

## Catalyst-free N-methylation of 3-methylxanthine with dimethyl carbonate in water: green synthesis of theobromine

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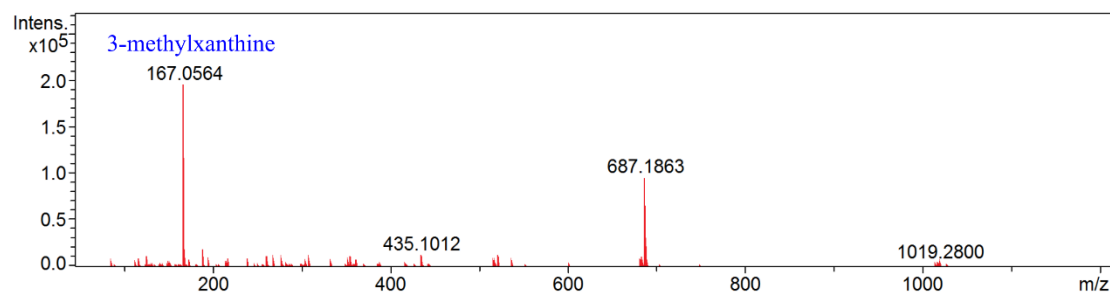


Figure S1 LC-MS diagram of pure 3-methylxanthine

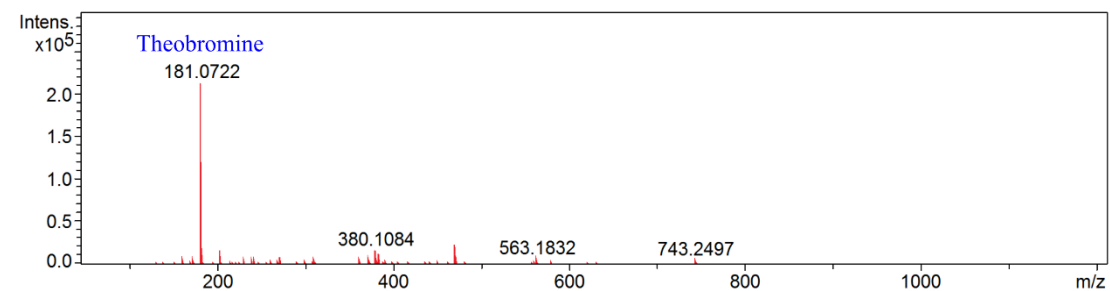
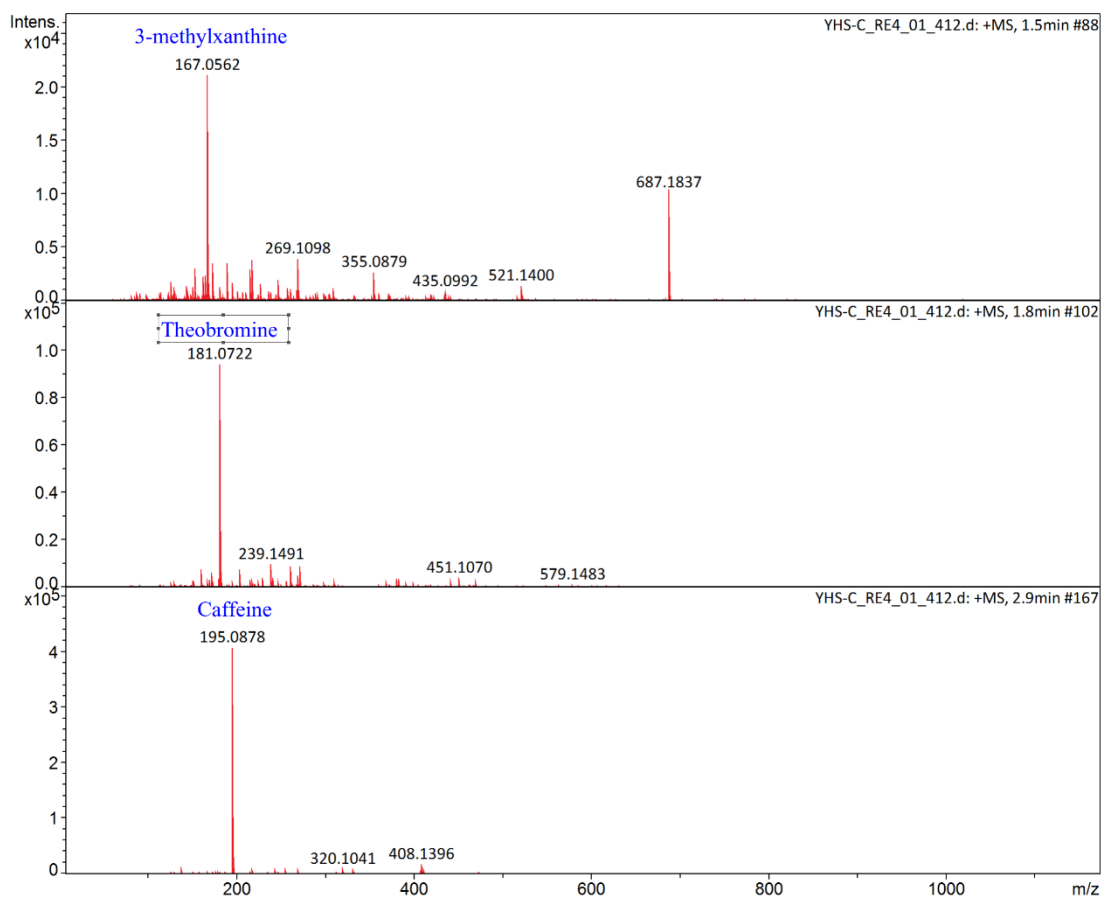
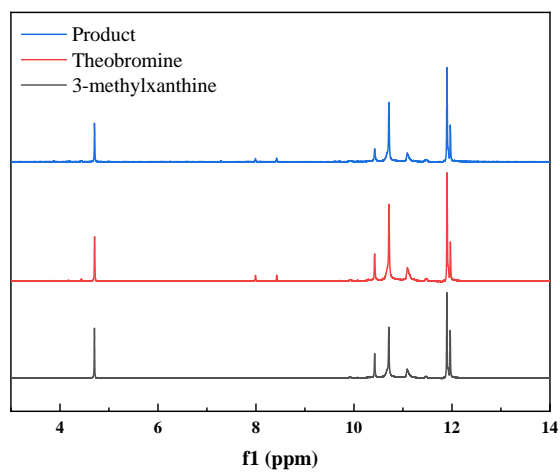


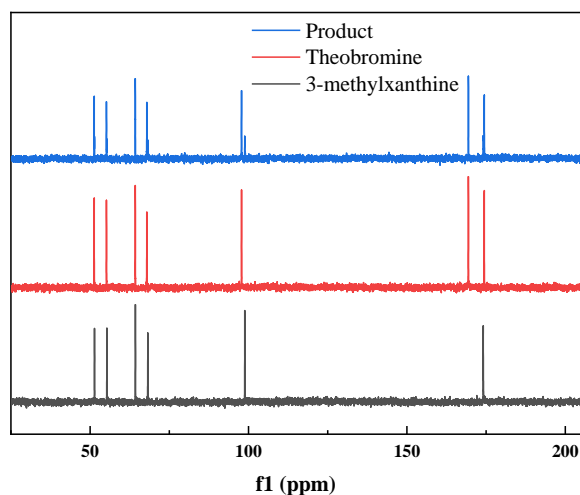
Figure S2 LC-MS diagram of pure theobromine



**Figure S3** LC-MS diagram of Product mixture



**Figure S4** <sup>1</sup>H NMR spectra of 3-methylxanthine, theobromine and product



**Figure S5**  $^{13}\text{C}$  NMR spectra of 3-methylxanthine, theobromine and product

**Table S1** Effect of the ratio of mixed solvent water/DMF on methylation of 3-methylxanthine with DMC (Reaction conditions: 3-methylxanthine (2 g),  $\text{H}_2\text{O}$ , 9 h,  $160\text{ }^\circ\text{C}$ ,  $n(\text{DMC}):n(3\text{-methylxanthine}) = 5.5:1$ )

No.	Solvent (mL)		3-methylxanthine conversion (%)	selectivity (%)	
	$\text{H}_2\text{O}$	DMF		Theobromine	Caffeine
1	10	0	59.4	96.3	1.1
2	9	1	64.0	93.9	3.3
3	8	2	76.8	91.7	5.9
4	7	3	78.5	88.1	9.8
5	6	4	86.6	85.0	12.4
6	5	5	90.4	80.9	16.5

**Table S2** Effect of reactant molar ratios on methylation of 3-methylxanthine with DMC. Reaction conditions: 3-methylxanthine (1 g),  $\text{H}_2\text{O}$  (10 mL), 9 h,  $160\text{ }^\circ\text{C}$

No.	$n(\text{DMC}):n(3\text{-methylxanthine})$	Initial pressure (MPa)	Residual pressure <sup>a</sup> (MPa)	3-methylxanthine conversion (%)	Theobromine selectivity (%)
1	5	0	0.9	60.3	96.8
2	8	0	1.4	82.1	97.4
3	11	0	1.8	89.9	98.2
4	14	0	2	89.7	98.3
5	17	0	2.1	89.9	98.7
6	20	0	2.1	89.8	98.1

**Table S3 Bond Energy Summary**

Bond Energy Summary					
Solvents	delta G (kcal/mol)			C-O bond energy (KJ/mol)	
	DMC	Methyl	Remaining group		
DMF	-343.50501	-39.799655	-303.57592		339.98
DMSO	-343.504256	-39.799029	-303.575599		340.49
H <sub>2</sub> O	-343.502763	-39.79789	-303.569785		354.83
MeOH	-343.503842	-39.799893	-303.568708		355.23
EG	-343.498538	-39.79765	-303.563663		360.44

Solvents	delta G (kcal/mol)				N <sup>1</sup> -H bond energy (KJ/mol)	N <sup>7</sup> -H bond energy (KJ/mol)
	3-methylxanthine	H	None H of N <sup>1</sup> group	None H of N <sup>7</sup> group		
DMF	-601.564018	-0.494167	-600.895491	-600.918702	457.99	397.02
DMSO	-601.564075	-0.49395	-600.89442	-600.917462	461.52	400.99
H <sub>2</sub> O	-601.559131	-0.492566	-600.895648	-600.914961	448.94	398.21
MeOH	-601.561068	-0.494485	-600.894067	-600.913431	453.14	402.28
EG	-601.553235	-0.493818	-600.886802	-600.906013	453.40	402.94