	14	90
11	i-PrOH	NaOH	22	75
12	MeOH	NaOH	17	86
13	PEG 200[d]	NaOH	36	65
14	bmim[Br][d]	NaOH	72	NR
15	EtOH	-	72	NR
16	EtOH	TEA	48	36
17	EtOH	K_2CO_3	72	NR
18	EtOH	DBU	28	38
19	EtOH	MgO	72	NR
20	EtOH	EtONa	18	40
21	EtOH	*t*-BuOK	24	35
22	EtOH	DBN	30	39
23	EtOH	DMAP	26	31
24	EtOH	DABCO	36	29

[a] Reaction conditions: phenethyl bromide (10 mmol), thiourea (12 mmol), 8-BC (10 mmol), solvent (25 mL) , base (20 mmol) and H_2O (2 mL)
[b] Except that of H_2O as a solvent (entry 9), NaOH was primarily dissolved in H_2O (2 mL) and then was added to reaction mixture.
[c] Isolated yield.
[d] The reaction was conducted at 100° C.
[e] No reaction.

Afterward of determining a proper solvent, we then examined the influence of diverse organic and inorganic bases. The use of an efficient base has undeniable role in progress of reaction. In absence of a base, the reaction was not conducted at all even if the reaction time has been extended to three days and more (Table 1, entry 15). As can be seen in Table 1, none of tested bases were proper for progress of reaction. The only base that found suitable for this synthesis was aqueous NaOH which employed for all reactions.

With the optimal reaction conditions in hand, we screened the versatility and the scope of this current approach. In this regard, a variety of alkyl bromides were proved to be effective to generate products **12** in excellent to almost quantitative yields (Table 2).

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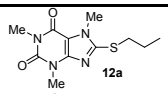
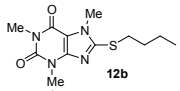
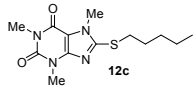
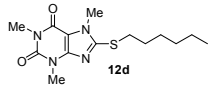
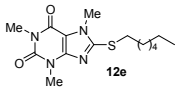
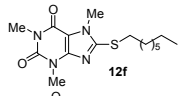
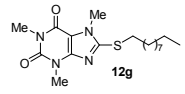
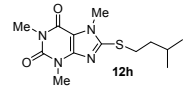
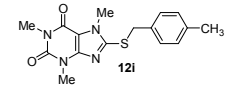
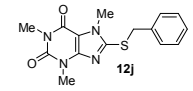
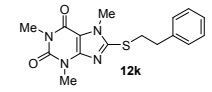
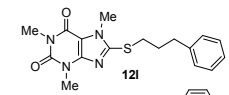
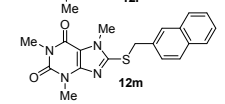
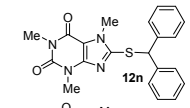
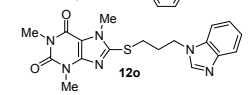
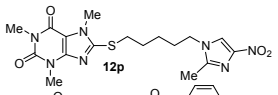
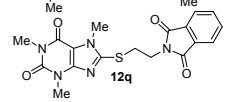
Table 2 Synthesis of 8-alkylmercaptocaffeine through one-pot two-Step three-component reaction using thiourea, alkyl bromide and 8-BC

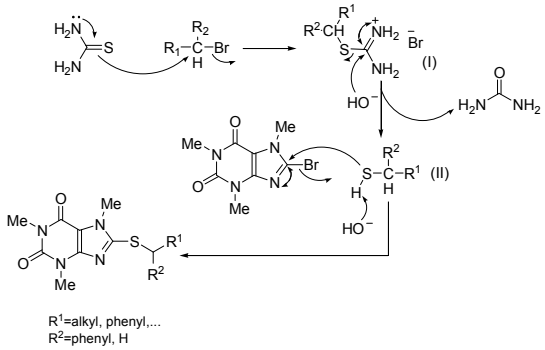
Entry	Product [a]	Time (h)	Yield [b] (%)
1	 **12a**	18	95
2	 **12b**	20	93
3	 **12c**	22	90
4	 **12d**	19	90
5	 **12e**	20	88
6	 **12f**	19	85
7	 **12g**	22	83
8	 **12h**	26	84
9	 **12i**	12	96
10	 **12j**	16	94
11	 **12k**	14	90
12	 **12l**	17	83
13	 **12m**	20	93
14	 **12n**	48	80
15	 **12o**	17	92
16	 **12p**	16	90
17	 **12q**	18	92

[a] All products were characterized by ^{1}H and ^{13}C NMR, IR, CHN, and MS analysis.

[b] Isolated yield.

The alkyl bromides with different normal carbon chains readily underwent the reactions with thiourea and 8-BC in excellent yields (Table 2, entries 1-7). Interestingly, as expected, among tested alkyl bromides, the maximum yields were obtained for alkyl bromides with shorter normal carbon chains; whereas, the yields were gradually diminished by increasing the number of carbons in a chain. Also the utilizing alkyl bromide with a branched aliphatic chain acquired a good yield of product (Table 2, entry 8). Moreover, alkyl bromides with ω-substituted phenyl moieties (Table 2, entries 11 and 12) were afforded the corresponding products **12k** and **12l** in excellent yields. This current approach also works well with benzyl bromide derivatives in which **9i**, **9j**, **9m** and benzhydryl bromide were efficiently converted to the corresponding products also in quantitative yields. In addition, alkyl bromides with N-heterocyclic compounds at ω-position involving benzimidazolyl (**9o**), 2-methyl-4-nitroimidazolyl (**9p**) and phthalimidyl **(9q**) were almost quantitatively converted to corresponding 8-alkylmercapto-caffeine (**12o-12q**). It is worth mentioning that the other alkyl halides involving alkyl chlorides and iodides along with alkyl sulfonates could be applied; however, to our experience the best results were obtained when alkyl bromides were employed.

On the basis of the experimental results, a plausible mechanism for the formation of products is proposed (Scheme 2). As shown in Scheme 2, the thiourea first performs the nucleophilic attack to alkyl bromide to generate alkylthiouronium hydrobromide salt (**I**). The generation of this salt was obviously observed during the reaction course. Afterward, salt (**I**) is hydrolyzed to urea and corresponding thiol (**II**) by addition of hydroxide ion. The *in situ* generated thiol (**II**) is then activated by extra hydroxide ion and attacks to 8-BC through S_NAr-type reaction to afford 8-alkylmercaptocaffeine.



Scheme 2 A plausible mechanism for synthesis of 8-alkylmercaptocaffeine using thiourea, alkyl bromide and 8-BC

Conclusions

In conclusion, we have developed an efficient, odourless and practical route for one-pot two-step three-component synthesis of some 8-alkylmercaptocaffeine derivatives. The three-component reaction of alkyl bromides, thiourea and 8-BC in the presence of aqueous NaOH in ethanol acquired 8-alkylmercaptocaffeine derivatives in excellent to quantitative yields. The influence of parameters effective on reaction

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progress involving solvent and base effects has been studied. This catalyst-free approach proceeds smoothly under mild conditions from readily available starting materials and provides diverse 8-alkylmercaptocaffeine as potential chemotherapeutic agents.

Experimental

All chemical reagents except that of 8-Bromocaffeine (8-BC)[34] were purchased from Fluka, Sigma-Aldrich or Merck companies. Solvents were purified by standard procedures, and stored over 3Å molecular sieves.[35] Reactions were followed by TLC using SILG/UV 254 silica-gel plates. Column chromatography was performed on silica gel 60 (0.063-0.200 mm, 70-230 mesh; ASTM). IR spectra were obtained using a Shimadzu FT-IR-8300 spectrophotometer. ^{1}H- and ^{13}C-NMR spectrum was recorded on Brüker Avance-DPX-250 spectrometer operating at 250/62.5 MHz, respectively. Chemical shifts are given in δ relative to tetramethylsilane (TMS) as an internal standard, coupling constants *J* are given in Hz. Abbreviations used for ^{1}H NMR signals are: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad and etc. GC/MS was performed on a Shimadzu GC/MS-QP 1000-EX apparatus (m/z; rel.%). Elemental analyses were performed on a Perkin–Elmer 240-B micro-analyser.

General Procedure for synthesis of 8-alkylmercaptocaffeine (12a-12q)

In a triple-necked round bottom flask (100 mL) equipped with a condenser and additional funnel, it was added a mixture, consisting of alkyl bromide (10 mmol) and thiourea (12 mmol, 0.91g) in 96% EtOH (25 mL). The mixture was heated at reflux and heating was continued until TLC indicated the completion of reaction. Afterward, the solution of NaOH (0.02 mol, 0.8 g) in distillated water (2 mL) was added to reaction mixture through the connected addition funnel at reflux for an extra hour. The reaction media was chilled to room temperature and then 8-BC (10 mmol, 2.73 g) was added and the mixture was stirred at room temperature. In most cases, the suspension of 8-BC crystals immediately vanished which is a good evidence for rapid progression of reaction (Note: 8-BC is not dissolved in EtOH at room temperature). After completion of the reaction (TLC check), the solvent was evaporated *in vacuo* and the remaining residue was diluted in $CHCl_3$ (100 mL) and subsequently washed with water (2×100 mL). The organic layer was dried (Na_2SO_4) and evaporated. The crude product was purified by recrystallization and/or column chromatography on silica gel eluting with proper solvents described below.[36]

1,3,7-Trimethyl-8-(propylthio)-1*H*-purine-2,6(3*H*,7*H*)-dione (12a)[24]

Recrystallization (EtOH) afforded a white solid; yield: 2.55 g (95%); mp 82–84 °C; R_f = 0.36 (EtOAc-*n*-hexane, 1:6).
IR (KBr): 2952, 2832, 1701, 1658, 1583, 1447, 1341 cm^{-1}.
^{1}H NMR ($CDCl_3$, 250 MHz): δ = 3.84 (s, 3 H, N(7)-CH_3), 3.55 (s, 3 H, N(1)-CH_3), 3.38 (s, 3 H, N(3)-CH_3), 3.25 (t, *J* = 7.2 Hz, 2 H, SCH_2), 1.86–1.71 (m, 2 H, SCH_2CH_2), 1.05 (t, *J* = 7.3 Hz, 3 H, CH_3).
^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 155.1, 152.2, 151.3, 150.4, 105.1, 38.7, 33.5, 30.0, 24.8, 21.3, 13.8.
MS (EI): *m*/z (%) = 268 (15.7) [M$^+$].
Anal. Calcd for $C_{11}H_{16}N_4O_2S$: C, 49.24; H, 6.01; N, 20.88. Found: C, 49.32; H, 6.15; N, 20.96.

8-(Butylthio)-1,3,7-trimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione (12b)[24]

Recrystallization (EtOH) afforded a white solid; yield: 2.62 g (93%); mp 81–83 °C; R_f = 0.36 (EtOAc-*n*-hexane, 1:6).
IR (KBr): 2964, 2873, 1701, 1671, 1560, 1426, 1372 cm^{-1}.
^{1}H NMR ($CDCl_3$, 250 MHz): δ = 3.69 (s, 3 H, N(7)-CH_3), 3.46 (s, 3 H, N(1)-CH_3), 3.32 (s, 3 H, N(3)-CH_3), 3.17 (t, *J* = 7.1 Hz, 2 H, SCH_2), 1.52–1.20 (complex, 4 H, 2 CH_2), 0.88 (t, *J* = 7.1 Hz, 3 H, CH_3).
^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 155.8, 152.8, 151.8, 150.6, 107.3, 37.2, 33.2, 32.6, 29.6, 22.0, 21.7, 13.8.
MS (EI): *m*/z (%) = 282 (13.4) [M$^+$].
Anal. Calcd for $C_{12}H_{18}N_4O_2S$: C, 51.04; H, 6.43; N, 19.84. Found: C, 51.17; H, 6.51; N, 19.76.

1,3,7-Trimethyl-8-(pentylthio)-1*H*-purine-2,6(3*H*,7*H*)-dione (12c)

Column chromatography (silica gel, EtOAc-*n*-hexane, 1:15) afforded a white solid; yield: 2.66 g (90%); mp 75–77 °C; R_f = 0.36 (EtOAc-*n*-hexane, 1:6).
IR (KBr): 2946, 2847, 1702, 1663, 1538, 1444, 1349 cm^{-1}.
^{1}H NMR ($CDCl_3$, 250 MHz): δ = 3.82 (s, 3 H, N(7)-CH_3), 3.53 (s, 3 H, N(1)-CH_3), 3.36 (s, 3 H, N(3)-CH_3), 3.26 (t, *J* = 7.3 Hz, 2 H, SCH_2), 1.82–1.70 (m, 2 H, SCH_2CH_2), 1.49–1.30 (m, 4 H, 2 CH_2), 0.92 (t, *J* = 7.0 Hz, 3 H, CH_3).
^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 154.9, 151.9, 150.6, 149.1, 108.8, 36.9, 32.3, 31.0, 30.1, 29.5, 22.7, 21.8, 14.4.
MS (EI): *m*/z (%) = 296 (18.9) [M$^+$].
Anal. Calcd for $C_{13}H_{20}N_4O_2S$: C, 52.68; H, 6.80; N, 18.90. Found: C, 52.83; H, 6.87; N, 19.02.

8-(Hexylthio)-1,3,7-trimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione (12d)

Column chromatography (silica gel, EtOAc-*n*-hexane, 1:15) afforded a white solid; yield: 2.79 g (90%); mp 67–69 °C; R_f = 0.35 (EtOAc-*n*-hexane, 1:6).
IR (KBr): 2942, 2910, 1710, 1652, 1551, 1478, 1362 cm^{-1}.
^{1}H NMR ($CDCl_3$, 250 MHz): δ = 3.73 (s, 3 H, N(7)-CH_3), 3.44 (s, 3 H, N(1)-CH_3), 3.26 (s, 3 H, N(3)-CH_3), 3.17 (t, *J* = 7.3 Hz, 2 H, SCH_2), 1.72–1.60 (m, 2 H, SCH_2CH_2), 1.38–1.22 (complex, 6 H, 3 CH_2), 0.78 (t, *J* = 7.3 Hz, 3 H, CH_3).
^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 155.6, 152.0, 151.1, 149.7, 106.5, 37.1, 33.3, 31.8, 30.6, 29.1, 28.5, 22.9, 21.7, 15.8.
MS (EI): *m*/z (%) = 310 (17.5) [M$^+$].
Anal. Calcd for $C_{14}H_{22}N_4O_2S$: C, 54.17; H, 7.14; N, 18.05. Found: C, 54.09; H, 7.21; N, 18.13.

8-(Heptylthio)-1,3,7-trimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione (12e)

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Recrystallization (EtOH) afforded a white solid; yield: 2.85 g (88%); mp 75–77 °C; R_f = 0.34 (EtOAc-*n*-hexane, 1:6).
IR (KBr): 2943, 2863, 1703, 1682, 1579, 1431, 1388 cm^{-1}.
^1H NMR ($CDCl_3$, 250 MHz): δ = 3.84 (s, 3 H, N(7)-CH_3), 3.55 (s, 3 H, N(1)-CH_3), 3.38 (s, 3 H, N(3)-CH_3), 3.26 (t, *J* = 7.3 Hz, 2 H, SCH_2), 1.80–1.72 (m, 2 H, SCH_2CH_2), 1.46–1.29 (complex, 8 H, 4 CH_2), 0.88 (t, *J* = 6.8 Hz, 3 H, CH_3).
^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 156.2, 152.9, 151.4, 150.2, 108.9, 37.0, 32.4, 31.8, 30.6, 29.7, 28.8, 27.9, 22.5, 21.8, 14.3.
MS (EI): *m*/z (%) = 324 (19.3) [M^+].
Anal. Calcd for $C_{15}H_{24}N_4O_2S$: C, 55.53; H, 7.46; N, 17.27. Found: C, 55.61; H, 7.40; N, 17.35.

1,3,7-Trimethyl-8-(octylthio)-1*H*-purine-2,6(3*H*,7*H*)-dione (12f)
Column chromatography (silica gel, EtOAc-*n*-hexane, 1:15) afforded a white solid; yield: 2.87 g (85%); mp 66–68°C; R_f = 0.34 (EtOAc-*n*-hexane, 1:6).
IR (KBr): 2945, 2852, 1702, 1672, 1586, 1463, 1357 cm^{-1}.
^1H NMR ($CDCl_3$, 250 MHz): δ = 3.76 (s, 3 H, N(7)-CH_3), 3.47 (s, 3 H, N(1)-CH_3), 3.30 (s, 3 H, N(3)-CH_3), 3.18 (t, *J* = 7.3 Hz, 2 H, SCH_2), 1.72–1.61 (m, 2 H, SCH_2CH_2), 1.36–1.20 (complex, 10 H, 5 CH_2), 0.77 (t, *J* = 6.8 Hz, 3 H, CH_3).
^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 154.8, 152.1, 151.8, 149.4, 105.1, 37.0, 32.6, 31.6, 30.8, 30.5, 29.9, 29.6, 28.7, 22.5, 20.4, 15.3.
MS (EI): *m*/z (%) = 338 (20.6) [M^+].
Anal. Calcd for $C_{16}H_{26}N_4O_2S$: C, 56.78; H, 7.74; N, 16.55. Found: C, 56.88; H, 7.81; N, 16.47.

8-(Decylthio)-1,3,7-trimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione (12g)
Recrystallization (EtOH) afforded a white solid; yield: 3.04 g (83%); mp 83–85 °C; R_f = 0.32 (EtOAc-*n*-hexane, 1:6).
IR (KBr): 2986, 2880, 1706, 1674, 1536, 1472, 1313 cm^{-1}.
^1H NMR ($CDCl_3$, 250 MHz): δ = 3.90 (s, 3 H, N(7)-CH_3), 3.62 (s, 3 H, N(1)-CH_3), 3.46 (s, 3 H, N(3)-CH_3), 3.29 (t, *J* = 7.3 Hz, 2 H, SCH_2), 1.74–1.21 (complex, 19 H, 8 CH_2, CH_3).
^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 155.4, 151.1, 150.5, 149.1, 105.0, 36.9, 33.1, 32.0, 30.6, 30.0, 29.1, 28.8, 28.6, 28.0, 27.4, 21.7, 20.2, 12.5.
MS (EI): *m*/z (%) = 366 (23.8) [M^+].
Anal. Calcd for $C_{18}H_{30}N_4O_2S$: C, 58.98; H, 8.25; N, 15.29. Found: C, 59.05; H, 8.36; N, 15.38.

8-(Isopentylthio)-1,3,7-trimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione (12h)[15]
Recrystallization (EtOH) afforded a white solid; yield: 2.48 g (84%); mp 82–84 °C; R_f = 0.39 (EtOAc-*n*-hexane, 1:6).
IR (KBr): 2956, 2864, 1710, 1678, 1557, 1468, 1369 cm^{-1}.
^1H NMR ($CDCl_3$, 250 MHz): δ = 3.76 (s, 3 H, N(7)-CH_3), 3.47 (s, 3 H, N(1)-CH_3), 3.31 (s, 3 H, N(3)-CH_3), 3.19 (t, *J* = 7.4 Hz, 2 H, SCH_2), 1.71–1.51 (m, 3 H, CH_2CH), 0.89 (d, *J* = 6.3 Hz, 6 H, 2 CH_3).
^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 155.4, 152.4, 151.5, 150.5, 106.1, 37.3, 34.2, 31.5, 29.3, 26.9, 22.0, 20.5.
MS (EI): *m*/z (%) = 296 (17.6) [M^+].
Anal. Calcd for $C_{13}H_{20}N_4O_2S$: C, 52.68; H, 6.80; N, 18.90. Found: C, 52.82; H, 6.87; N, 18.95.

1,3,7-Trimethyl-8-(4-methylbenzylthio)-1*H*-purine-2,6(3*H*,7*H*)-dione (12i)
Column chromatography (silica gel, EtOAc-*n*-hexane, 1:15) afforded a white solid; yield: 3.17g (96%); mp 75–77 °C; R_f = 0.28 (EtOAc-*n*-hexane, 1:6).
IR (KBr): 3028, 2987, 2931, 1698, 1674, 1596, 1469, 1368 cm^{-1}.
^1H NMR ($CDCl_3$, 250 MHz): δ = 7.28 (d, *J* = 8.0 Hz, 2 H, aryl), 7.16 (d, *J* = 7.9 Hz, 2 H, aryl), 4.45 (s, 2 H, SCH_2), 3.76 (s, 3 H, N(7)-CH_3), 3.63 (s, 3 H, N(1)-CH_3), 3.42 (s, 3 H, N(3)-CH_3), 2.36 (s, 3 H, PhCH_3).
^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 154.4, 151.8, 150.9, 150.3, 137.0, 136.6, 129.8, 127.2, 107.3, 39.1, 32.6, 30.0, 25.2, 22.2.
MS (EI): *m*/z (%) = 330 (14.6) [M^+].
Anal. Calcd for $C_{16}H_{18}N_4O_2S$: C, 58.16; H, 5.49; N, 16.96. Found: C, 58.29; H, 5.40; N, 16.85.

8-(Benzylthio)-1,3,7-trimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione (12j)[15,24]
Column chromatography (silica gel, EtOAc-*n*-hexane, 1:15) afforded a white solid; yield: 2.97 g (94%); mp 74–76 °C; R_f = 0.26 (EtOAc-*n*-hexane, 1:6).
IR (KBr): 3030, 2946, 2895, 1711, 1671, 1544, 1436, 1310 cm^{-1}.
^1H NMR (DMSO-d_6, 250 MHz): δ = 7.45–7.31 (m, 5 H, aryl), 4.49 (s, 2 H, SCH_2), 3.63 (s, 3 H, N(7)-CH_3), 3.41 (s, 3 H, N(1)-CH_3), 3.17 (s, 3 H, N(3)-CH_3).
^{13}C NMR (DMSO-d_6, 62.5 MHz): δ = 155.1, 152.4, 151.8, 149.4, 138.6, 128.7, 128.4, 127.3, 104.8, 37.4, 31.4, 30.5, 22.1.
MS (EI): *m*/z (%) = 316 (20.1) [M^+].
Anal. Calcd for $C_{15}H_{16}N_4O_2S$: C, 56.94; H, 5.10; N, 17.71. Found: C, 57.03; H, 5.21; N, 17.79.

1,3,7-Trimethyl-8-(phenethylthio)-1*H*-purine-2,6(3*H*,7*H*)-dione (12k)[14,15]
Column chromatography (silica gel, EtOAc-*n*-hexane, 1:8) afforded a white solid; yield: 2.97 g (90%); mp 71–73 °C; R_f = 0.23 (EtOAc-*n*-hexane, 1:6).
IR (KBr): 3032, 2941, 1719, 1668, 1542, 1456, 1372 cm^{-1}.
^1H NMR (DMSO-d_6, 250 MHz): δ = 7.29–7.14 (m, 5 H, aryl), 3.62 (s, 3 H, N(7)-CH_3), 3.44 (t, *J* = 7.2 Hz, 2 H, SCH_2), 3.34 (s, 3 H, N(1)-CH_3), 3.13 (s, 3 H, N(3)-CH_3), 2.97 (t, *J* = 7.1 Hz, 2 H, PhCH_2).
^{13}C NMR (DMSO-d_6, 62.5 MHz): δ = 157.6, 152.7, 151.8, 150.3, 139.6, 128.7, 127.5, 125.9, 105.3, 38.3, 36.5, 33.1, 30.7, 22.5.
MS (EI): *m*/z (%) = 330 (22.6) [M^+].
Anal. Calcd for $C_{16}H_{18}N_4O_2S$: C, 58.16; H, 5.49; N, 16.96. Found: C, 58.27; H, 5.55; N, 16.90.

1,3,7-Trimethyl-8-(3-phenylpropylthio)-1*H*-purine-2,6(3*H*,7*H*)-dione (12l)[14]
Column chromatography (silica gel, EtOAc-*n*-hexane, 1:10) afforded a white solid; yield: 2.86 g (83%); mp 86–88 °C; R_f = 0.23 (EtOAc-*n*-hexane, 1:6).
IR (KBr): 3050, 2934, 2843, 1701, 1661, 1544, 1431, 1376 cm^{-1}.

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^{1}H NMR ($CDCl_3$, 250 MHz): δ = 7.32–7.17 (m, 5 H, aryl), 3.82 (s, 3 H, N(7)-CH_3), 3.51 (s, 3 H, N(1)-CH_3), 3.37 (s, 3 H, N(3)-CH_3), 3.26 (t, *J* = 7.0 Hz, 2 H, SCH_2), 2.77 (t, *J* = 7.3 Hz, 2 H, PhCH_2), 2.16–2.03 (m, 2 H, SCH_2CH_2).
^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 156.3, 153.3, 152.1, 151.6, 139.7, 129.3, 128.0, 126.3, 107.9, 36.1, 35.8, 35.2, 33.7, 30.1, 21.8.
MS (EI): *m*/z (%) = 344 (21.8) [M^+].
Anal. Calcd for $C_{17}H_{20}N_4O_2S$: C, 59.28; H, 5.85; N, 16.27. Found: C, 59.41; H, 5.94; N, 16.14.

1,3,7-Trimethyl-8-(naphthalen-2-ylmethylthio)-1*H*-purine 2,6(3*H*,7*H*)-dione (12m)
Column chromatography (silica gel, EtOAc-*n*-hexane, 1:10) afforded a white solid; yield: 3.40 g (93%); mp 126–128°C; R_f = 0.23 (EtOAc-*n*-hexane, 1:6).
IR (KBr): 3037, 2934, 2843, 1701, 1661, 1542, 1431, 1376 cm^{-1}.
^{1}H NMR ($CDCl_3$, 250 MHz): δ = 8.03 (d, *J* = 7.9 Hz, 1 H, aryl), 7.83–7.68 (m, 2 H, aryl), 7.52–7.27 (m, 4 H, aryl), 4.86 (s, 2 H, SCH_2), 3.57 (s, 3 H, N(7)-CH_3), 3.54 (s, 3 H, N(1)-CH_3), 3.31 (s, 3 H, N(3)-CH_3).
^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 156.9, 152.4, 151.2, 150.9, 134.2, 133.0, 132.1, 129.3, 128.8, 128.2, 127.9, 127.3, 126.1, 125.2, 106.4, 39.5, 33.5, 30.8, 23.1.
MS (EI): *m*/z (%) = 366 (18.3) [M^+].
Anal. Calcd for $C_{19}H_{18}N_4O_2S$: C, 62.28; H, 4.95; N, 15.29. Found: C, 62.19; H, 5.01; N, 15.22.

8-(Benzhydrylthio)-1,3,7-trimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione (12n)
Column chromatography (silica gel, EtOAc-*n*-hexane, 1:15) afforded a white solid; yield: 3.1 g (80%); mp 74–76 °C; R_f = 0.22 (EtOAc-*n*-hexane, 1:6).
IR (KBr): 3025, 2964, 1701, 1671, 1660, 1426, 1372 cm^{-1}.
^{1}H NMR ($CDCl_3$, 250 MHz): δ = 7.43–7.40 (m, 4 H, aryl), 7.34–7.24 (m, 6 H, aryl), 6.17 (s, 1 H, SCH), 3.71 (s, 3 H, N(7)-CH_3), 3.53 (s, 3 H, N(1)-CH_3), 3.34 (s, 3 H, N(3)-CH_3).
^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 156.7, 152.4, 151.6, 150.6, 142.8, 129.5, 128.6, 127.2, 105.5, 51.3, 33.9, 30.2, 22.6.
MS (EI): *m*/z (%) = 392 (25.4) [M^+].
Anal. Calcd for $C_{21}H_{20}N_4O_2S$: C, 64.27; H, 5.14; N, 14.28. Found: C, 64.39; H, 5.23; N, 14.35.

8-(3-(1*H*-Benzo[*d*]imidazol-1-yl)propylthio)-1,3,7-trimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione (12o)
Column chromatography (silica gel, EtOAc-*n*-hexane, 2:1) afforded a pale-yellow foam; yield: 3.53 g (92%); R_f = 0.38 (EtOAc-*n*-hexane, 4:1).
IR (KBr): 3050, 2991, 2876, 1715, 1678, 1537, 1464 cm^{-1}.
^{1}H NMR ($CDCl_3$, 250 MHz): δ = 8.25 (s, 1H, C(2)-H, benzimidazole), 7.77–7.74 (m, 2 H, aryl), 7.66–7.62 (m, 2 H, aryl), 3.71 (t, *J* = 6.8 Hz, 2H, NCH_2), 3.62 (s, 3 H, N(7)-CH_3), 3.41 (s, 3 H, N(1)-CH_3), 3.27 (s, 3 H, N(3)-CH_3), 3.06 (t, *J* = 6.8 Hz, 2H, SCH_2), 2.34–2.25 (m, 2H, NCH_2CH_2).
^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 155.5, 152.5, 152.1, 151.0, 144.9, 139.1, 134.6, 123.6, 123.0, 115.7, 115.4, 107.0, 54.8, 35.1, 32.9, 31.7, 29.6, 21.7.
MS (EI): *m*/z (%) = 384 (21.6) [M^+].
Anal. Calcd for $C_{18}H_{20}N_6O_2S$: C, 56.23; H, 5.24; N, 21.86. Found: C, 56.35; H, 5.32; N, 21.78.

1,3,7-Trimethyl-8-(5-(2-methyl-4-nitro-1*H*-imidazol-1-yl)pentylthio)-1*H*-purine-2,6(3*H*,7*H*)-dione (12p)
Column chromatography (silica gel, EtOAc-*n*-hexane, 2:1) afforded a yellow oil; yield: 3.79 g (90%); R_f = 0.36 (EtOAc-*n*-hexane, 4:1).
IR (film): 3047, 2965, 2861, 1718, 1680, 1552, 1534, 1473, 1348 cm^{-1}.
^{1}H NMR ($CDCl_3$, 250 MHz): δ = 7.65 (s, 1H, C(5)-H, imidazole), 3.86 (t, *J* = 7.0 Hz, 2H, NCH_2), 3.64 (s, 3 H, N(7)-CH_3), 3.44 (s, 3 H, N(1)-CH_3), 3.29 (s, 3 H, N(3)-CH_3), 3.13 (t, *J* = 7.0 Hz, 2H, SCH_2), 1.79–1.73 (m, 2H, CH_2), 1.49–1.43 (m, 2H, CH_2), 1.34–1.28 (m, 2H, CH_2).
^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 155.9, 152.9, 152.6, 151.7, 151.1, 139.0, 132.5, 106.5, 46.0, 36.8, 33.3, 31.2, 30.9, 29.4, 27.7, 22.4, 12.6.
MS (EI): *m*/z (%) = 421 (20.3) [M^+].
Anal. Calcd for $C_{17}H_{23}N_7O_4S$: C, 48.44; H, 5.50; N, 23.26. Found: C, 48.35; H, 5.41; N, 23.34.

8-(2-(1,3-Dioxoisoindolin-2-yl)ethylthio)-1,3,7-trimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione (12q)
Column chromatography (silica gel, EtOAc-*n*-hexane, 1:1) afforded a creamy foam; yield: 3.67 g (92%); R_f = 0.49 (EtOAc-*n*-hexane, 4:1).
IR (KBr): 3068, 2971, 2879, 1716, 1697, 1662, 1541, 1460 cm^{-1}.
^{1}H NMR ($CDCl_3$, 250 MHz): δ = 7.18–7.13 (m, 2H, aryl), 6.99–6.92 (m, 2H, aryl), 3.77 (s, 3 H, N(7)-CH_3), 3.43–3.30 (complex, 10 H, NCH_2, SCH_2, N(1)-CH_3, N(3)-CH_3).
^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 168.4, 155.3, 152.1, 151.9, 151.0, 133.5, 132.4, 127.7, 107.1, 35.6, 33.0, 30.4, 29.8, 22.3.
MS (EI): *m*/z (%) = 399 (21.2) [M^+].
Anal. Calcd for $C_{18}H_{17}N_5O_4S$: C, 54.13; H, 4.29; N, 17.53. Found: C, 54.21; H, 4.40; N, 17.65.

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Notes and references

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Table of Content (Graphical Abstract)

Two-Step Three-Component Process for One-Pot Synthesis of 8-Alkylmercaptocaffeine Derivatives

Mohammad Navid Soltani Rad and Saeid Maghsoudi

A two-step three-component process for one-pot synthesis of some 8-alkylmercaptocaffeine derivatives has been described using alkyl bromides, thiourea, and 8-bromocaffeine.