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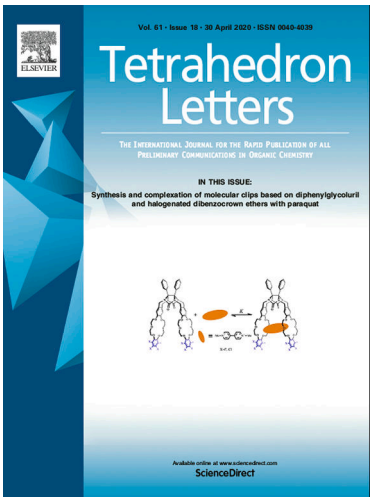

Direct synthesis of piperazines containing dithiocarbamate derivatives via DABCO bond cleavage

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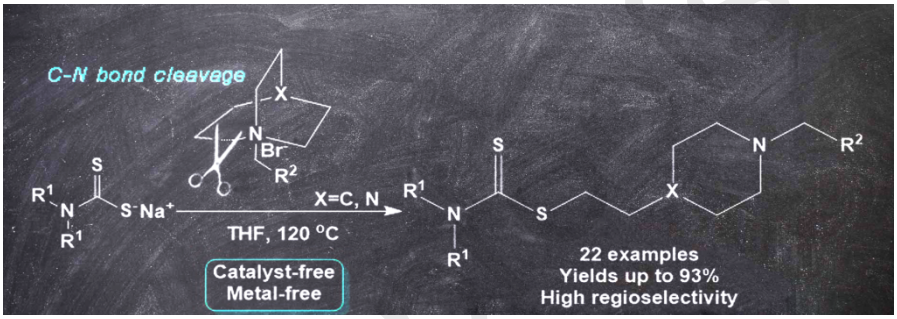

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Direct synthesis of piperazines containing dithiocarbamate derivatives via DABCO bond cleavage

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ABSTRACT

DABCO bond cleavage with dithiocarbamic acid salts was applied as a direct synthetic route for the preparation of a novel category of piperazines containing dithiocarbamate functional group. This metal-free and operationally simple approach can be applied with good to excellent yields and high selectivity. Besides, substituted bis-piperazines and piperidines containing dithiocarbamate groups were successfully prepared via the same protocol using quaternized quinuclidine and bis-quaternized DABCO.

To meet the challenges encountered in organic synthesis accompanied by total synthesis implementation, in recent years, organic chemists have constantly tried to introduce efficient synthetic route *via* a various range of new substrates. Within the organic transformation, several neoteric synthetic approaches such as re-engineering method,[1] pot, atom, step economy (PASE) method and also alternative reactants for common reactions have gained widespread attention.[2] The most prominent trends in this scientific area during the past decade are abridged including using thiols and phenols instead of acid in Ugi-multicomponent reactions,[3,4] amides and ammonium salts rather than alkyl halides,[5,6] nitroalkenes instead of phenylacetylenes in Huisgen click reaction.[7] These state-of-the-art synthetic strategies not only enable chemists and pharmacists to tackle the problems in total synthesis, but also provide privilege tools for a direct, expeditious and viable synthesis to access more complex compounds containing several functional groups and heterocyclic moieties.

It is true that among the top 25 best-selling pharmaceuticals in the year 2014, there have been 12 small-molecule drugs with heterocyclic moieties. In the meanwhile, nearly 90% of all marketed drugs contain at least one nitrogen atom as a key structural element in their structure[8] and account for exceeding 50 billion USD in annual revenue.[9] Among FDA approved drugs, one of the most important heterocyclic rings is piperazine. Additionally, substituted piperazines have found enormous applications as drugs, intermediates of biologically active molecules, agrochemicals, and also ligands.[10,11] Functionalized piperazine motif is considered as a key structural scaffold in a variety of marketed drugs such as Geodon™ and Sprycel™ which have been approved for treatment of schizophrenia and cancer respectively (Figure 1).[12,13]

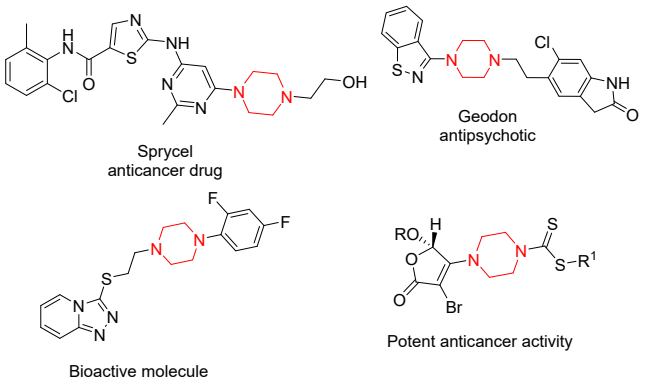


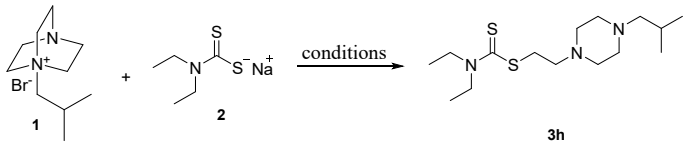
Figure 1. Selected piperazine-based drugs and bioactive molecules

Moreover, dithiocarbamate derivatives are a remarkable pharmacophore which indicated various biological activities when incorporated in a particular structure.[14] Take, for instance, thiram which could be used in dermatology as a scabicide.[15] Dithiocarbamates also constitute an important class of fungicides, herbicides, and pesticides and many compounds of this category namely ferbam, mancozeb, zineb, and ziram have been commercialized.[16] Hence, the combination of these pharmacophores (piperazine and dithiocarbamate) in a single scaffold *via* a synergistic effect is likely to be a potential candidate for the development of new pharmacologically active molecules.

In the light of the crucial role of functionalized piperazines in several medical disciplines, a synthetic route to

ac s on been highly sought after. In the past, *N*-alkylated piperazine scaffolds are commonly achieved by multi-step reactions and these methods have suffered from several drawbacks. These synthetic routes typically are based on transition- metal-catalyzed carbon-nitrogen bond-forming transformation *via* expensive metals and ligands.[17,18] Costly catalysts and additives, relatively detrimental metals as well as harsh reaction conditions are considered as main shortcomings for reported methods. As a result, designing a direct, straightforward, and step economy strategy to access piperazines heterocyclic compounds have been gained widespread attention in recent years. As a result, very recently, 1,4-diazabicyclo[2.2.2]octane (DABCO) which has commonly addressed as an organic catalyst[19,20] in chemical progress has been used as a substrate in carbon-nitrogen bond cleavage reactions for the synthesis of outstanding piperazines derivatives. Diversities of nucleophiles including thiols, carboxylic acid salts, phenolates, alkoxides, halides, amines, azide, and enolates were applied successfully for DABCO bond cleavage.[21–26]

Table 1. Selected conditions for optimization of the reaction



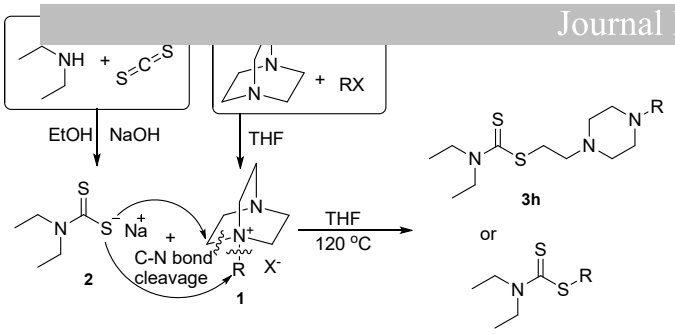
Entry	Solvent	Temp. (°C)	Time (h)	Yield (%)[a]
1	THF	25	24	trace
2	THF	120	4	62
3	THF	120	8	70
4	THF	120	16	75
5	**THF**	**120**	**24**	**80**
6	MeOH	120	24	65
7	EtOH	120	24	70
8	*i*PrOH	120	24	70
9	CH_3CN	120	24	56
10	DMF	120	24	60
11	DMSO	120	24	63
12	Toluene	120	24	15
13	Dioxane	120	24	45
14	H_2O	120	24	5
15	PEG 1500	120	24	45
16	PEG 400	120	24	61
17	THF	120	24	40[b]

[a] Isolated yields. [b] Isolated yield for one-pot three-component route using diethylamine, CS_2 and DABCO salt **1**.

dithiocarbamate chemistry,[27–29] we report the synthesis of 1,4-disubstituted piperazine derivatives **3a-p** *via* the reaction of quaternized derivatives of DABCO **1** with dithiocarbamate salts **2** in the absence of any catalyst, additive or metals. First of all, to optimize the reaction conditions, various organic solvents were applied to the model reaction forming **3h** (Table 1).

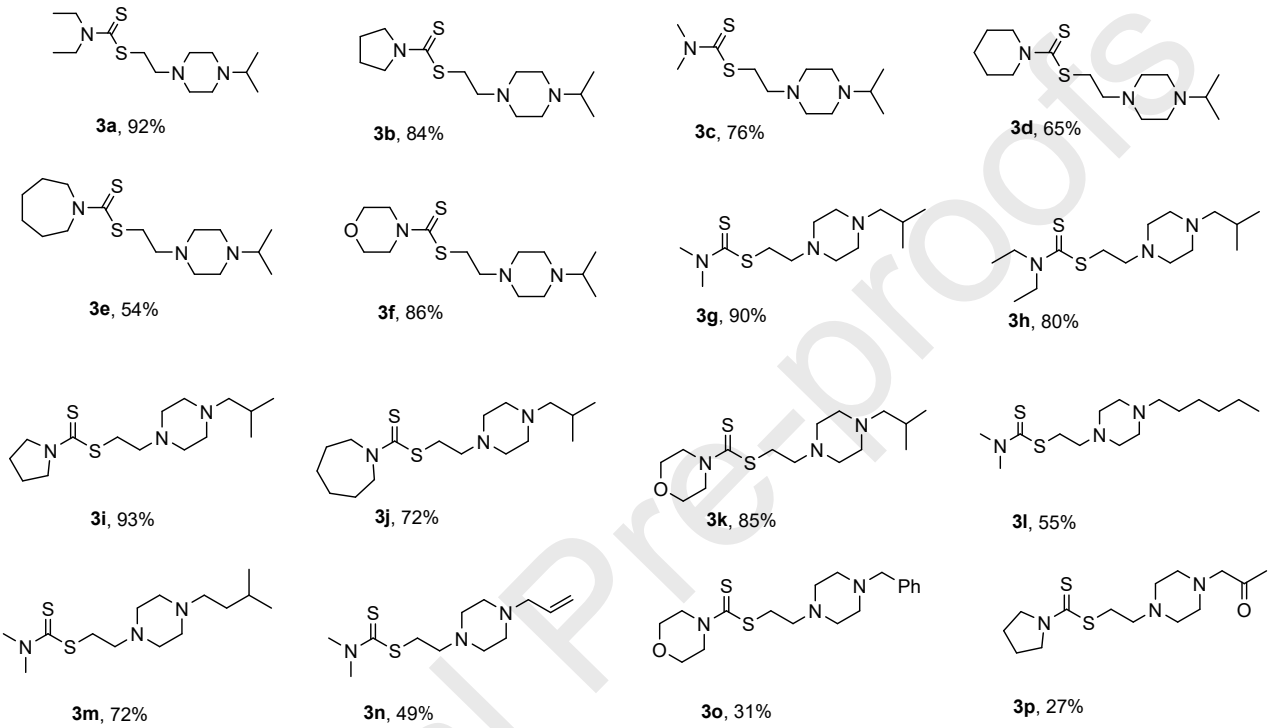
Owing to the importance of reaction temperature in carbon-nitrogen bond cleavage reactions, expectedly no reaction was occurred at room temperature in THF (Table 1, entry 1). When, reaction temperature was raised to 120 °C in THF for 4h, the yield of **3h** improved to 62% (Table 1, entry 2). Prolonging the reaction time to 8, 16 and 24 hours improved the yields to 70, 75 and 80 %, respectively (Table 1, entries 3-5). No further improvement in reaction yield was observed by further prolonging the reaction time. By screening the model reaction in protic and aprotic organic solvents such as MeOH, EtOH, *i*PrOH, MeCN, DMF, DMSO, toluene and dioxane lower yields were obtained (Table 1, entries 6-13). Using water gave inferior results in yield (Table 1, entry 14). The use of polyethylene glycol (PEG) led to the formation of the desired product, whereas the yield was not satisfactory and work-up is extremely harsh and time-consuming (Table 1, entries 15-16). In addition, a one-pot three-component reaction was examined using amine and carbon disulfide instead of dithiocarbamate salt along with quaternized derivatives of DABCO, which afforded the corresponding product in 40% isolated yield (Table 1, entry 17). Finally, using THF as the reaction medium and heating the reaction mixture to 120 °C for 24 h was considered as optimal conditions for further synthesis. Evidently, as this temperature is much higher than THF boiling point, these reactions carried out in sealed tube and under high pressure.

The scope of this reaction was examined using various secondary amines including diethylamine, dimethylamine, and cyclic amines namely morpholine, pyrrolidine, piperidine and azepane and the corresponding 1,4-disubstituted piperazines containing dithiocarbamate **3a-p** were obtained in high to excellent yields (Scheme 1). Interestingly, using cyclic amines in this approach leads to synthesize novel *bis*-heterocycle scaffolds containing dithiocarbamates. A combination of two remarkable heterocyclic rings in one complex structure must undoubtedly create new entities with privileged biological properties due to synergistic effect.[30] Moreover, a wide range of quaternized derivatives of DABCO which prepared *via* the reaction of DABCO with primary and secondary alkyl halides were applied in this synthetic route. Then, quatenized DABCO salts with benzyl, allyl and 2-oxopropyl groups were used for further investigation. These reactions have progressed through the S_N2 mechanism that quaternized DABCO undergoes ring opening with the aid of a dithiocarbamate salt to furnish desired products. To sum up, the desired carbon-sulfur bond formation proceeded well through a carbon-nitrogen bond cleavage in DABCO ring. According to the experimental results, the regioselectivity of the reaction rely on the type of alkyl group attached to the DABCO salt whereby the nucleophilic attack on the carbon of bridge or the carbon of the alkyl group have invariably competed. In the cases of **3o** and **3p**, in addition to desired products, alkyl dithiocarbamates as a main byproduct have been synthesized. On the basis of the previous reports,[24] a plausible mechanism for this reaction is suggested in Scheme 2. The outcome pertains to the hard-soft properties of the nucleophiles and electrophiles (HSAB theory) as well as the steric hindrance of the alkyl halides.[31] This mechanism can be justified by the theory of stable carbocation and transition state formation for benzyl, allyl, and carbonyl groups as a softer nucleophilic site through which contributed to reduce yields in the corresponding products.



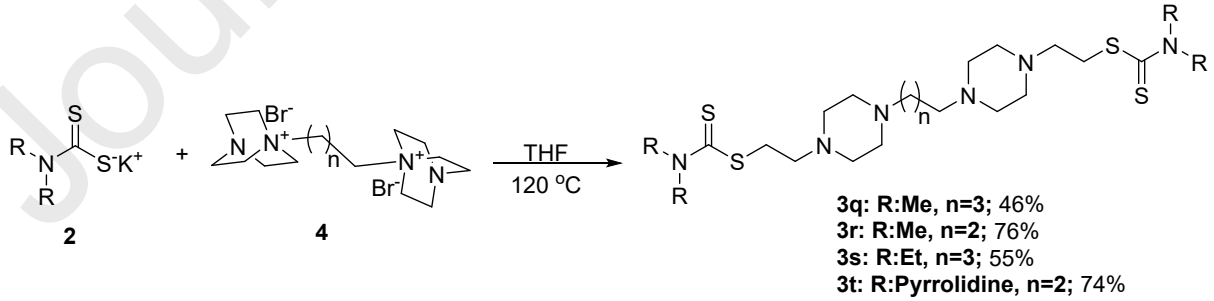
Scheme 2. Proposed reaction mechanism.

Scheme 1. Diversity in the synthesis of piperazines containing dithiocarbamate motif[a]



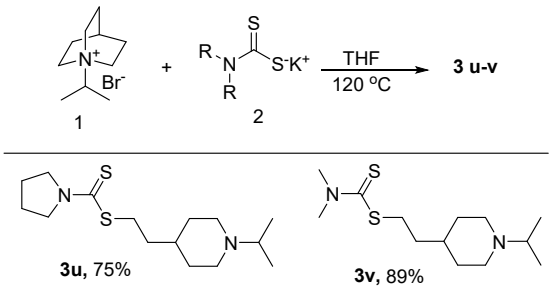
[a] Isolated yield.

In the next step, we turned to implement *bis*-ammonium salt **4** to access *N, N′-bis* piperazine containing dithiocarbamate compounds **3q-t**, which in all cases, pure products have been obtained in appropriate yields (Scheme 3). Basically, fungicidal activity of a molecule is depend on the number of dithiocarbamate moieties in the scaffolds and can be improved by increasing the number of dithiocarbamate motifs.[32]



Scheme 3. Diversity in the synthesis of *N, N′-bis* piperazines containing dithiocarbamate groups

Thereafter, to expand the diversity of the synthetic strategy, aside from DABCO, quaternized derivatives of quinuclidine have been applied. Hereupon, *N*-alkyl piperidine containing dithiocarbamates **3u-v** were synthesized with high selectivity (Scheme 4).



dithiocarbamates with quinuclidine salts

Conclusion

In the light of the medicinal properties of piperazine and also dithiocarbamate motifs, we introduce an initiative procedure to synthesize piperazines containing dithiocarbamate derivatives *via* carbon-nitrogen bond cleavage of DABCO. With this direct and practical synthetic pathway, a library of piperazines and piperidines containing dithiocarbamates were easily obtained by the reaction of a diversified number of quaternized derivatives of DABCO and quinuclidine accompanied by various dithiocarbamate salts. Joyfully, despite most of the carbon-nitrogen bond cleavage reports, our novel desired products were achieved in the absence of any catalyst, additive, and metals. A great deal of benefits can be derived from catalyst-free reactions, take decreasing chemical pollutions and improving the E-factor as critical parameters in an environmentally benign organic reaction, for instance.[33] Furthermore, metal-free organic transformations are particularly interesting to the pharmaceutical industry as they overcome the problem of toxic metal contaminants being present in the final products. Finally, we anticipate that these synthetic strategies come up with a solution to a certain number of barriers to drug design and total synthesis.

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Declaration of interests

✓ ☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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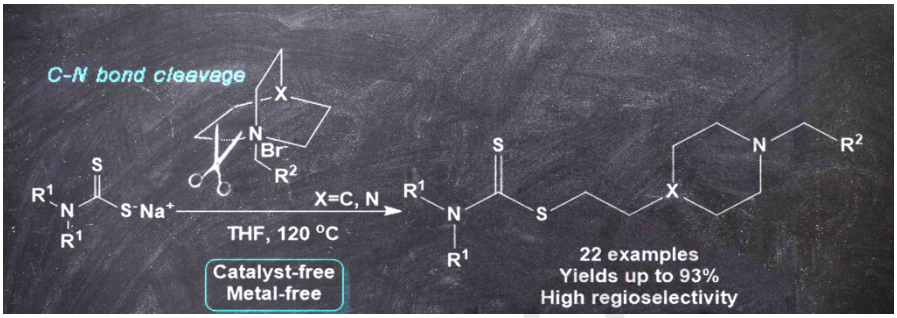

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