Monatsh Chem
DOI 10.1007/s00706-017-1944-6

ORIGINAL PAPER

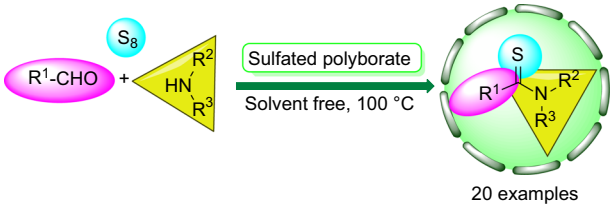
Sulfated polyborate catalyzed Kindler reaction: a rapid, efficient, and green protocol

Chetan K. Khatri[1] · Anil S. Mali[1] · Ganesh U. Chaturbhuj[1]

Received: 16 January 2017 / Accepted: 19 February 2017

Abstract A rapid, green, and efficient one-pot, three-component Kindler reaction was developed using a sulfated polyborate catalyst. The method described the reaction of aldehydes, amines/ammonium acetate, and sulfur for the synthesis of thioamides using sulfated polyborate under a solvent free condition at 100 °C. The key features of the present protocol are high yields, short reaction time, easy workup, and recyclability of a catalyst which gives economical as well as ecological rewards. The present method also has an ability to tolerate a variety of functional groups.

Graphical abstract



Keywords Sulfated polyborate · Kindler reaction · Thioamides · Solvent free · Recyclable catalyst

Electronic supplementary material The online version of this article (doi:10.1007/s00706-017-1944-6) contains supplementary material, which is available to authorized users.

✉ Ganesh U. Chaturbhuj
gu.chaturbhuj@gmail.com

[1] Department of Pharmaceutical Sciences and Technology, Institute of Chemical Technology, Mumbai, Maharashtra, India

Introduction

A multicomponent condensation reaction of aldehydes, amines, and sulfur for the synthesis of thioamides was reported by Kindler [1]. Thioamides are the most widely used functional groups in the synthesis of sulfur-containing molecules, including heterocycles, natural products, and biologically active compounds [2–4]. Thioamides are an important class of compounds with diverse pharmacological activities such as antifungal [5], antibacterial [6], antimycobacterial [7], antioxidant [8], anticonvulsant [9], antithyroid [10], spasmolytic [11], antiulcerative [12], anticancer [13], aldose reductase inhibitors [14], and inhibitor of estrogens receptors [15]. In addition, thioamides also have wide applications as intermediates in the synthesis of a variety of five and six membered heterocycles [16] and active pharmaceutical ingredients such as fatostatin [17], fenclosic acid [18], fentiazac [19], and febuxostate [20]. There are many thioamides containing drugs including ethionamide and prothionamide are used as anti-tubercular [21, 22], tolrestat is used to prevent diabetic complications [14], and the fimasartan is an antihypertensive agent [23] (Fig. 1).

There are a number of methods reported for the synthesis of thioamides including thionation of amides using reagents like P_4S_{10} [24], Lawesson's reagent [25], boron sulfide [26], ethylaluminum sulfide [27], and diethylthiocarbamoyl chloride [28]. These methods suffered from shortcomings like toxic, corrosive, explosive, and foul smelling reagents along with undesirable by-products and lower yields.

Classical three components Kindler reaction of aldehydes, amines, and sulfur, is widely applicable because of its high atom economy and with water as the by-product [1]. However, to the best our knowledge, only few

Published online: 18 May 2017

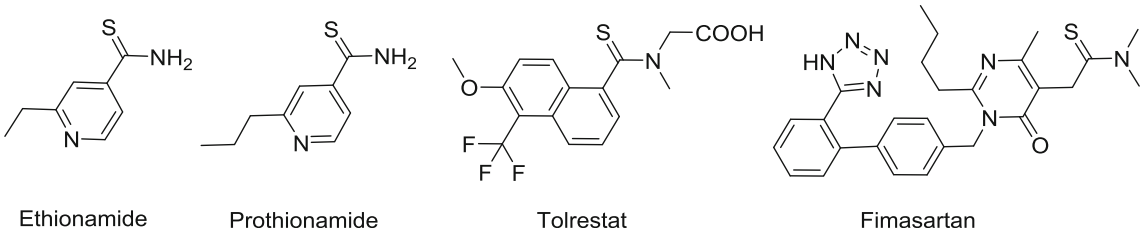


Fig. 1 Pharmaceutically active thioamide molecules

improvements have been reported for the Kindler reaction using various catalysts such as $Na_2S{\cdot}9H_2O$ [29], 4-methylmorpholine [30], montmorillonite K-10 [31], *p*-TSA [32], sulfated tungstate [33], nano *n*-propyl sulfonated γ-Fe_2O_3 [34], and sulfonic acid functionalized nano γ-Al_2O_3 [35]. Despite, these catalyst protocols also suffered from drawbacks of the use of expensive metallic catalysts, harsh reaction conditions, low yield, prolonged reaction time, and cumbersome product isolation. Hence, the exploration of a mild, efficient, and eco-friendly protocol for the synthesis of thioamides is highly desirable.

In the perpetuation green, convenient, and practical catalytic methods for the current interest in organic synthesis and commercial process; recently we have introduced sulfated polyborate catalyst and demonstrated its efficiency for catalyzing the three-component Biginelli reaction [36], Kabachnik–Fields reaction [37], two-component quinoxalines [38], and Hantzsch 1,4-dihydropyridines [39], all under solvent-free condition. Its mild acidity, easy preparation, eco-friendliness, and reusability have encouraged us to investigate its potential to catalyze many other useful organic transformations. Therefore, inspired by our previous finding, in this paper, we extended the application of sulfated polyborate as a highly effective catalyst for the synthesis of thioamides *via* Kindler reaction (Scheme 1).

Results and discussion

For initial screening, the study was structured to investigate the suitability of sulfated polyborate as a catalyst at different reaction conditions. For the preliminary experiment, a mixture of benzaldehyde; a representative substrate, morpholine, and sulfur were used. The results are summarized in Table 1.

The effect of the catalyst loading on time and yields of the reaction was assessed. In the absence of a catalyst, the reaction proceeded at 100 °C but took longer reaction time with a poor yield (Table 1, entry 1). An increase in the catalyst loading increased the product yield with a significant reduction in the reaction time (Table 1, entries 2–5). The catalyst loading beyond 10 wt% was not advantageous (Table 1, entries 5 and 6). Hence, a 10 wt% catalyst loading was chosen for further study.

Temperature played an important role for the synthesis thioamides. The temperature effect was examined at ambient, 50, 80, and 100 °C using sulfated polyborate (Table 1, entries 5 and 7–9). The reaction did not proceed at room temperature (Table 1, entry 7). An increase in the temperature to 100 °C resulted in significantly increased product yield in shorter reaction time (Table 1, entries 5, 8, and 9). Therefore, 100 °C was chosen as optimum temperature for the reaction.

The effect of various solvents on time and yield of the reaction was ascertained (Table 1, entries 5 and 10–15). None of the solvents have shown an advantage over solvent free condition. Hence, the solvent free condition was regarded as best for the cost and environmental acceptability.

There are only a few catalysts reported for the synthesis of thioamides via Kindler reaction of benzaldehyde, morpholine, and sulfur. Herein, in comparison with other catalysts, sulfated polyborate catalyst showed an advantage

Scheme 1

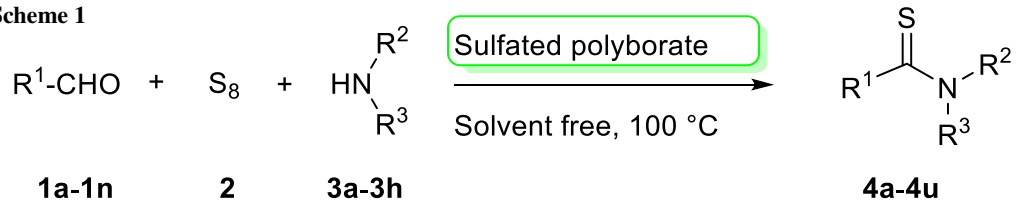


Table 1 Results of optimization studies

Entry	Catalyst/wt%	Solvent	Temperature/°C	Time/h	Yield[a]/%
1	0	Solvent free	100	12	24
2	2.5	Solvent free	100	1	56
3	5.0	Solvent free	100	1	86
4	7.5	Solvent free	100	1	90
5	10.0	Solvent free	100	1	97
6	15.0	Solvent free	100	1	97
7	10.0	Solvent free	rt	6	NR[b]
8	10.0	Solvent free	50	6	54
9	10.0	Solvent free	80	6	83
10	10.0	EtOH	Reflux	2	63
11	10.0	MeCN	Reflux	2	41
12	10.0	THF	Reflux	2	44
13	10.0	Water	Reflux	2	36
14	10.0	Toluene	Reflux	2	53
15	10.0	DMF	100	2	56

[a] Isolated yield

[b] No reaction

Table 2 Efficiency of sulfated polyborate in comparison with literature reported catalysts for the Kindler reaction

Entry	Catalyst	Condition	Time/h	Yield[a]/%	References
1	Sulfated polyborate	Solvent free/100 °C	1	97	This work
2	Polyboric acid	Solvent free/100 °C	2	96	This work
3	Boric acid	Solvent free/100 °C	3	92	This work
4	*p*-Toluenesulfonic acid	Solvent free/130 °C	3	98	[32]
5	Sulfonic acid functionalized nano γ-Al_2O_3	DMF/100 °C	5	93	[35]
6	Sulfated tungstate	DMF/110 °C	8	89	[33]

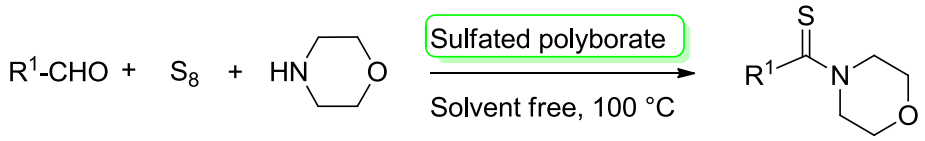
[a] Isolated yield

with respect to reaction conditions, workup procedure, time and yields (Table 2, entries 1–6).

To study the generality and scope, optimized reaction conditions were applied to various aromatic/aliphatic aldehydes and amines. All the substrate variants reacted well and afforded higher yields of thioamides in shorter reaction time (Tables 3, 4). Various electron donating or electron withdrawing substituents at the *ortho* and *para* position of aromatic aldehydes have been examined (Table 3, entries 2–11). In comparison with *para*, the *ortho* substituted aromatic aldehydes took longer reaction time may be due to steric hindrance, hence the nature of substitutions on aromatic aldehydes have a remarkable effect on the reaction time with good yields. However, electron withdrawing groups did not show a significant effect but the nitro group took less time than others. Whereas electron donating groups also showed similar behavior, but surprisingly less reaction time was observed with hydroxy group presumably due to acidic nature of phenolic OH. The protocol is also extended to heterocyclic and alicyclic aldehyde variants to get the corresponding thioamides in shorter reaction time with good yield (Table 3, entries 12–14).

On the other side, the applicability of this protocol on aromatic and aliphatic amines was also examined using butylamine, benzylamine, aniline, dibenzylamine, piperidine, pyrrolidine, and ammonium acetate variants. All the amine variants were reacted well and afforded good yields of the corresponding thioamides in shorter reaction time (Table 4, entries 1–7) except aniline (Table 4, entry 3). However, piperidine and pyrrolidine variants took lesser time than others. Whereas aniline variant did not react and showed traces of desired product on TLC.

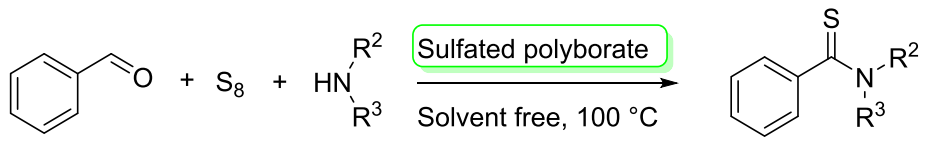
Table 3 Synthesis of thioamides using a variety of aldehydes



Entry	Aldehydes/R^1	Product	Time/h	Yield[a]/%	Melting point/°C	
					Obs	Literature
1	C_6H_5	**4a**	1	97	136–137	137–139 [40]
2	4-O_2N-C_6H_4	**4b**	0.5	93	190–192	194–195 [41]
3	4-Br-C_6H_4	**4c**	2	96	134–135	135–137 [42]
4	4-Cl-C_6H_4	**4d**	2	94	138–139	138–140 [40]
5	4-F-C_6H_4	**4e**	2	96	91–92	93–96 [32]
6	4-CH_3-C_6H_4	**4f**	2	94	124–125	126–128 [40]
7	4-CH_3O-C_6H_4	**4g**	4	95	98–99	100–101 [43]
8	4-HO-C_6H_4	**4h**	0.5	95	206–207	204–205 [44]
9	2-Cl-C_6H_4	**4i**	4	90	114–115	115–116 [45]
10	2-CH_3O-C_6H_4	**4j**	4	92	78–79	80–82 [46]
11	2-HO-C_6H_4	**4k**	0.75	94	168–169	167–168 [47]
12	4-Pyridine-carboxaldehyde	**4l**	1	91	150–151	151 [48]
13	5-Methylfurfural	**4m**	1	93	62–63	–
14	Cyclohexane-carboxaldehyde	**4n**	1	92	122–123	124–125 [42]

[a] Isolated yields

Table 4 Synthesis of thioamides using various amines



Entry	Amines		Product	Time/h	Yield[a]/%	Melting point/°C	
	R^2	R^3				Obs	Literature
1	C_4H_9	H	**4o**	2	88	Liq	–
2	$C_6H_5CH_2$	H	**4p**	4	87	76–77	77–78 [49]
3	C_6H_5	H	**4q**	6	Traces	–	97–98 [33]
4	$C_6H_5CH_2$	$C_6H_5CH_2$	**4r**	4	89	95–97	NR
5	–$(CH_2)_5$–		**4s**	0.5	96	59–60	60–61 [35]
6	–$(CH_2)_4$–		**4t**	0.5	95	73–74	72–74 [50]
7	H	H	**4u**	6	77	111–112	113–115 [35]

[a] Isolated yields. Ammonium acetate used as an ammonia source

The reusability of the catalyst in the model reaction of benzaldehyde, morpholine, and sulfur under solvent-free conditions at 100 °C was evaluated. After completion of each reaction cycle, the reaction mixture was cooled, quenched with water followed by product filtration. The filtrate was evaporated in vacuum rotary evaporator to recover the catalyst quantitatively. The recovered catalyst was recycled for four times with no significant loss in a catalytic activity (Fig. 2).

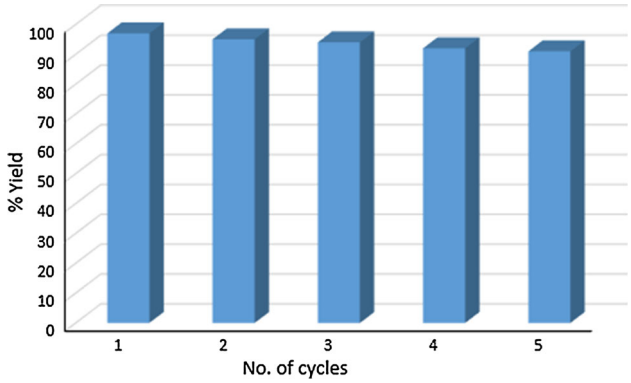


Fig. 2 Recyclability of the catalyst

Conclusion

In conclusion, the present procedure is a rapid, efficient, and eco-friendly protocol for the Kindler reaction of various aldehydes, amines, and sulfur under optimized conditions. High yields, shorter reaction time, mild reaction conditions, easy of workup procedure, and recyclability of the catalyst are the key features of this protocol. Moreover, the present method has the ability to tolerate a wide variety of substituents along with enhanced product purity which promises economical as well as ecological rewards.

Experimental

Melting points of all the compounds were recorded by Analab ThermoCal melting point apparatus in the open capillary tube. The FT-IR spectra (KBr) were recorded on Shimadzu FTIR Affinity-1 Fourier Transform Infrared spectrophotometer. ^{1}H NMR spectra were recorded on MR400 Agilent Technology NMR spectrometer using tetramethylsilane (TMS) as an internal standard and DMSO-d_6 or $CDCl_3$ as a solvent. Chemicals and solvents used were of LR grade and purchased from SD fine, Avra Synthesis, and Spectrochem and used without purification. The purity determination of the starting materials and reaction monitoring was accomplished by thin layer chromatography (TLC) on Merck silica gel G F_{254} plates. The sulfated polyborate catalyst was prepared following the procedure reported in the literature [36].

General procedure for the Kindler reaction

To a mixture of an aldehyde (2 mmol), amine (2.4 mmol), and sulfur (2.4 mmol) was added sulfated polyborate (10 wt%). The mixture was heated at 100 °C in an oil bath. The reaction was monitored by thin layer chromatography. After completion of the reaction, the mixture was cooled to room temperature and quenched with 5 cm^3 water. Solid was filtered at vacuum pump, washed with water (3 × 5 cm^3), dried under vacuum to get the products in pure form or recrystallized from ethanol. The products obtained were known compounds and were identified by melting point, FT-IR, and ^{1}H NMR spectroscopy. The spectral data were compared with those in the literature.

Acknowledgements The authors are grateful to University Grants Commission, New Delhi, India for their financial supports.

References

1. Kindler K (1923) Justus Liebigs Ann Chem 431:187
2. Suzuki Y, Iwata M, Yazaki R, Kumagai N, Shibasaki M (2012) J Org Chem 77:4496
3. Murai T, Hori F, Maruyama T (2011) Org Lett 13:1718
4. Gopinath P, Watanabe T, Shibasaki M (2012) J Org Chem 77:9260
5. Shekarchi M, Pirali-Hamedani M, Navidpour L, Adib N, Shafiee A (2008) J Iran Chem Soc 5:150
6. Nadeem S, Bolte M, Ahmad S, Fazeelat T, Tirmizi SA, Ahmed S, Rauf MK, Sattar SA, Siddiq S, Hameed A, Haider SZ Fazeelat T, Tirmizi SA, Ahmed S, Rauf MK, Sattar SA, Siddiq S, Hameed A, Haider SZ (2010) Inorg Chim Acta 363:3261
7. Kuneš J, Balšánek V, Pour M, Waisser K, Kaustová J (2002) Farm 57:777
8. Chernovyants MS, Aleshina NV (2012) J Anal Chem 67:214
9. Kulandasamy R, Adhikari AV, Stables JP (2010) Bull Korean Chem Soc 31:3318
10. Chernov'yants MS, Dolinkin AO (2010) J Struct Chem 51:1176
11. Brunhofer G, Studenik C, Ecker GF, Erker T (2011) Eur J Pharm Sci 42:37
12. Gibinski K (1981) Curr Med Res Opin 7:516
13. Hu W-P, Yu H-S, Chen Y-R, Tsai Y-M, Chen Y-K, Liao C-C, Chang S-N, Wang J-J (2008) Bioorg Med Chem 16:5295
14. Showalter HDH, Johnson JL, Werbel LM, Leopold WR, Jackson RC, Elslager EF (1984) J Med Chem 27:255
15. Stauffer SR, Coletta CJ, Tedesco R, Nishiguchi G, Carlson K, Sun J, Katzenellenbogen SB, Katzenellenbogen JA (2000) J Med Chem 43:4934
16. Hisano T, Yabuta Y (1973) Chem Pharm Bull 21:511
17. Kamisuki S, Mao Q, Abu-Elheiga L, Gu Z, Kugimiya A, Kwon Y, Choo HYP (2009) Chem Biol 16:882
18. Martin S, Lenz EM, Keene W, Clench MR (2014) Anal Chem 86:11281
19. Brown K, Cater DP, Cavalla JF, Green D, Newberry RA, Wilson AB (1974) J Med Chem 17:1177
20. Becker MA, Kisicki J, Khosravan R, Wu J, Mulford D, Hunt B, Joseph-Ridge N (2004) Nucleotides Nucleic Acids 23:1111
21. Quemard A, Laneelle G, Lacave C (1992) Antimicrob Agents Chemother 36:1316
22. Wang F, Langley R, Gulten G, Dover LG, Besra GS, Jacobs WR, Sacchettini JC (2007) J Exp Med 204:73
23. DeMello WC, Re RN (2009) Renin angiotensin system and cardiovascular disease. Springer, New York, p 1
24. Raucher S, Klein P (1981) J Org Chem 46:3558
25. Cava MP, Levinson MI (1985) Tetrahedron 41:5061
26. Wojtkowski PW, Dolfini JE, Kocy O, Cimarusti CM (1975) J Am Chem Soc 97:5628
27. Hirabayashi T, Inoune K, Yokota K, Ishii Y (1975) J Organomet Chem 92:139

28. Ogata M, Matsumoto H (1978) Heterocycles 11:139
29. Okamoto K, Yamamoto T, Kanbara T (2007) Synlett 2687
30. Poupaert JH, Duarte S, Colacino E, Dover LG, Besra GS, Jacobs WR, Sacchettini JC (2004) Phosphorus. Sulfur Silicon Relat Elem 179:1959
31. Agnimonhan FH, Ahoussi L, Kpoviessi SDS, Gbaguidi FA, Kapanda CN, Moudachirou M, Accrombessi GC (2014) Int J Biol Chem Sci 8:386
32. Kul'ganek VV, Yanovskaya LA (1979) Bull Acad Sci USSR Div Chem Sci 28:2402
33. Pathare SP, Chaudhari PS, Akamanchi KG (2012) Appl Catal A Gen 425–426:125
34. Yin Z, Zheng B (2013) J Sulfur Chem 34:527
35. Yin Z, Zheng B, Ai F (2013) Phosphorus. Sulfur Silicon Relat Elem 188:1412
36. Khatri CK, Rekunge DS, Chaturbhuj GU (2016) New J Chem 40:10412
37. Khatri CK, Satalkar VB, Chaturbhuj GU (2017) Tetrahedron Lett 58:694
38. Indalkar KS, Khatri CK, Chaturbhuj GU (2017) J Chem Sci 129:141
39. Rekunge DS, Khatri CK, Chaturbhuj GU (2017) Tetrahedron Lett 58:1240
40. Matloubi Moghaddam F, Hojabri L, Dohendou M (2003) Synth Commun 33:4279
41. Okuma K, Komiya Y, Ohta H (1988) Chem Lett 17:1145
42. Otten PA, Van der Gen A (2010) Recl Trav Chim Pays Bas 113:499
43. Fazylov SD, Nurkenov OA, Akhmetkarimova ZS, Zhienbaeva DR (2012) Russ J Gen Chem 82:781
44. Gompper R, Schmidt RR (1965) Chem Ber 98:1385
45. Kuliev AB, Kurbanov MM, Mamedov AG, Kuliev FA (1985) J Appl Chem USSR 58:139
46. Chabrier P, Renard SH, Smarzewska K (1950) Bull Soc Chim Fr 17:1167
47. Shibuya I, Honda K, Gama Y, Shimizu M (2002) Heterocycles 57:429
48. Nguyen TB, Ermolenko L, Al-Mourabit A (2012) Org Lett 14:4274
49. Pace V, Castoldi L, Monticelli S, Safranek S, Roller A, Langer T, Holzer W (2015) Chem Eur J 21:18966
50. Smith DC, Lee SW, Fuchs PL (1994) J Org Chem 59:348