

DIPEA-Promoted Reaction of 2-Nitrochalcones with Elemental Sulfur: An Unusual Approach to 2-Benzoylbenzothiophenes

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Supporting Information

ABSTRACT: DIPEA was found to be an excellent sulfur activator to promote the reaction of 2-nitrochalcones with elemental sulfur. A wide range of 2-benzoylbenzothiophenes was obtained as a result of a cascade of alkene C=C bond thiolation, aromatic sulfur-denitration.



A romatic nitro compounds are one of the most common and versatile starting materials in organic synthesis due to their easy preparation and ready availability. In most of theorganic reactions involving aromatic nitro groups, this function plays the building-block role and is transformed into other nitrogen-containing functional groups or a part of newly created aza-heterocycles. The transformations in which aromatic nitro groups act as leaving groups are, however, much less encountered and developed. In these kinds of reactions,¹ the presence of either transition metal catalysts such as Cu,² Rh,³ Pd,⁴ or strongly activating groups⁵ is required.

During the course of our study in the development of new reactions involving aromatic nitro compounds using elemental sulfur as a polyvalent synthetic tool, the building-block behaviors of the nitro groups are the most frequently observed.⁶ For example, on heating with elemental sulfur in *N*-methylmorpholine or 3-picoline, we found recently that 2-nitrochalcones 1 transformed smoothly into sultames 3 (Scheme 1).⁷

When diisopropylethylamine (DIPEA) was used as base, we noticed that the reaction proceeded in a totally different





pathway, giving rise to 2-benzoylbenzothiophene 2 at 100 $^{\circ}\mathrm{C}$ (Table 1, entry 1).



\bigcirc	O Ph + S NO ₂ n equiv 1a	base (5 equi	v)	S Ph
entry	base (equiv) $(pK_a)^8$	п	temp (°C)	yield (%) ^b
1	DIPEA (10.61)	5	100	70
2	NEt ₃ (10.65)	5	100	65 ^e
3	$N(n-Pr)_3$ (10.65)	5	100	62
4	TMEDA^d (10.40)	5	100	15
5	DIPEA (10.61)	5	80	74 (76 ^f)
6	DIPEA (10.61)	5	70	45 ^c
7	N-methylmorpholine (7.41)	5	80	0 ^{<i>c</i>}
8	pyridine (5.23)	5	80	0 ^{<i>c</i>}
9	N-methylpiperidine (10.08)	5	80	20
10	DIPEA (10.61)	2	80	35
11	NEt_3 (10.65)	5	80	70

^{*a*}Reaction conditions: **1a** (0.2 mmol), S (2 or 5 equiv, 0.4 or 1 mmol, 13 mg or 32 mg), base (1 mmol, 5 equiv) under an argon atmosphere. ^{*b*}Isolated yield. ^{*c*}Determined by ¹H NMR of the crude reaction mixture. ^{*d*}N,N,N',N'-tetramethylethylenediamine. ^{*c*}Reaction performed in a sealed tube under an argon atmosphere. ^{*f*}Yield for the reaction performed on 1 mmol scale.

This unexpected result prompted us to carry out a comparative study on the behaviors of some related tertiary amines (Table 1). Under similar conditions, triethylamine and tri-*n*-propylamine behaved in the same manner and gave rise to a similar product, benzothiophene 2a, despite in lower yields (entries 2 and 3). When TMEDA was used as a dibasic activator, 2a was also formed along with extensive degradation

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of the base (entry 4). The reaction with DIPEA could be efficiently performed at a temperature as low as 80 °C but the conversion was incomplete at 70 °C (entries 5 and 6 vs entry 1). At the optimal temperature for DIPEA (80 °C), Nmethylmorpholine and pyridine did not display any activating effect, 2-nitrochalcone 1a remained unchanged (entries 7-8). On the other hand, N-methylpiperidine exhibited stronger activating effect, leading to a complex mixture from which we could isolate both benzothiophene 2a and sultam 3a in low yields (20 and 23%, respectively) (entry 9). Under optimal conditions, lower sulfur loading resulted in lower yield (entry 10). Finally, we noticed that the reaction could be performed also with less expensive triethylamine at 80 °C (entry 11).

We next studied the substrate scope. A variety of 2nitrochalcones bearing different substituents at different positions of the phenyl ring was evaluated under our optimized conditions (Scheme 2).



The methyl substituted chalcones 1b,c reacted in the same manner as 1a, even with o-substituted one 1c. The structure of benzothiophene **2b** was unambiguously determined by an X-ray diffraction study (see the Supporting Information). Halogenated substrates 1e-h were well tolerated, leading to the corresponding halogenated benzothiophenes 2e-h in good to excellent yields, regardless the nature and the positions of the halogen atoms. Gratifyingly, when dinitrochalcones 1i,j were subjected to the optimized conditions, the expected benzothiophenes 2i,j were formed without any parasite reaction on the remaining nitro groups. Polyaromatic and heteroaromatic

chalcones 1k-n were found to react in the same manner, giving rise to benzothiophenes 2k-n in good to excellent yields.

The reactions were subsequently investigated with substrates bearing different substituents on the nitrobenzene ring (Scheme 3). Chalcone 10 bearing two methoxy groups

Scheme 3. Formation of 2-Benzoylbenzothiophene 2b-n



remained intact and failed to give the expected benzothiophene 20 at 80 °C, possibly due to its low solubility. Gratifyingly, clean conversion was observed when the reaction was performed at 100 °C. Halogen substituted chalcones 1p,q were showed to be competent substrates, leading to the corresponding product in reasonable yields, although these halogen atom are activated by the 2-nitro group.

While the detailed mechanism is not clear at this moment, the choice of base additives is obviously vital to the reaction outcomes. From the screening results of bases presented in Table 1 and the previously reported observation, we noticed that the first determining factor is the basicity of the base additive. Weaker bases such as N-methylmorpholine (pK_{2} , 7.41) or pyridine $(pK_a 5.23)$ did not activated sufficiently at lower temperature (80 $^{\circ}$ C) although they were found to be efficiently promoted the formation of sultam 3a at higher temperatures. Second, for stronger bases such as DIPEA (pK_1 , 10.61), NEt₃ $(pK_1 10.65)$, N $(n-Pr)_3$ $(pK_1 10.65)$, N-methylpiperidine (pK_1) 10.08) and TMEDA (pK_{2} 10.40), other structural factors could play additional roles in modifying the reactivity of the present transformation. DIPEA, distinguished by its highest steric hindrance around the basic nitrogen atom compared to other bases discussed here, could attack only the most reachable electrophile sites. Among sulfur and nitrochalcone 1a, only cyclooctasulfur is available for this attack thanks to longer S-S distance and bivalent nature of sulfur atoms. Consequently, although it is still early to present detailed mechanistic evidence, we suggest that the transformation is probably initiated by ring opening of cyclooctasulfur promoted by DIPEA, providing zwitterion polysulfide A (Scheme 4). As the alkene double bond of nitrochalcone 2a is activated by both nitro and benzoyl group, both α and β positions are activated. Nucleophilic attack of \mathbf{A} on the α position of nitrochalcone $2\mathbf{a}$ would proceed with temporary dearomatization of the nitrobenzene ring of B. Cyclization of B to C would proceed with elimination of a polysulfide chain. Finally, an aromatizing denitration of C would lead to benzothiophene 2a.

The unique role of the nitro group as both activating and leaving group in the present reaction without any transition metal catalyst is further demonstrated by a comparative reaction with 2-chloro- and 2-bromochalcones 1x,y (Scheme 5). Their alkene double bond was hydrogenated cleanly to

Scheme 4. Proposed Mechanism







propanone 4x,y without any departure of the halogen substituents. Although detailed mechanism of this transformation is unknown, similar results were documented for thermal reaction of chalcone with sulfur.⁹ In this case, hydrogen sulfide generated in situ from the sulfuration of DIPEA with elemental sulfur is responsible for the hydrogenation (eq 1, Scheme 5).¹⁰

In conclusion, we have demonstrated a simple synthesis of 2benzoylbenzothiophene by simply heating 2-nitrochalcone with elemental sulfur in DIPEA. This reaction once again highlighted complex, multifaceted, but highly attractive chemical behaviors of both elemental sulfur and nitro group. By selecting appropriate reaction conditions (in the present case, is the use of DIPEA as activating base), unconventional reactivities and selectivities could be observed. Compared to a recent work on copper-catalyzed synthesis of 2-benzoylbenzothiophenes starting from 2-bromo- or 2-iodo-chalcones using xanthate as sulfur source,¹¹ our strategy is markedly simpler with higher atom efficiency and does not require any transition metal catalyst. Further study on activated sulfur as a polyvalent synthetic tool is underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications Web site. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02321.

Experimental procedures, characterizations of new compounds, copies of their NMR spectra (PDF) Crystal data for compound **2b** (CIF)

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Notes

The authors declare no competing financial interest.

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