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Regioselective synthesis of polysubstituted 4*H*-thiopyrans from β-oxodithioesters

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ABSTRACT

A simple and efficient method for the synthesis of polyfunctionalized 4*H*-thiopyrans by highly regioselective cyclocondensation of β-oxodithioesters with 1,1,3-trialkyl or aryl substituted prop-2-yn-1-ols using $BF_3{\cdot}Et_2O$ as the catalyst is described.

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Among the sulfur containing heterocycles, thiopyran structure has high significance as a versatile scaffold for the synthesis of certain natural and unnatural products.[1] In the literature, however, only a few methods exist for the construction of 4*H*-thiopyrans and the classical approach is the Diels–Alder reaction of thiabutadiene with an activated dienophile.[2] Some of the recent methods reported in the literature for the preparation of thiopyrans include Grubb's metathesis approach,[3] microwave assisted multicomponent reaction of α,β-unsaturated ketones with Lawesson's reagent and alkynes,[4] and condensation of β-oxodithioesters with an aldehyde and a nitrile under base catalysis.

In recent years, studies were extensively focused on the development of novel catalytic methods for carbon—sulfur bond formation reactions, particularly through addition of sulfur to alkenes and alkynes owing to the growing industrial importance of organosulfur compounds as reactive intermediates, pharmaceuticals, and agrochemicals.[5] In recent years, β-oxodithioesters have emerged as versatile building blocks for the construction of a variety of sulfur heterocycles such as thiophenes,[6] dihydro-4*H*-thiopyrans,[7] 2*H*-chromene-2-thiones,[8] tetrahydrothiochromen-5-ones,[9] and benzo[*a*]quinolizine-4-thiones[10] and in addition, they were also employed as reactive intermediates in the preparation of other heterocycles such as pyrazoles,[11] pyrroles,[12] indoles,[13] 4*H*-benzo[*f*]chromenes,[14] imidazo[1,2-*a*]pyridines,[15] dihydropyrimidinones[16] etc.

In our laboratory, we recently found that 1,1,3-trisubstituted prop-2-yn-1-ol readily undergoes dehydrative cyclocondensation reaction with phenols under Lewis acid catalysis producing polyfunctionalized chromenes in high yields.[17] In view of this, we studied the scope of similar cyclocondensation reaction of 1,1,3-trisubstituted prop-2-yn-1-ols with β-oxodithioesters and herein we report for the first time a new and efficient method for the preparation of polyfunctionalized 4*H*-thiopyrans in high yields (72–95%) by the regioselective cyclocondensation of β-oxodithioesters with a 1,1,3-trisubstituted prop-2-yn-1-ol in the presence of $BF_3{\cdot}Et_2O$ as the catalyst as shown in Scheme 1.

In our initial experiments, we studied the reaction of methyl 3-oxo-3-phenylpropanedithioate **1a** with 1,1,3-triphenylprop-2-yn-1-ol **2a** in dichloromethane using a variety of Lewis acid catalysts such as $BF_3{\cdot}Et_2O$, $Zn(OTf)_2$, $Bi(OTf)_3$, $Sc(OTf)_3$, $InBr_3$, $ZnCl_2$, $AlCl_3$, and $FeCl_3$ and also with Bronsted acids such as *p*-toluene sulfonic acid, and acetic acid. The results are shown in Table 1. In

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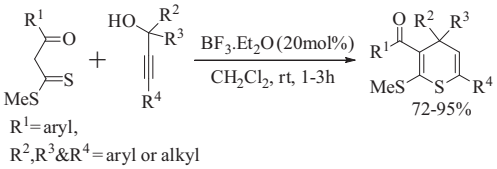
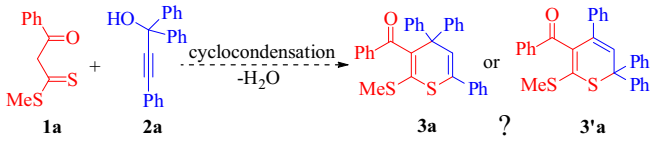


Scheme 1. Synthesis of polyfunctionalized 4*H*-thiopyrans.



Scheme 2. Structural isomers **3a** and **3′a**.

this study, we obtained the best results with $BF_3{\cdot}Et_2O$, which promoted the reaction of **1a** with **2a** in a very short reaction time (1 h) producing 2-(methylthio)-4,4,6-triphenyl-4*H*-thiopyran-3-yl)(phenyl)methanone **3a** in high yield (95%) when compared to other catalysts. In our study, the solvent was found to have profound influence on the reaction. For example, solvents such as toluene, methanol, tetrahydrofuran, and acetonitrile, promoted the reaction relatively slowly when compared to dichloromethane and they produced **3a** in 55%, 50%, 45%, and 20% yields, respectively, in 12 h.

In our study, the present cyclocondensation reaction of **1a** with **2a** was found to give exclusively one product. However, based on the NMR, IR, and Mass spectral data (refer Supplementary information file) obtained for the product we initially arrived at two possible structures **3a** and **3′a** as shown in Scheme 2. To rule out one of the structures, we obtained a crystal of the product suitable for X-ray crystallography and confirmed the structure of the product to be **3a**, that is, (2-(methylthio)-4,4,6-triphenyl-4 thiopyran-3-yl)(phenyl)methanone **3a** (R = R^1 = R^2 = R^3 = Ph). The ORTEP view of the single crystal X-ray analysis of **3a** with atomic numbering is shown in Figure 1.[18]

In this study, we prepared a variety of β-oxodithioesters **1a–d** by a base mediated reaction of corresponding acetophenone with dimethyltrithiocarbonate[19] and obtained 1,1,3-trisubstituted prop-2-yn-1-ols **2a–f** by reacting the corresponding lithium acetalide with a ketone.[20] Next, we studied reactions of **1a–d** with **2a–f** using $BF_3{\cdot}Et_2O$ as the catalyst in dichloromethane to obtain the corresponding polyfunctionalized 4*H*-thiopyrans **3a–t** in 72–95% yields as shown in Table 2.[21]

The plausible reaction pathway for the formation of **3** from the Lewis acid (LA) catalyzed reaction of **1** and **2** is shown in Scheme 3. In this mechanism, we believe that initially 3-oxodithiocarbonate **1** and propargyl alcohol **2** undergo Lewis acid assisted dehydration reaction followed by intramolecular cyclization of the resulting allenyl vinyl thioether and 3,5-*H* transfer to give a 4*H*-thiopyran **3**.

In summary, we showed a new and efficient method for the preparation of polyfunctionalized 4*H*-thiopyrans by highly regioselective two-component cyclocondensation of β-oxodithioesters and 1,1,3-trisubstituted prop-2-yn-1-ols using $BF_3{\cdot}Et_2O$ as the catalyst.

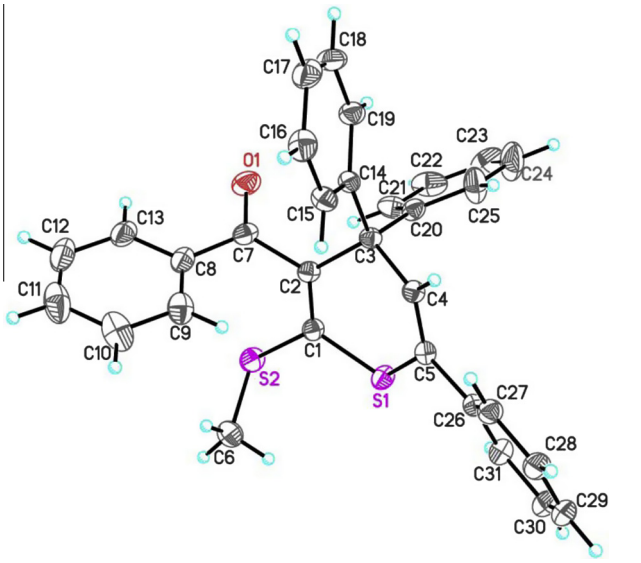


Figure 1. ORTEP diagram of **3a**. Displacement ellipsoids are drawn at the 25% probability level and H atoms are shown as small spheres of arbitrary radius. (CCDC 986964).

Acknowledgments

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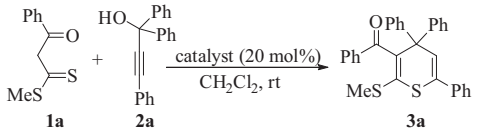
Supplementary data

Supplementary data (experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra of the compounds **3a–t**)

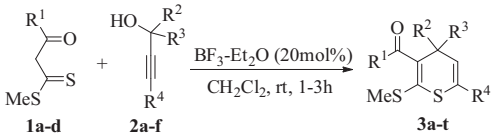
Table 1
Screening of acid catalysts for the preparation of **3a**



Entry	Catalyst	Time (h)	%Yield[a]	Entry	Catalyst	Time (h)	%Yield[a]
1	$BF_3{\cdot}OEt_2$	1	95	6	$ZnCl_2$	12	37
2	$Zn(OTf)_2$	12	60	7	$AlCl_3$	12	44
3	$Bi(OTf)_3$	12	47	8	$FeCl_3$	12	40
4	$Sc(OTf)_3$	12	64	9	PTSA	12	55
5	$InBr_3$	12	26	10	CH_3COOH	12	N.R.

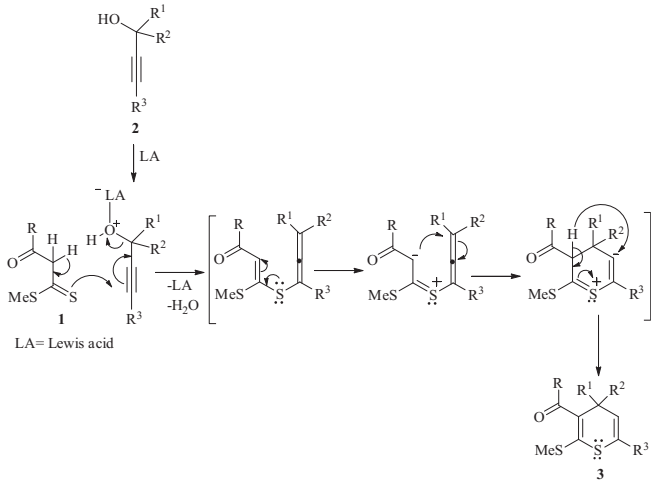
[a] Isolated yields.

Table 2
Synthesis of polyfunctionalized 4*H*-thiopyrans



Entry	R^1	R^2	R^3	R^4	%Yield[a] of **3**	Reaction time (h)	Mp (°C)
a	Ph	Ph	Ph	Ph	95	1.0	162–164
b	Ph	Ph	Me	Ph	83	2.0	135–137
c	Ph	4-ClPh	Me	Ph	79	1.5	122–124
d	Ph	4-MeOPh	Me	Ph	78	3.0	Liquid
e	4-ClPh	Ph	Ph	Ph	90	1.0	216–218
f	4-ClPh	Ph	Me	Ph	81	2.0	113–115
g	4-ClPh	4-ClPh	Me	Ph	77	1.5	Liquid
h	4-ClPh	4-MeOPh	Me	Ph	72	2.5	138–140
i	4-MeOPh	Ph	Ph	Ph	90	1.5	189–191
j	4-MeOPh	Ph	Me	Ph	88	2.5	120–122
k	4-MeOPh	4-ClPh	Me	Ph	85	3.0	Liquid
l	4-MeOPh	4-MeOPh	Me	Ph	82	2.0	Liquid
m	2-Thiophenyl	Ph	Ph	Ph	87	1.5	142–143
n	2-Thiophenyl	Ph	Me	Ph	80	2.5	102–104
o	2-Thiophenyl	4-ClPh	Me	Ph	72	3.0	Liquid
p	2-Thiophenyl	4-MeOPh	Me	Ph	77	2.5	Liquid
q	Ph	Ph	Me	Cyclopropyl	73	1.0	Liquid
r	Ph	Ph	Me	*n*-Hexyl	75	1.0	Liquid
s	Ph	Me	Me	Ph	72	1.0	Liquid
t	Ph	$-CH_2-(CH_2)_3-CH_2-$		Ph	76	1.0	Liquid

All the products gave satisfactory ^1H and ^{13}C NMR, IR, and Mass spectral data.
[a] Isolated yields.



Scheme 3. Plausible mechanism for the formation of 4*H*-thiopyrans.

associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.06.013.

References and notes

1. (a) Lane, S.; Quick, S. J.; Taylor, R. K. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2549–2552; (b) Ward, D. E. *Chem. Commun.* **2011**, 11375–11393; (c) Ward, D. E.; Gai, Y.; Lai, Y. *Synlett* **1996**, 261–262; (c) Poleschner, H.; Seppelt, K. *Eur. J. Org. Chem.* **2001**, 2477–2480; (d) Lucassen, A. C. B.; Zwanenburg, B. *Eur. J. Org. Chem.* **2004**, 74–83; (e) Rosiak, A.; Frey, W.; Christoffers, J. *Eur. J. Org. Chem.* **2006**, 4044–4054.
2. (a) Tominaga, Y.; Okuda, H.; Kohra, S.; Mazume, H. *J. Heterocycl. Chem.* **1991**, *28*, 1245–1255; (b) Bell, A. S.; Fishwick, C. W. G.; Reed, J. E. *Tetrahedron* **1998**, *54*, 3219–3234; (c) Saito, T.; Takekawa, K.; Takahashi, T. *Chem. Commun.* **1999**, 1001–1002.
3. Yoshimura, Y.; Yamazaki, Y.; Kawabata, M.; Yamaguchi, K.; Takahataa, H. *Tetrahedron Lett.* **2007**, *48*, 4519–4522.
4. Barthakur, M. G.; Chetia, A.; Boruah, C. R. *Tetrahedron Lett.* **2006**, *47*, 4925–4927.
5. (a) Kondo, T.; Mitsudo, T.-a. *Chem. Rev.* **2000**, *100*, 3205–3220; (b) Arisawa, M.; Yamaguchi, M. *Pure Appl. Chem.* **2008**, *80*, 993–1003; (c) Xu, H. J.; Zhao, X.-Y.; Fu, Y.; Feng, Y.-S. *Synlett* **2008**, 3063–3067; (d) Ananikov, V. P.; Zalesskiy, S. S.; Beletskaya, I. P. *Curr. Org. Synth.* **2011**, *8*, 2–52.
6. (a) Chandran, R. S. P.; Retnamma, S.; Sasikala, K. A.; Sreedevi, N. K.; Anabha, E. R.; Asokan, C. V. *Tetrahedron* **2008**, *64*, 5944–5948; (b) Nandi, G. C.; Samai, S.; Singh, M. S. *J. Org. Chem.* **2011**, *76*, 8009–8014.
7. Koley, S.; Chowdhury, S.; Chanda, T.; Ramulu, B. J.; Singh, M. *Tetrahedron* **2013**, *69*, 8013–8018.
8. (a) Verma, R. K.; Verma, G. K.; Raghuvanshi, K.; Singh, M. S. *Tetrahedron* **2011**, *67*, 584–589; (b) Devi, N. S.; Singh, S. J.; Devi, L. R.; Singh, O. M. *Tetrahedron Lett.* **2013**, *54*, 183–187.
9. Chowdhury, S.; Nandi, G. C.; Samai, S.; Singh, M. S. *Org. Lett.* **2011**, *13*, 3762–3765.
10. Roy, A.; Nandi, S.; Illa, H.; Junjappa, H. *Org. Lett.* **2011**, *3*, 229–232.
11. (a) Peruncheralathan, S.; Khan, T. A.; Ila, H.; Junjappa, H. *J. Org. Chem.* **2005**, *70*, 10030–10035; (b) Nandi, G. C.; Singh, M. S.; Ila, H.; Junjappa, H. *Eur. J. Org. Chem.* **2012**, *5*, 967–974; (c) Khan, A. T.; Ghosh, A.; Basha, S. R.; Mir, M. H. *Asian J. Org. Chem.* **2013**, *2*, 126–129.
12. Mathew, P.; Asokan, C. V. *Tetrahedron* **2006**, *62*, 1708–1716.
13. Singh, T. P.; Bhattarcharya, S.; Singh, O. M. *Org. Lett.* **2013**, *15*, 1974–1977.
14. Samai, S.; Nandi, G. C.; Singh, M. S. *Tetrahedron* **2012**, *68*, 1247–1252.
15. Wen, L. R.; Li, Z. R.; Li, M.; Cao, H. *Green Chem.* **2012**, *14*, 707–716.
16. (a) Singh, O. M.; Devi, N. S.; Devi, L. R.; Khumanthem, N. *Int. J. Drug Des. Discovery* **2010**, *1*, 258–264; (b) Nandi, G. C.; Samai, S.; Singh, M. S. *J. Org. Chem.* **2010**, *75*, 7785–7795.
17. Madabhushi, S.; Jillella, R.; Godala, K. R.; Mallu, K. K. R.; Beeram, C. R.; Chinthala, N. *Tetrahedron Lett.* **2012**, *53*, 5275–5279.
18. *X-ray data for* ***3a****:* $C_{31}H_{24}OS_2$, $M = 476.62$, colorless block, $0.26 \times 0.21 \times 0.14$ mm^3, orthorhombic, space group $Pna2_1$ (No. 33), $a = 12.0959(10)$, $b = 21.3527(18)$, $c = 9.6135(8)$ Å, $V = 2483.0(4)$ Å^3, $Z = 4$, $D_c = 1.275$ g/cm^3, $F_{000} = 1000$, CCD area detector, MoKα radiation, $\lambda = 0.71073$ Å, $T = 293(2)$K, $2\theta_{max} = 50.0°$, 23,090 reflections collected, 4368 unique ($R_{int} = 0.0227$), Final *GooF* = 1.078, *R1* = 0.0318, *wR2* = 0.0807, *R* indices based on 4263 reflections with $I > 2\sigma(I)$ (refinement on F^2), 308 parameters, $\mu = 0.236$ mm^{-1}. X-ray diffraction measurement was made on a Bruker Smart Apex CCD diffractometer with graphite monochromated MoKα radiation ($\lambda = 0.71073$ Å) with the ω-scan method. Preliminary lattice parameters and orientation matrices were obtained from four sets of frames. Unit cell dimensions were determined using 5482 reflections for AU49 data. Integration and scaling of intensity data were accomplished using SAINT program. The structure was solved by Direct Methods using SHELXS97[2] and refinement was carried out by full-matrix least-squares technique using SHELXL97.[2] Anisotropic displacement parameters were included for all non-hydrogen atoms. All H atoms were positioned geometrically and treated as riding on their parent C atoms, with C–H distances of 0.93–0.97 Å, and with

$U_{iso}(H) = 1.2\ U_{eq}$ (C) or $1.5\ U_{eq}$ for methyl atoms. The crystallographic information file has been deposited with the Cambridge Crystallographic Data Centre, CCDC 986964

19. Nandi, G. C.; Samai, S.; Singh, M. S. *J. Org. Chem.* **2010**, *75*, 7785–7795.
20. Hashmi, A. S. K.; Wang, T.; Shi, S.; Rudolph, M. *J. Org. Chem.* **2012**, *77*, 7761–7767.
21. *Typical procedure for the synthesis of 4H-thiopyrans* ***3a–t:*** Methyl 3-oxo-3-phenylpropanedithioate **1a** (500 mg, 2.38 mmol), 1,1,3-triphenylprop-2-yn-1-ol **2a**, (812 mg, 2.85 mmol) and 5 ml dichloromethane were taken in a 50 ml round bottom flask and to this mixture, $BF_3{\cdot}OEt_2$ (0.053 ml, 0.4 mmol) was added and stirred at room temperature for 1 h. After completion of the reaction (TLC), solvent was removed and the crude product was purified by normal column chromatography (silica gel 60–120 mesh, ethyl acetate/hexane = 1:20) to obtain 2-(methylthio)-4,4,6-triphenyl-4*H*-thiopyran-3-yl)(phenyl)methanone **3a**, as a white solid (1.10 g, 95%, mp 162–164 °C) which was characterized by the following spectral data: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.65–7.61 (m, 4H), 7.41–7.36 (m, 4H), 7.29–7.25 (m, 6H), 7.17–7.08 (m, 6H), 6.73 (s, 1H), 2.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.8, 144.2, 137.3, 136.9, 136.8, 134.7, 132.9, 132.5, 129.3, 128.9, 128.8, 128.6, 128.2, 127.8, 127.6, 126.7, 126.6, 57.8, 18.1 ; IR (KBr): ν 3053, 2920, 1648, 1594, 1545, 1490, 1260, 750, 693 cm^{-1}; MS (ESI) 477 (M+H). ESI-HRMS obtained for $C_{31}H_{25}OS_2$ (M+H) = 477.1332 (calculated: 477.1341).