Unclicking of thioureas

Vlatkovic, Matea; Feringa, Ben L.

Published in:
Tetrahedron

DOI:
10.1016/j.tet.2019.02.035

Publication date:
2019

Tetrahedron 75 (2019) 2188–2192

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Unclicking of thioureas: Base catalyzed elimination of anilines and isothiocyanates from thioureas

Matea Vlatković, Ben L. Feringa*

Stratingh Institute for Chemistry, University of Groningen, Nijenborgh 4, 9749 Groningen, the Netherlands

ARTICLE INFO

Article history:
Received 16 January 2019
Received in revised form
13 February 2019
Accepted 15 February 2019
Available online 25 February 2019

Keywords:
Thioureas
Unclicking of thioureas
Base catalyzed elimination

ABSTRACT

Bisaromatic thioureas are widely used in e.g. asymmetric organocatalysis and considered to be robust compounds. Herein we show, in strong contrast to common notion, that thioureas dissociate to amines and isothiocyanates in a base catalyzed reaction under mild conditions. This 'unclicking' process can occur in the presence of weak organic bases even at moderate temperatures. The influence of the substituents at the aromatic rings of the thiourea on the regioselectivity of this unclicking process is also shown.

1. Introduction

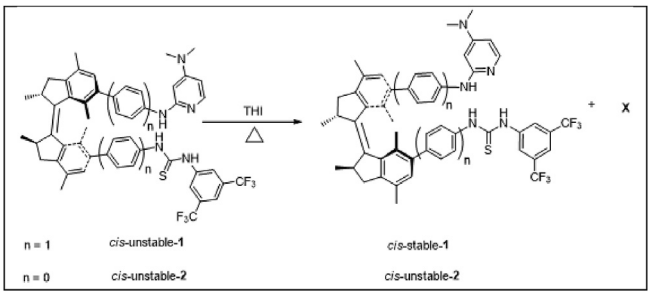
Functional molecules bearing thioureas are widely used (*e.g.* in catalysis [1], medicine [2], bioconjugation [3a] and supramolecular self-assembly [3b-d]) and the thiourea motif is considered to be very robust. The formation of thioureas can be regarded as a click reaction [4] and this is one of the main reasons for their broad application; especially in the preparation of bioconjugates and in material science (*e.g.* as a linker in nanoparticle and polymer functionalization [5]). The synthesis of thioureas is typically accomplished by mixing an appropriate isothiocyanate with an amine at ambient temperatures, although in the literature there are some procedures that are performed at elevated temperatures [6] (even at reflux [7]) in the presence of a base (*e. g.* Et_3N). It should be noted that the yields reported in those cases were typically lower than obtained at milder temperatures.

It is known that by heating a mixture of thioureas with acids [8,9] above 130 °C or by heating neat thioureas [10] above 200 °C, isothiocyanates can be obtained. It was also reported that isothiocyanates can be obtained from thioureas with very good yields using Viehe's salt (*N*-(Dichloromethylene)-*N*-methylmethanaminium chloride) [11] in the presence of a base. Because of its acidity, the thiourea moiety has been employed in the design of catalysts. Thiourea based organocatalysts are widely used in carbon-carbon and carbon-heteroatom bond forming reactions [12]. Similar to Takemoto's pioneer example of a bifunctional thiourea catalyst [13], many of these organocatalysts contain a basic tertiary alkyl amine group, which together with the thiourea enables simultaneous activation of both electrophilic and nucleophilic substrates [15,16]. Examples of using more nucleophilic bases, *e.g.* DMAP instead of trialkyl amines in combination with thiourea are scarce [14]. Although there are now numerous examples of reactions employing these catalysts, decomposition of the catalyst was not reported; even for reactions in which 10 mol % of the catalyst was used, with reaction time as long as 3 d [17]. This created the notion that the thiourea moiety is robust enough not to suffer from any unwanted decomposition. Our group has used DMAP as a base unit to build motor - based thiourea organocatalysts (**1** and **2**) with which dual stereocontrol of Michael and Henry reaction was achieved [14b,c]. For both catalysts some degradation was observed during the thermal helix inversion (THI) step (Scheme 1).

The first motor-based catalyst **1** made in our group which contained a phenyl spacer in between the motor core and the catalytic DMAP and thiourea moieties, was reported to undergo partial thermal degradation during the THI process. Albeit an intriguing observation unfortunately the degradation products were not characterized at that stage. We discovered a highly relevant elimination process which is of considerable importance in the development of thiourea-based systems ranging from catalysts to supramolecular materials. Here we will discuss the elimination products obtained during thermal helix inversion from catalyst **2**.

* Corresponding author.
E-mail address: b.l.feringa@rug.nl (B.L. Feringa).

https://doi.org/10.1016/j.tet.2019.02.035
0040-4020/



Scheme 1. Thermal helix inversion of catalysts **1** and **2** and side-product X formation.

Additionally, we will address the implications and generality of this process focussing on the question, is it specific only for our catalyst or is this a more common phenomenon?

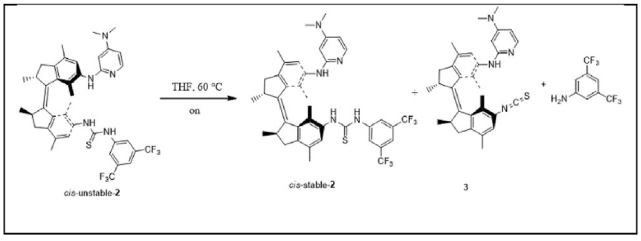
2. Results and discussion

We studied this elimination process in more detail and characterize the formed byproduct for catalyst **2** as well as examined related thioureas. After heating the *cis*-unstable form of the catalyst **2** in THF for 16 h, apart from the expected *cis*-stable form of the catalyst (the result of thermal helix inversion) also a second product (Scheme 1) was formed. We anticipated that the degradation product is formed due to the elimination of thiourea, assisted by the basic nitrogen of the DMAP moiety. In such case, the released molecule could either be the isothiocyanate or the corresponding aniline. The degradation product could be separated by silica column chromatography and was characterized by ^{1}H NMR [13],-C-NMR and HRMS (Scheme 2). Product **3** was isolated in 15% yield and was found to have an isothiocyanate moiety instead of thiourea at the motor core, suggesting that the leaving group was the 3,5-bis(trifluoromethyl)aniline, which was isolated and fully characterized.

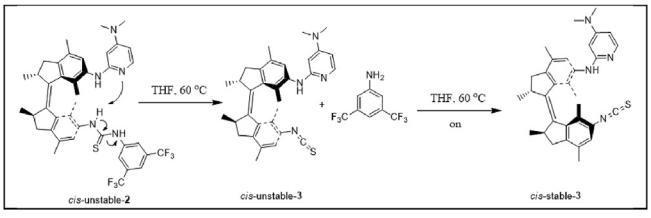
A possible mechanism for the elimination with intramolecular DMAP assistance followed by THI of *cis*-unstable isothiocyanate **3** is presented in Scheme 3.

Unfortunately, the isothiocyanate **3** was unreactive in its *cis*-stable configuration, and no product was observed during 24 h after addition of 4-methoxyaniline at room temperature. This low reactivity is most probably due to the steric reasons, and is likely to be a driving force for the decomposition.

In a control experiment it was found that the water content in the reaction mixture did not influence the elimination. The experiment was repeated with various THF sources containing 5, 50 and 100 ppm of water, always showing the same result.



Scheme 2. Formation of three new products during thermal helix inversion from *cis*-unstable motor **2**.



Scheme 3. Plausible elimination pathway for *cis*-unstable-**2**.

2.1. Elimination from model compounds

In order to test the generality of the base catalyzed elimination upon prolonged exposure to organic bases and heating a set of simple model thiourea compounds **4**–**7** (Fig. 1) were synthesized from the corresponding isothiocyanate and aniline substrates. Both donor and acceptor substituted anilines were used.

The elimination from model compounds **4**–**7** was followed over time in the presence of one equivalent of DMAP, at room temperature and at 60 °C in THF. At room temperature during 24 h only traces of elimination products could be observed (*ca.* 1% according to ^{1}H NMR measurements). Fig. 2 shows the ^{1}H NMR spectra of thiourea **4** immediately upon addition of 1 equivalent of DMAP and after 24 h at room temperature, showing only traces of elimination products.

When the elimination process of 4 was followed at 60 °C in THF, in the presence of 1 equivalent of DMAP as a base (Fig. 3), significant elimination was evident within a few hours after 3 h 30% conversion to the isothiocyanate and aniline elimination products was observed. After 72 h conversion to the elimination products has reached 44% based on ^{1}H NMR measurements.

The same process was followed for the non-symmetric thioureas **5**, **6** and **7**. With thiourea **5** which contains the electron withdrawing CF_3 group on one of the phenyl moieties, remarkably no preference for abstraction of a proton from the two nitrogens was observed. After 3 h, the ratio between the formed aniline and *p*-(trifluoromethyl)aniline was *approx.* 1:1 (Fig. 4). Nevertheless, when the reaction was continued, the disappearing of the aniline peaks could be observed, along with the formation of 1,3-diphenylthiourea (**4**). After 72 h no aniline peaks could be

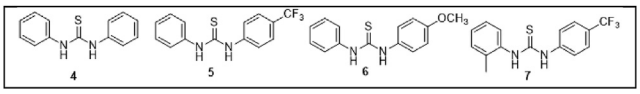


Fig. 1. Model thiourea compounds.

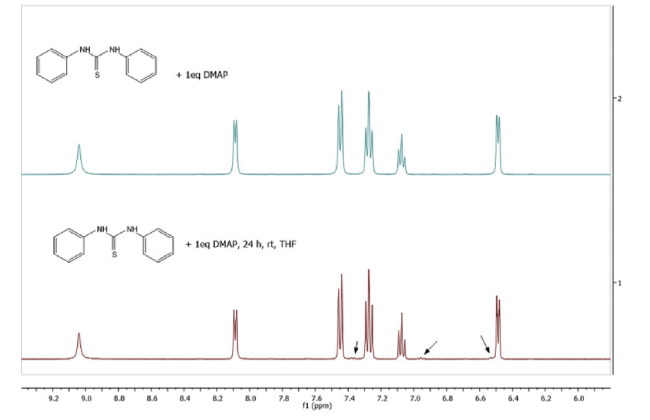


Fig. 2. ^{1}H NMR spectra of thiourea **4** in the presence of DMAP and after 24 h at room temperature (arrows indicate traces of elimination product).

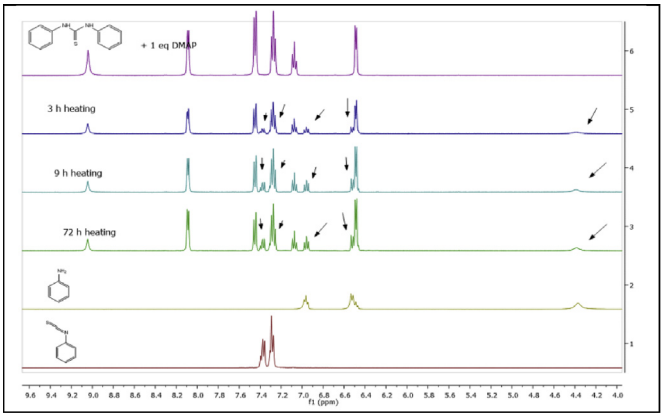


Fig. 3. ^{1}H NMR spectra of symmetric thiourea **4** in presence of 1 eq of DMAP at 60 °C followed over time (arrows indicate elimination product).

observed, showing that the more reactive aniline reacted with the formed isothiocyanate, causing accumulation of the less reactive *p*-trifluoromethylaniline (Scheme 4).

With thiourea **6** bearing an electron donating group the observed effect was similar (Fig. 5). Since the *p*-methoxyaniline is more electron rich and hence a better nucleophile, its accumulation cannot be observed as upon formation it reacts with the available isothiocyanates. With eliminated *p*-methoxyphenyl isothiocyanate it is forming a symmetric thiourea containing two methoxy groups (as seen in Fig. 5 in the ^{1}H NMR spectrum after 3 h). After longer heating period, the formation of symmetric thiourea **4** could also be observed (Scheme 5).

Interestingly for thiourea **7** which had an *o*-methyl substituent on one phenyl ring and *p*-trifluoromethyl substituent on the other ring only the elimination products and no new thiourea products were observed. In the beginning both anilines are observed as elimination products but over time mostly *p*-trifluoromethylamine is observed and the *o*-toluidine signals diminish (Fig. 6). Only one aniline was present at the end as the product of elimination (90% conversion to elimination products in 72 h), indicating a strong preference for elimination of the more electron deficient aniline. The lack of formation of the new thiourea indicates that sterics plays a crucial role in determining the thermodynamic equilibrium– the reversed reaction (formation of the thiourea) is strongly hindered by steric crowding.

Since DMAP is a particularly nucleophilic base, we decided to check, whether the character of the organic base also has an

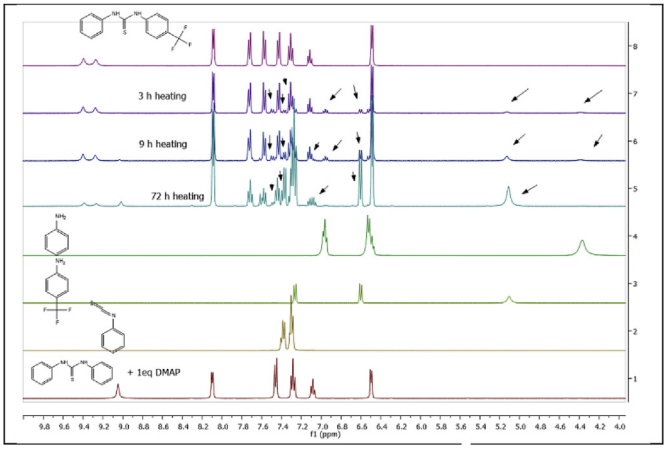
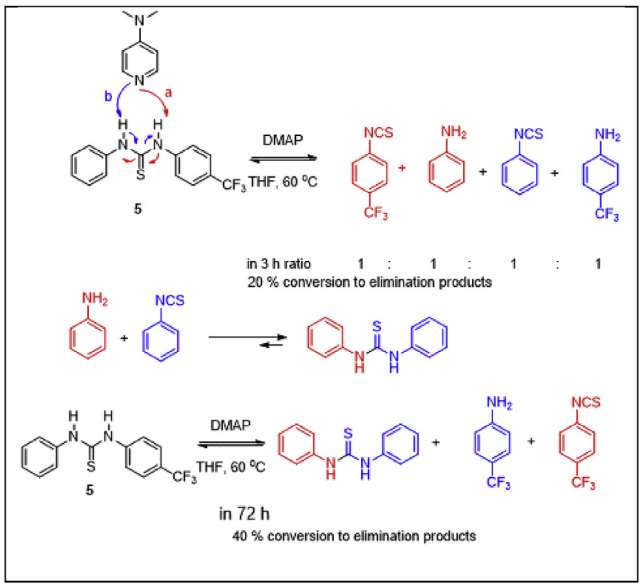


Fig. 4. Elimination from thiourea **5** over time at 60 °C.



Scheme 4. Elimination pathway from thiourea **5** mediated by DMAP.

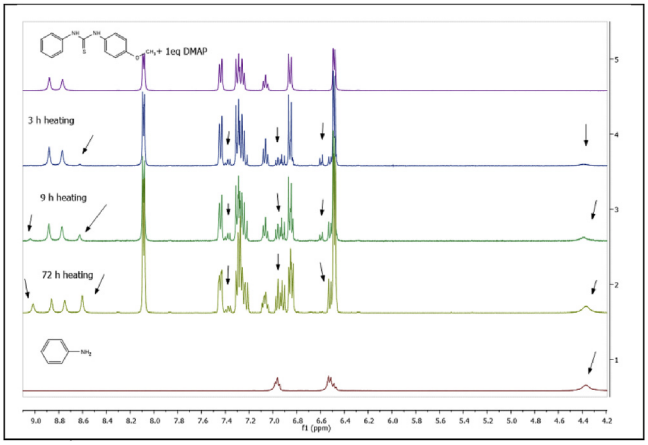
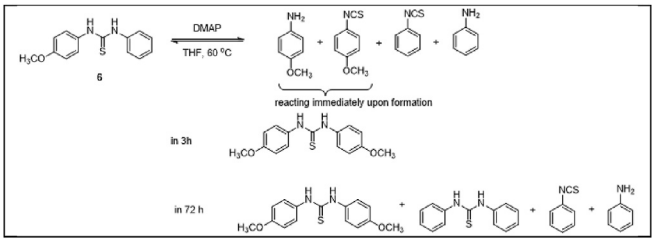


Fig. 5. ^{1}H-NMR spectra of elimination products from thiourea **6** over time at 60 °C in THF-d_6.



Scheme 5. Elimination process from thiourea **6**.

influence on the elimination. For this purpose, elimination studies with thiourea **4** were conducted with triethyl amine and pyridine, at 60 °C. In the presence of triethyl amine, the elimination was not significant during the first 3 h resulting in only 4% elimination products, but after 72 h conversion to the elimination products was 38%. When pyridine was used as a base, the effect was the same as with DMAP during the first 3 h (30% conversion to the eliminated products), and after 72 h conversion to the elimination product was

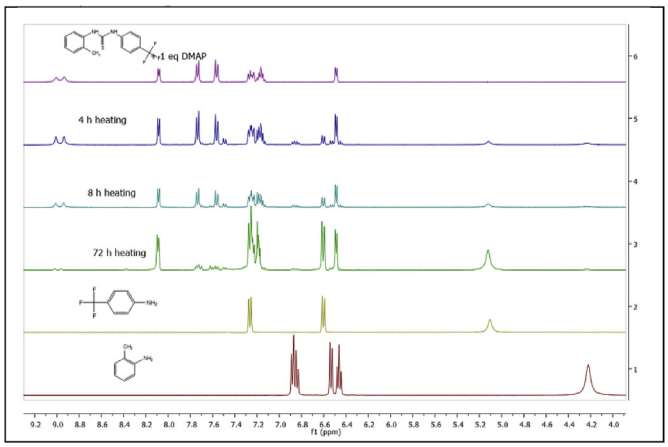


Fig. 6. ^{1}H NMR spectra of elimination products from thiourea **7** over time at 60 °C in THF.

38%. Based on this observation it can be concluded that the elimination of aniline from thiourea compound always happens in a presence of a base at elevated temperatures. To which extent elimination is observed depends on the duration of heating and the base used.

3. Conclusions

Catalyst **2** unexpectedly undergoes elimination of 3,5-bis(trifluoromethyl)aniline during the thermal helix inversion process. Such elimination appears to be a general reaction for thioureas. It was shown with the model thiourea compounds that the process of elimination in the presence of a base in THF is slow at room temperature, but becomes significant at increased temperatures. Preferentially, the electron poor amine is eliminated from thiourea, leaving the more electron rich isothiocyanate. It is an equilibrium process, as it was demonstrated by following elimination in time on model thiourea compounds. The reversed reaction does not occur in case steric hindrance is present in the aniline, as observed with thiourea **7**. The rate of elimination is dependent of the nature of the base (it is slower with triethyl amine than with DMAP). All the observations with model compounds have provided more insight into the factors determining the elimination process from catalyst **2**. Just like with model compounds, elimination from catalyst **2** was observed at elevated temperatures. Since catalyst **2** contains in its structure the highly electron deficient 3,5-bistrifluoromethyl moiety, it dictates that during the elimination process 3,5-bistrifluoroaniline is released and the isothiocyanate moiety remains at the motor core. The reversed reaction is disabled most probably due to the steric reasons as it was observed with the thiourea model compound **7**.

These results indicate that during the synthesis of thiourea compounds bases should be omitted, if possible, to avoid the formation of elimination byproducts. Additionally, these findings suggest that it would be possible to make dynamic combinatorial libraries composed of thioureas in the presence of base. As far as we know this is the first study of elimination of anilines, in presence of base, of various aromatic thioureas.

4. Experimental section

4.1. General information

Solvents and commercial starting materials were used as received (from Fluorochem or Sigma Aldrich). Catalyst **2** was prepared as described in reference 14c. Technical grade solvents were used for chromatography. Merck silica gel 60 (230–400 mesh ASTM) was used in flash chromatography. NMR spectra were obtained using a Varian Mercury Plus (400 MHz) and a Varian VXR-300S (300 MHz). Chemical shift values are reported in ppm with the solvent resonance as the internal standard ($CHCl_3$: 7.26 for ^{1}H, 77.0 for ^{13}C, THF: 1,73 and 3.58 for ^{1}H, 25.4 and 67.6 for ^{13}C) Exact mass spectra were recorded on a LTQ Orbitrap XL (ESI+) or on a DART Xevo G2 QTof. All reactions requiring inert atmosphere were carried out under argon atmosphere using oven dried glassware and standard Schlenk techniques. Dichloromethane was used from the solvent purification system using a MBraun SPS-800 column. THF was distilled over sodium under nitrogen atmosphere prior to use. Melting points were determined using a Büchi Melting Point B-545 apparatus.

Compound **3** N^{2}(Z)-6′-isothiocyanato-2,2′,4,4′,7,7′-hexamethyl-2,2′,3,3′-tetrahydro-[1,1′-biindenylidene]-6-yl-N4,N4-dimethylpyridine-2,4-diamine: 15 mg of the stable trans-**2**-catalyst was irradiated at 312 nm in DCM (3 mg/mL) till the PSS was reached (containing 93% of cis-unstable form of the catalyst, as determined by ^{1}H NMR). The resulting solution in THF was heated for 16 h at 60 °C achieving thermal helix inversion accompanied by the elimination product **3** which was purified via column chromatography (DCM:MeOH = 95:5), Rf = 0.1 mp = 133 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 6.1 Hz,1H), 7.14 (s,1H), 6.90 (s,1H), 6.08(dd, J = 6.2 Hz, J = 2.3 Hz, 1H), 6.00 (bs, 1H), 5.73 (d, J = 2.3 Hz, 1H), 3.35 (m,2H), 3.08 (m,2H), 2.94 (s,6H), 2.43 (m,2H), 2.25 (s,3H), 2.22 (s,3H), 60 (s,3H), 1.38 (s,3H), 1.08 (m,6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2, 156.2, 147.9, 143.8, 142.7, 142.2, 141.6, 141.0, 139.5, 137.2, 133.5, 131.9, 131.4, 129.3, 128.2, 128.0, 125.9, 124.8, 100.0, 88.5, 41.9, 41.7, 39.3, 38.6, 38.5, 20.4, 20.3, 18.5, 18.2, 16.8, 16.1. HRMS (APCI+, *m/z*): calculated for $C_{32}H_{37}N_4S$ $[M+H]^+$: 509.2721, found: 509.2724.

4.1.1. Elimination of model compounds followed by ^{1}H-NMR

In an NMR tube, 0.1 mL of the solution of 0.02 mmol DMAP in d_8-THF was added to a solution of 0.02 mmol of the model thiourea compound dissolved in 0.5 mL d_8-THF. The NMR tube was sealed and placed in an oil bath at 60 °C and the ^{1}H NMR spectrum was recorded every hour during the initial 8 h, and then every 12 h.

4.1.2. Synthesis of model compounds

In a dry flask equipped with a stirring bar under nitrogen atmosphere, 1 mmol of aniline or *p*-trifluoromethylaniline or *o*-toluidine was dissolved in 12 mL of dry DCM. 1 mmol of the appropriate isothiocyanate was added dropwise to the corresponding aniline solution at room temperature. The reaction mixture was left to stir overnight and then was evaporated to dryness. The thiourea products were purified by column chromatography on a short column, using pentane/EtOAc as eluent.

181:

yield = 92% mp = 152–153 °C. (lit. 152 °C) [18]

^{1}H NMR (400 MHz, THF-d_8) δ 9.05 (s, 2H), 7.46 (d, J = 7.9 Hz, 4H), 7.29 (t, J = 7.7 Hz, 4H), 7.09 (t, J = 7.3 Hz, 2H).

^{13}C NMR (101 MHz, THF-d_8) δ 181.2, 140.5, 129.5, 125.6, 124.7.

HRMS (APCI+, *m/z*): calculated for $C_{13}H_{13}N_2S$ $[M+H]^+$: 229.0794, found: 229.0792.

Compound **5** (*1-phenyl-3-(4-(trifluoromethyl)phenyl)thiourea*):

yield = 80%

mp = 147–148 °C

^{1}H NMR (400 MHz, THF-d8) δ 9.33 (s, 1H), 9.19 (s, 1H), 7.73 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 8.5 Hz, 2H), 7.43 (d, J = 8.1 Hz, 2H), 7.32 (t, 2H), 7.13 (t, 1H).

^{13}C NMR (101 MHz, THF-d_8) δ 181.3, 144.56, 144.55, 140.3, 129.8,

126.4 (q, $J = 3.9$ Hz), 126.3 (q, $J = 270.2$ Hz), 125.9, 124.6, 123.8. HRMS (APCI+, *m/z*): calculated for $C_{14}H_{12}F_3N_2S$ $[M+H]^+$: 297.0668, found: 259.0666.

Compound **6** (1-(4-methoxyphenyl)-3-phenylthiourea):

yield = 90%

mp = 141–142 °C (lit.reported from 125 °C [19a] to 160 °C [19b]).

^{1}H NMR (400 MHz, THF-d_8) δ 8.87 (s, 1H), 8.76 (s, 1H), 7.44 (d, $J = 8.0$ Hz, 2H), 7.34–7.21 (m, 4H), 7.07 (t, $J = 7.4$ Hz, 1H), 6.86 (d, $J = 8.7$ Hz, 2H), 3.74 (s, 3H).

^{13}C NMR (101 MHz, thf) δ 181.71, 158.76, 140.79, 133.16, 129.51, 127.32, 125.59, 124.86, 114.87, 55.79. HRMS (APCI+, *m/z*): calculated for $C_{14}H_{15}N_2S$ $[M+H]^+$: 259.0899, found: 259.0898.

Compound **7** (*1-(4-methoxyphenyl)-3-(o-tolyl)thiourea*):

yield = 75%

mp = 136–137 °C

^{1}H NMR (400 MHz, THF-d_8) δ 9.06 (s, 1H), 8.98 (s, 1H), 7.75 (d, $J = 8.4$ Hz, 2H), 7.58 (d, $J = 8.4$ Hz, 2H), 7.33–7.11 (m, 4H), 2.33 (s, 3H).

^{13}C NMR (101 MHz, THF-d_8) δ 181.0, 143.43, 143.42,137.2, 135.2, 130.7, 127.4, 127.0, 126.5, 125.3 (q, $J = 3.9$ Hz), 124.5 (q, $J = 270.4$ Hz), 123.3, 17.3.

HRMS (APCI+, *m/z*): calculated for $C_{15}H_{14}F_3N_2S$ $[M+H]^+$: 311.0824, found: 311.0825.

Acknowledgments

We gratefully acknowledge support from The Netherlands Organization for Scientific Research (NWO-CW, Top grant to B. L. F), the Royal Netherlands Academy of Arts and Sciences (KNAW), the Ministry of Education, Culture and Science (Gravitation program 024.001.035) and the European Research Council (Advanced Investigator Grant no. 694345 to B. L. F.).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2019.02.035.

References

[1] a) W.-Y. Siau, J. Wang, Catal. Sci. Technol. 1 (2011) 1298–1310;
b) M. North, Sustainable Catalysis: without Metals or Other Endangered Elements, Part 2, Chapter 19, RSC Green Chemistry, London, UK, 2015;
c) R.S. Klausen, C.R. Kennedy, A.M. Hyde, E.N. Jacobsen, J. Am. Chem. Soc. 139 (35) (2017) 12299–12309;
d) B. Lin, R.M. Waymouth, Macromolecules 51 (2018) 2932–2938.
[2] a) O.J. D'Cruz, F.M. Uckun, Curr. HIV Res. 4 (2006) 329–345;
b) O.J. D'Cruz, T.K. Venkatachalam, F.M. Uckun, Biol. Reprod. 63 (2000) 196–205.
[3] a) R. Narain, Chemistry of Bioconjugates: Synthesis , Characterization and Biomedical Application, Wiley, New Jersey, US, 2014;
b) N. Prusinowska, J. Szymkowiak, M. Kwit, J. Org. Chem. 83 (2018) 1167–1175;
c) M.E. Khansari, A. Mirchi, A. Pramanik, C.R. Johnson, J. Leszczynski, Md. A. Hossain, Sci. Rep. 7 (2017) 6032;
d) Y. Yanagisawa, Y. Nan, K. Okuro, T. Aida, Science 359 (2017) 72–76.
[4] H.C. Kolb, H.C. Finn, K.B. Sharpless, Angew. Chem. Int. Ed. 40 (2001) 2004–2021.
[5] N. Muhr, R. Puchleitner, W. Kern, Eur. Polym. J. 49 (2013) 3114–3124.
[6] a) G. Nagalakshmi, T.K. Maity, B.C. Maiti, Int. J. Chem. Tech. Res. 5 (2013) 2079–2089;
b) N. Berber, M. Arslan, E. Yavuz, C. Bilen, N. Gencer, J. Chem. (2013), 742178.
[7] M. Hearn, M. Chen, M. Cynamon, R. Wang Ondum, E. Webster, J. Sulfur Chem. 27 (2006) 149–164.
[8] R.S. Bly, G.A. Perkins, W.L. Lewis, J. Am. Chem. Soc. 44 (1922) 2896–2903.
[9] M. Bollini, J.J. Casal, D.E. Alvarez, L. Boiani, M. Gonzalez, H. Cerecetto, A.M. Bruno, Bioorg. Med. Chem. 17 (2009) 1437–1444.
[10] N. Habib, A. Rieker, Synthesis 10 (1984) 825–827.
[11] M.V. Vovk, M.K. Bratenko, L.I. Samarai, Ukr. Khim. Zh. 57 (1991) 431–432.
[12] X. Fang, C.-J. Wang, Chem. Commun. 51 (2015) 1185–1197.
[13] O. Tomotaka, Y. Hoashi, Y. Takemoto, J. Am. Chem. Soc. 125 (2003) 12672–12673.
[14] a) C. Rabalakos, W.D. Wulff, J. Am. Chem. Soc. 130 (2008) 13524–13525;
b) J. Wang, B.L. Feringa, Science 331 (2011) 1429–1431;
c) M. Vlatković, L. Bernardi, E. Otten, B.L. Feringa, Chem. Commun. 50 (2014) 7773–7775.
[15] D.E. Fuerst, E.N. Jacobsen, J. Am. Chem. Soc. 127 (2005) 8964–8965.
[16] a) V. Benedek, S. Varga, A. Csámpai, T. Soós, Org. Lett. 7 (2005) 1967–1969;
b) S.H. Mc Cooey, S.J. Connon, Angew. Chem. Int. Ed. 44 (2005) 6367–6370.
[17] Y.-Q. Wang, J. Song, R. Hongm, H. Liand, L. Deng, J. Am. Chem. Soc. 128 (2006) 8156.
[18] N. Azizi, A. Khajeh-Amiri, H. Ghafuri, M. Bolourtchain, M. Mol. Divers. 15 (2011) 157–161.
[19] a) S. Begum, M.I. Choudhary, M. Khalid, Nat. Prod. Res. 23 (2009) 1719–1730;
b) A. Natarajan, Y. Guo, H. Arthanari, G. Wagner, J.A. Halperin, M. Chorev, J. Org. Chem. 70 (2005) 6362–6368.