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Diastereoselective synthesis of benzo[*d*]chromeno[3′,4′:3,4]pyrrolo[2,1-*b*]thiazoles *via* cycloaddition reaction of benzothiazolium salts with 3-nitrochromenes†

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The triethylamine mediated 1,3-dipolar cycloaddition reaction of 2-phenacyl- or 2-alkoxycarbonylmethylbenzothiazolium bromides with 3-nitrochromenes in ethanol at room temperature afforded functionalized tetrahydrobenzo[*d*]chromeno[3′,4′:3,4]pyrrolo[2,1-*b*]thiazoles in 83–95% yields and with high diastereoselectivity. The corresponding dehydrogenated benzo[*d*]chromeno[3′,4′:3,4]pyrrolo[2,1-*b*]thiazoles were also easily obtained by sequential oxidation with DDQ. The stereochemistry of the polycyclic compounds was clearly elucidated by analysis of NMR spectroscopy results and determination of single crystal X-ray structures. The reaction is believed to proceed *via endo*-[3 + 2] cycloaddition of the *in situ* generated anti-form ylides to the cyclic dipolarophiles.

Introduction

Chromane (benzopyran) is one of the most important oxygen-containing heterocycles. Its derivatives are not only widespread in many natural products, but also are known as the biological compounds which exhibit a wide range of biological properties such as anticancer, diuretic, anticoagulant, and anti-anaphylactic activity.[1,2] For examples, benzopyranopyrrolidine derivatives are antagonistic towards 5-HT2C receptors and adrenoreceptor antagonists.[3] Many chromane derivatives are also natural lipophilic antioxidants and radical scavengers in the vitamin E family.[4] Therefore, continuous efforts have been devoted to the development of more efficient synthetic methodologies for this class of compound.[5–8] Over the last few decades, heteroaromatic *N*-ylides have been drawing the attention of chemists due to their wide spectrum of utilities in numerous chemical transformations.[9] The cycloaddition of the heteroaromatic *N*-ylides to various dipolarophiles showed very interesting chemical, regio- and stereo-selectivity, from which indolizine, cyclopropane, dihydrofuran and zwitterionic derivatives as well as other polycyclic systems can be selectively obtained by adjusting molecular structures of the substrates and the reaction conditions.[10] Particularly, the 1,3-dipolar cycloaddition reaction of the heteroaromatic *N*-ylides with nitroolefins have been widely investigated in the literature.[11] On this respect, the well-known conjugated 3-nitrochromenes, which could be derived from the condensation reaction of substituted salicylaldehyde with nitroolefins, were also widely employed as Michael acceptors and dipolarophiles in various reactions.[12,13] Recently, we have successfully found that *N*-phenacylisoquinolinium salts reacted with 3-nitrochromenes in basic system to give complex tetrahydro-6*H*-5-oxa-12*a*-azadibenzo[*a*,*g*]fluorene derivatives.[14] Against this background and in continuation of our aim to exploit the versatile synthetic applications of the heteroaromatic *N*-ylides for diverse heterocyclic compounds,[15,16] herein we wish to report the base promoted 1,3-dipolar cycloaddition reaction of various benzothiazolium salts with 3-nitrochromenes for diastereoselective synthesis of tetrahydrobenzo[*d*]chromeno[3′,4′:3,4]pyrrolo[2,1-*b*]thiazole and their aromatic derivatives.

Results and discussions

According to the previously reported reaction conditions of the various heteroaromatic *N*-ylides with nitroalkenes,[11] a mixture of 3-phenacylbenzothiazolium bromide (**1**) with 3-nitrochromene (**2**) in ethanol in the presence of triethylamine was stirred at room temperature. TLC monitor indicated that the reaction proceeded smoothly in three hours. The resulting products were readily precipitated from solution. After filtration and washing with cold alcohol, the pure products were easily obtained from this very simple procedure. The other organic bases such as piperidine and DABCO were also effective for the

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† Electronic supplementary information (ESI) available: Crystallographic data **3a** (CCDC 1546830), **3e** (CCDC 1546831), **3n** (CCDC1546832), **3r** (CCDC 1546833), **4d** (CCDC 1546834), **5c** (CCDC 1546835), **5e** (CCDC 1546836), **5g** (CCDC 1546837), and **5h** (CCDC 1546838). CCDC 1546830–1546838. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7ra06548e

reaction. Because triethylamine is the most cheap and common organic base, thus, it is employed as the base for this reaction. The results are summarized in Table 1. It can be seen that all reactions afforded the polycyclic products in satisfactory yields. The substituent on the aromatic ring showed very little effect on the yields. The structures of the products **3a–3t** were fully characterized by IR, HRMS, ^{1}H NMR and ^{13}C NMR spectra. There are five chiral carbon atoms in the polycyclic compounds, therefore, several diastereoisomers might be formed in the reaction. We were pleased to find that the ^{1}H NMR and ^{13}C NMR spectra of **3a–3t** clearly reveals one set of characterized absorptions for the groups and scaffolds in the molecules, which strongly indicated that only one diastereoisomer was predominately formed in this 1,3-dipolar cycloaddition reaction. In order to determine the relative configuration of the obtained products, four single crystal structures of the compounds **3a** (Fig. 1), **3e**, **3n** and **3r** (Fig. s1–s3†) were successfully determined by X-ray crystallographic method. The single crystals suitable for X-ray crystallographic analysis were usually obtained by slower evaporation the solution of the compounds in a mixed chloroform and ethanol. The four molecules actually have same configuration. Thus, it can be certainly conclude that all compounds **3a–3t** have this kind of configuration and this [3 + 2] cycloaddition reaction has very high diastereoselectivity. From the Fig. 1, it can be seen that the benzoyl group and the benzo-moiety of chromene exist in trans-position in the newly formed pyrrolidine ring. The nitro group

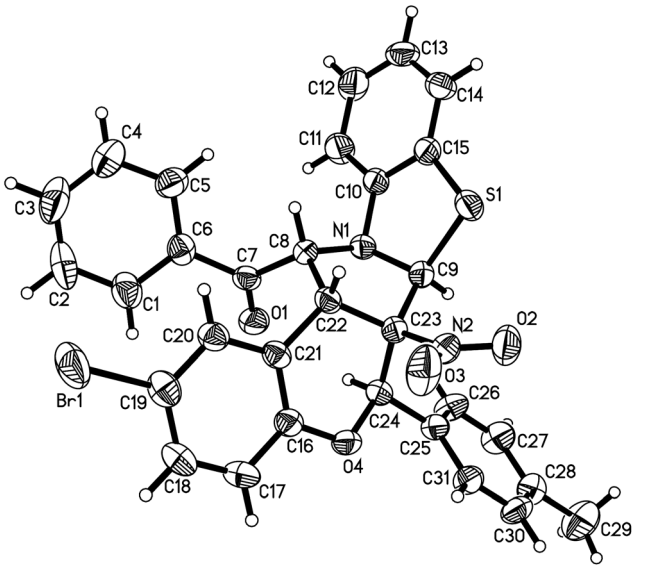
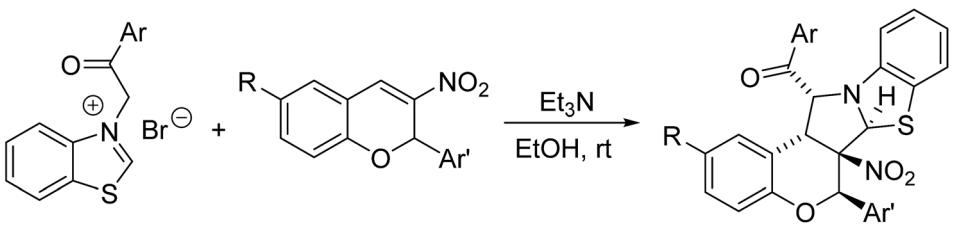


Fig. 1 ORTEP-drawing (50% ellipsoid probability) of the compound **3a**.

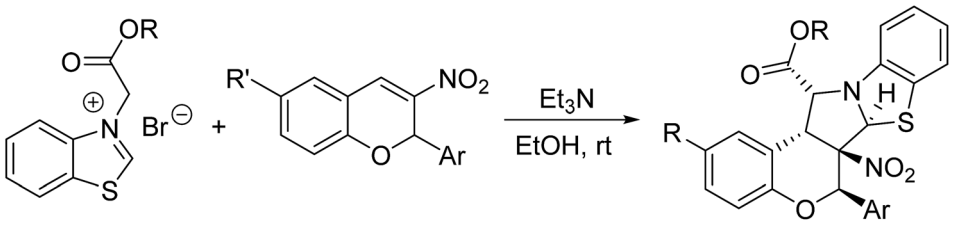
Table 1 Synthesis of benzo[*d*]chromeno[3′,4′:3,4]pyrrolo[2,1-*b*]thiazoles **3a–3t**[a]



Entry	Compd	Ar	R	Ar′	Yield[b] (%)
1	**3a**	C_6H_5	Br	*p*-$CH_3C_6H_4$	87
2	**3b**	*p*-$CH_3C_6H_4$	H	*p*-$CH_3C_6H_4$	89
3	**3c**	*p*-$CH_3C_6H_4$	H	*p*-$CH_3OC_6H_4$	91
4	**3d**	*p*-$CH_3C_6H_4$	Cl	*p*-$CH_3C_6H_4$	91
5	**3e**	*p*-$CH_3C_6H_4$	Br	*p*-$CH_3C_6H_4$	89
6	**3f**	*p*-$CH_3OC_6H_4$	H	C_6H_5	91
7	**3g**	*p*-$CH_3OC_6H_4$	H	*p*-$CH_3C_6H_4$	87
8	**3h**	*p*-$CH_3OC_6H_4$	H	*p*-$CH_3OC_6H_4$	88
9	**3i**	*p*-$CH_3OC_6H_4$	H	*p*-ClC_6H_4	93
10	**3j**	*p*-$CH_3OC_6H_4$	Cl	C_6H_5	86
11	**3k**	*p*-$CH_3OC_6H_4$	Cl	*p*-$CH_3C_6H_4$	89
12	**3l**	*p*-$CH_3OC_6H_4$	Cl	*p*-$CH_3OC_6H_4$	86
13	**3m**	*p*-$CH_3OC_6H_4$	Cl	*p*-ClC_6H_4	89
14	**3n**	*p*-$CH_3OC_6H_4$	Br	C_6H_5	83
15	**3o**	*p*-$CH_3OC_6H_4$	Br	*p*-$CH_3C_6H_4$	88
16	**3p**	*p*-$CH_3OC_6H_4$	Br	*p*-$CH_3OC_6H_4$	92
17	**3q**	*p*-$CH_3OC_6H_4$	Br	*p*-ClC_6H_4	86
18	**3r**	*p*-ClC_6H_4	Br	*p*-$CH_3C_6H_4$	95
19	**3s**	*p*-$NO_2C_6H_4$	H	*p*-ClC_6H_4	87
20	**3t**	*p*-$NO_2C_6H_4$	Br	*p*-$CH_3C_6H_4$	83

[a] Reaction condition: benzothiazolium bromide (1.0 mmol), 3-nitrochromene (1.0 mmol), Et_3N (1.2 mmol), EtOH (10.0 mL), rt, 3 h. [b] Isolated yield.

Table 2 Synthesis of benzo[*d*]chromeno[3′,4′:3,4]pyrrolo[2,1-*b*]thiazoles **4a–4d**[a]



Entry	Compd	R′	Ar	R	Yield[b] (%)
1	**4a**	Br	*p*-$CH_3C_6H_4$	Me	72
2	**4b**	Br	*m*-$CH_3OC_6H_4$	Me	69
3	**4c**	Br	C_6H_5	Et	76
4	**4d**	Cl	*p*-ClC_6H_4	Et	72

[a] Reaction condition: benzothiazolium bromide (1.0 mmol), 3-nitrochromene (1.0 mmol), Et_3N (1.2 mmol), EtOH (10.0 mL), rt, 12 h. [b] Isolated yield.

and phenylsulfanyl group stand on the trans-position in the newly formed pyrrolidine ring. Additionally, the aryl group at C1-position of the moiety of chromene also exists in a *cis* relationship with the NO_2 group. On the other hand, the benzopyran and benzothiazole rings are found on the opposite faces of the central pyrrolidine ring. Thus, the 1,3-dipolar cycloaddition reaction proceeded in a highly diastereoselective fashion. According to the stereochemical precedent established by Tsuge and co-workers,[11] the heteroaromatic ylide usually adopted the anti-form configuration to proceed with the *endo*-addition type in [3 + 2] cycloaddition reaction. In accord with the stereochemical precedent established by Tsuge and co-workers,[11] the products are formed *via* a single regioisomeric endo transitions state involving the anti-form of the ylide.

For developing the scope of this reaction, 2-alkoxycarbonylmethylbenzothiazolium bromides were also employed in the reaction. However, the reactivity of the corresponding 2-alkoxycarbonylmethylbenzothiazolium bromides is obviously lower than the above mentioned 2-phenacylbenzothiazolium bromides. The reaction of the benzothiazolium bromides bearing methoxy and ethoxy groups with 3-nitrochromenes could be finished overnight at room temperature to give the expected benzo[*d*]chromeno[3′,4′:3,4]pyrrolo[2,1-*b*]thiazoles **4a–4d** in moderated yields (Table 2). The reaction of 2-(*tert*-butoxycarbonylmethyl) benzothiazolium bromides with 3-nitrochromenes cannot afforded the desired products both at room temperature and in refluxing ethanol, which might be the steric effect of the *t*-butyl ester group on the energy of the cycloaddition transition state. The structures of the polycyclic products **4a–4d** were established by the spectroscopic analyses. The crystal structure of the compound **4d** was successfully determined by X-ray diffraction (Fig. 2). We were pleased to find that the compound **4d** has same configuration to that of the above mentioned compounds **3a–3t**, in which the benzoyl group is just replaced by the ethoxycarbonyl group. This result also revealed that the 1,3-dipolar cycloaddition of the base promoted benzothiazolium ylides with 3-nitrochromenes has same controlling effect on the stereochemistry.

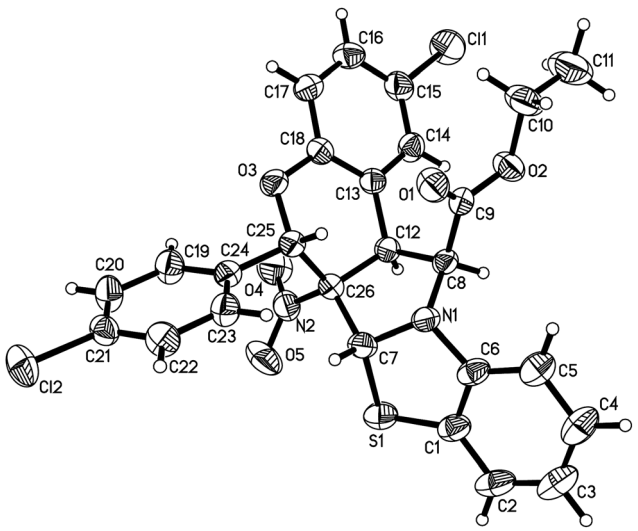
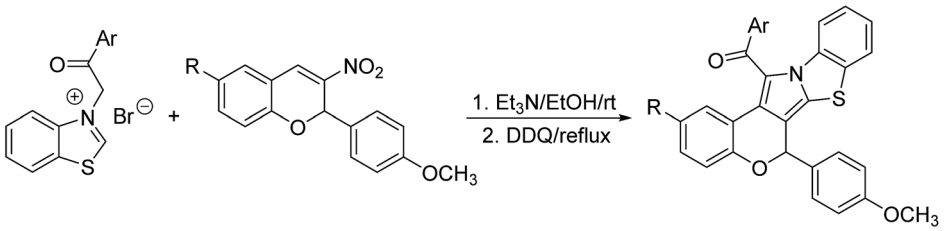


Fig. 2 ORTEP-drawing (50% ellipsoid probability) of the compound **4d**.

For developing the molecular diversity of the reaction, a dehydrogenation process was employed. After finishing the base promoted 1,3-dipolar cycloaddition reaction, an excess of DDQ was added and the reaction mixture was refluxed in ethanol for four hours. After workup, the aromatized benzo[*d*]chromeno[3′,4′:3,4]pyrrolo[2,1-*b*]thiazoles **5a–5i** were obtained in satisfactory yields by dehydrogenation and elimination of nitro group process (Table 3). Because the aromatic pyrrole ring was formed, there is only one stereogenic C2 carbon atom in the molecules **5a–5i**. The molecular structures of the compounds **5a–5i** were easily established by the spectroscopy. Additionally, four single crystal structures **5c** (Fig. 3), **5e**, **5g** and **5h** (Fig. s4–s6†) were successfully determined by X-ray crystallographic method. Therefore, the functionalized benzo[*d*]chromeno[3′,4′:3,4]pyrrolo[2,1-*b*]thiazoles were efficiently prepared by one-pot two-step 1,3-dipolar cycloaddition and oxidation procedure.

Table 3 Synthesis of benzo[*d*]chromeno[3′,4′:3,4]pyrrolo[2,1-*b*]thiazoles **5a–5i**[a]



Entry	Compd	R	Ar′	Yield[b] (%)
1	**5a**	H	C_6H_5	67
2	**5b**	Cl	C_6H_5	77
3	**5c**	Cl	*p*-$CH_3C_6H_4$	79
4	**5d**	Cl	*p*-$CH_3OC_6H_4$	83
5	**5e**	Cl	*p*-ClC_6H_4	81
6	**5f**	Br	C_6H_5	74
7	**5g**	Br	*p*-$CH_3C_6H_4$	75
8	**5h**	Br	*p*-$CH_3OC_6H_4$	81
9	**5i**	Br	*p*-ClC_6H_4	79

[a] Reaction condition: benzothiazolium bromide (1.0 mmol), 3-nitrochromene (1.0 mmol), Et_3N (1.0 mmol), EtOH (10.0 mL), rt, 3 h; DDQ (2.2 mmol), reflux, 4 h. [b] Isolated yield.

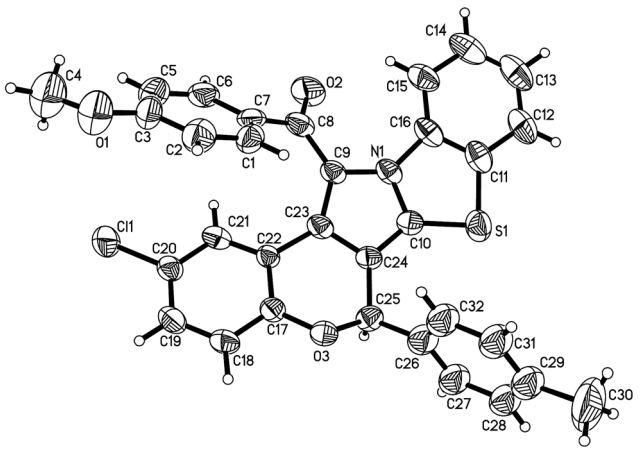


Fig. 3 ORTEP-drawing (50% ellipsoid probability) of the compound **5c**.

Conclusion

In summary, we have developed a base promoted 1,3-dipolar cycloaddition reaction of benzothiazolium bromides with 3-nitrochromenes for the diastereoselective synthesis of tetrahydrobenzo[*d*]chromeno[3′,4′:3,4]pyrrolo[2,1-*b*]thiazoles in high yields. The corresponding benzo[*d*]chromeno[3′,4′:3,4]pyrrolo[2,1-*b*]thiazoles were also efficiently prepared by the one-pot sequential 1,3-dipolar cycloaddition and oxidation procedure. The reaction has the advantages of readily available starting material, mild reaction conditions, operational simplicity, diastereoselectivity and molecular diversity. This reaction not only provided efficient synthetic method for complex polycyclic compounds containing N, O, S heteroatoms, but also developed potential applications of the heteroaromatic *N*-ylides in synthetic and medicinal chemistry. Further expansions of this methodology for the preparation of complex nitrogen-containing heterocycles are in progress in our laboratory.

Experimental section

General procedure for the preparing the compounds 3a–3t and 4a–4d

A mixture of 2-phenacylbenzothiazolium bromide (1.0 mmol) and 3-nitrochromene (1.0 mmol) and triethylamine (1.2 mmol) in ethanol (10.0 mL) was stirred at room temperature for three hours. The resulting precipitates were collected by filtration and washed with cold alcohol to give the pure product for analysis. The same procedure was used for preparation of compounds **4a–4d** excepting prolonging the reaction time to twelve hours.

(2-Bbromo-6*a*-nitro-6-(*p*-tolyl)-6*a*,6*b*,13,13*a*-tetrahydro-6*H*-benzo[*d*]chromeno[3′,4′:3,4]-pyrrolo[2,1-*b*]thiazol-13-yl)(phenyl) methanone (3a). Yellow solid, 87%, mp 197–199 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.88 (d, J = 7.6 Hz, 2H, ArH), 7.71–7.67 (m, 1H, ArH), 7.55–7.52 (m, 2H, ArH), 7.36–7.34 (m, 1H, ArH), 7.29–7.25 (m, 5H, ArH), 7.17 (dd, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 1H, ArH), 7.06–7.01 (m, 2H, ArH), 6.83 (d, J = 8.8 Hz, 1H, ArH), 6.66–6.64 (m, 1H, ArH), 6.24 (s, 1H, CH), 6.22 (s, 1H, CH), 6.07 (d, J = 10.8 Hz, 1H, CH), 5.26 (d, J = 10.8 Hz, 1H, CH), 2.35 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 199.3, 152.2, 149.2, 139.7, 137.1, 134.8, 133.1, 131.7, 130.9, 130.8, 129.6, 129.3, 128.9, 127.7, 126.6, 125.7, 122.4, 120.8, 119.0, 116.3, 113.3, 96.6, 77.4, 77.2, 71.8, 44.3, 21.2; MS (*m*/*z*): HRMS (ESI) calc. for $C_{31}H_{24}BrN_2O_4S$ ($[M + H]^+$): 599.0635. Found: 599.0620; IR (KBr) ν: 3057, 3016, 2914, 1692, 1540, 1472, 1452, 1316, 1227, 1175, 1127, 920, 858, 839, 753, 700 cm^{-1}.

General procedure for the preparing the compounds 5a–5i

A mixture of 2-phenacylbenzothiazolium bromide (1.0 mmol) and 3-nitrochromene (1.0 mmol) and triethylamine (2.0 mmol) in ethanol (10.0 mL) was stirred at room temperature for three hours. Then, DDQ (2.2 mmol) was added. The mixture was heated to refluxing in ethanol for four hours. After cooling, the resulting precipitates were collected by filtration and washed with cold alcohol to give the pure product for analysis.

(4-Methoxyphenyl)(6-phenyl-6*H*-benzo[*d*]chromeno[3′,4′:3,4]pyrrolo[2,1-*b*]thiazol-13-yl)methanone (5a). Yellow solid, 67%, mp 235–236 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.01–7.99 (m, 2H, ArH), 7.74 (d, J = 8.0 Hz, 1H, ArH), 7.65–7.62 (m, 2H, ArH), 7.53–7.50 (m, 3H, ArH), 7.43–7.41 (m, 1H, ArH), 7.24–7.15 (m, 2H, ArH), 7.08–7.01 (m, 2H, ArH), 6.97–6.95 (m, 1H, ArH), 6.88 (d, J = 7.6 Hz, 2H, ArH), 6.66–6.61 (m, 1H, ArH), 6.12 (s, 1H, CH), 3.84 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 186.2, 164.3, 154.2, 138.1, 134.0, 132.7, 130.9, 130.8, 129.6, 129.2, 129.1, 128.4, 126.5, 126.4, 125.1, 124.9, 124.7, 122.1, 122.1, 122.1, 120.5, 119.6, 118.3, 114.9, 111.3, 75.7, 56.0; MS (m/z): HRMS (ESI) calcd for $C_{31}H_{21}NO_3S$ ($[M + H]^+$): 488.1320. Found: 488.0436; IR (KBr) ν: 3064, 2962, 2876, 1622, 1561, 1501, 1455, 1383, 1293, 1251, 1212, 1025, 915, 827, 746 cm^{-1}.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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