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Late-stage *N*-functionalization of diazo NH-heterocycles via alkylation by Mitsunobu reaction or with alkyl halides

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Abstract

α-Diazo carbonyl compounds are widely used as reagents of vast synthetic potential, capable delivering biologically relevant compounds and diverse molecular scaffolds. Herein we present methods for selective *N*-alkylation of various diazo NH-heterocycles while maintaining the diazo function for further modifications. α-Diazo homophthalimide, diazo arylidene succinimides, diazo barbituric and thiobarbituric acids, and α-diazo pyrazolones were readily alkylated with alkyl halides or alcohols under Mitsunobu reaction conditions. This is the first time that the Mitsunobu reaction has been applied for the functionalization of diazo carbonyl compounds. The method

expands the scope of substituents that can be introduced into the diazo molecule, including such challenging moieties as adamantyl, cholesteryl and menthyl.

Keywords

diazocarbonyl compounds; *N*-alkylation; Mitsunobu reaction; alkyl halides; NH-heterocycles

Introduction

Diazo carbonyl compounds are highly useful reagents in modern organic chemistry. Their diverse reactivity mainly as carbene precursors is widely explored for the construction of complex molecules and biologically relevant frameworks [1] in a concise and efficient manner with high stereochemical control.

Generally, the diazo function is introduced into the molecule immediately prior to its replacement. However, the synthesis of certain *N*-alkyl substituted heterocyclic imide and amide frameworks containing active methylene group required for Regitz diazo transfer reaction is challenging. Exemplarily, the direct alkylation of 2-oxoindoles or homophthalimides with alkyl halides leads to a mixture of mono and bis C-alkyl compounds [2-10] rather than to *N*-alkylated products. Another advantage of the approach of introducing a substituent into the prepared diazo heterocyclic reagent is its convergent nature, which allows easy variation of the moiety to be attached in the final step of the synthesis.

To date several examples of cyclic amide group modification in the preformed diazo scaffolds with alkyl halides [11-17] or halogen anhydrides [18-23] previously to metal catalyzed decomposition of diazo group were described in the literature. The scope was limited by simple alkyl halides.

Meanwhile *N*-alkylation reactions represent a versatile tool for rapid diversification of the molecules, introduction of reactive functionalities into the structure and are actively used in medicinal chemistry and in the synthesis of pharmaceutical compounds.

Most common alkylating agents are no doubt alkyl halides; however, their use is limited due to concurrent elimination or overalkylation processes. Besides some halogen derivatives are hardly accessible, many of them are hazardous. In this respect alcohols are more available, easier to store and to handle and often cheaper comparing to alkyl halides. From industrial perspectives alcohols are often preferred alkylating agents [24]. Mitsunobu reaction finds widespread use in medicinal chemistry and in total synthesis and could be good alternative to alkylation with alkyl halides. To date there is no mention in the literature of the use of Mitsunobu alkylation for the synthesis of diazo heterocycle derivatives.

Following our continuing interest in the chemistry of diazo heterocycles coupled with its medicinal chemistry applications we focused on exploration of diverse alkylating agents for *N*-alkylation of selected diazo heterocyclic compounds. Such functionalization will allow to obtain cyclic diazo scaffolds bearing certain set of substituents which can subsequently be used to generate libraries of compounds for biological studies.

Results and Discussion

As part of our ongoing studies, we needed a series of *N*-substituted diazo imides as synthetic intermediates. For these purposes some important from medicinal chemistry view scaffolds depicted on figure 1 were selected. Compounds **1-5** were synthesized by direct diazo transfer on NH-heterocyclic precursors using ‘SAFE’ protocol [25] (for **1**,**3-5**) or via standard procedure (for **2**) (see ESI).

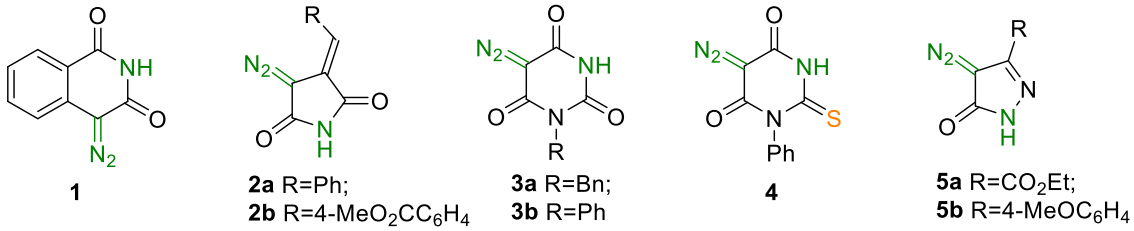
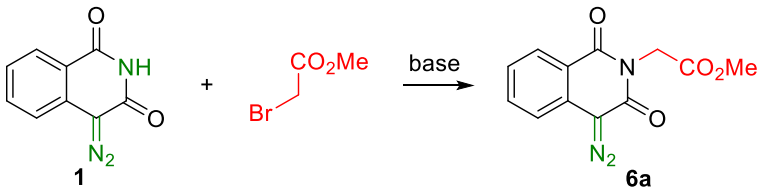


Fig. 1: Selected diazo compounds for alkylation studies.

We began our investigation with the model reaction of diazo homophthalimide **1** with methyl bromoacetate in the presence of base (Table 1). It should be noted that the synthesis of **6a** using other protocols is quite labour intensive, whereas direct alkylation of homophthalimide without diazo function results in *C*-alkylation products. Considering that diazo homophthalimide **1** possesses very low solubility in common organic solvents at standard conditions, we first examined DMF as a solvent under mild heating.

Table 1: Optimization studies [a].



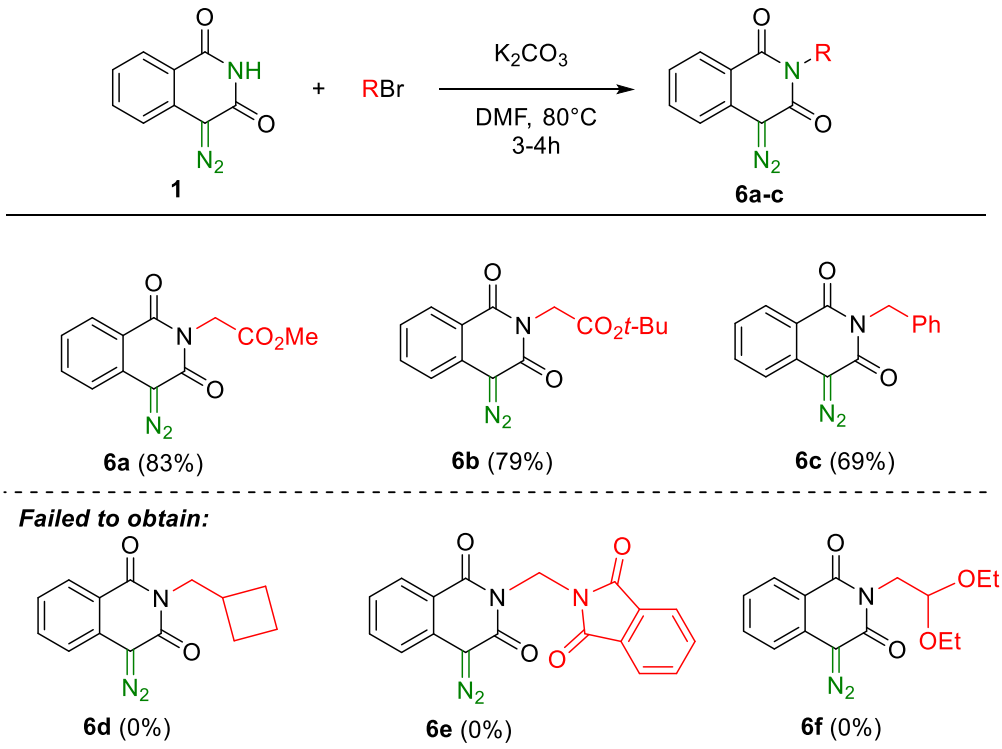
	Solvent	Base	Temperature	Time	Yield[b], %
1	DMF	Cs_2CO_3	65 °C	20 h	65
2	DMF	K_2CO_3	65 °C	20 h	69
3	DMF	DBU	80 °C	3 h	tar formation
4	DMF	DMAP	80 °C	3 h	NR[c]
5	**DMF**	**K_2CO_3**	**80 °C**	**3.5 h**	**83**
6	DMF	*t*BuOK	80 °C	3 h	tar formation
7	1,4-Dioxane	20% aq KOH	20 °C	20 h	NR
8	1,4-Dioxane	*t*BuOK	80 °C	20 h	10
9	1,4-Dioxane	K_2CO_3	80 °C	20 h	18
10	1,4-Dioxane	NaH	80 °C	20 h	28
11	Toluene	NaH	65 °C	20 h	25
12	MeCN	Et_3N	80 °C	3 days	NR

13	MeCN	DBU	80 °C	3 days	NR

[a] Reagents: **1** (0.27 mmol), methyl bromoacetate (0.30 mmol), base (0.33 mmol), solvent 1.5 mL; [b] Isolated yields; [c] NR – no reaction.

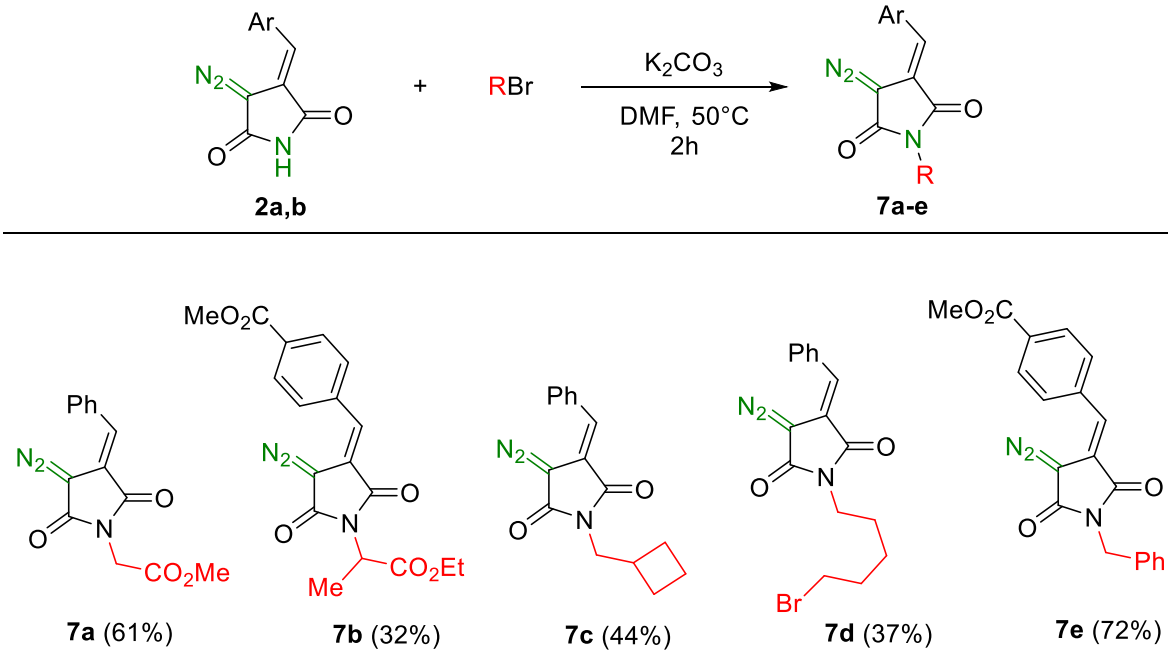
As can be seen from the table above, caesium and potassium carbonates demonstrated better results (entries 1, 2). Organic bases were found to be not suitable (entries 3, 4, 12, 13). The increase of the temperature from 65 °C to 80 °C significantly enhanced the yield (compare entries 2 and 5). We also examined 1,4-dioxane with different bases. Unfortunately, the reaction did not proceed with aqueous potassium hydroxide even at elevated temperature. Heating with K_2CO_3 at 80 °C resulted in dramatic drop of the yield (entry 9) compared to DMF. The use of stronger bases such as *t*-BuOK or NaH did not improve the reaction outcome (entries 8 and 10). Prolonged heating of **1** in acetonitrile resulted in no target product formation, starting diazo compound remained unchanged. This could be explained by low solubility of starting diazo homophthalimide **1** in aforementioned solvents even at heating. Thus, for further studies K_2CO_3, DMF and heating at 80 °C were chosen.

With the optimal conditions in hand, we explored the reaction with other alkyl halides. The reaction worked well with *tert*-butyl bromoacetate and benzyl bromide furnishing corresponding *N*-alkylated diazo derivatives in 79% and 69% yield (scheme 1). It turned out that alkyl chlorides were not suitable for alkylation of compound **1**, reaction gave complex mixtures with chloroacetonitrile, 2-chloroethanol, 2-chloro-*N*,*N*-diethylacetamide, and ethyl chloroacetate. Moreover, we were not able to obtain the desired products with several bromides, viz. (bromomethyl)cyclobutane, 2-(bromomethyl)isoindoline-1,3-dione, 2-bromo-1,1-diethoxyethane. Thus, *N*-alkylation of diazo homophthalimide **1** can be carried out using a rather limited range of very active bromides.



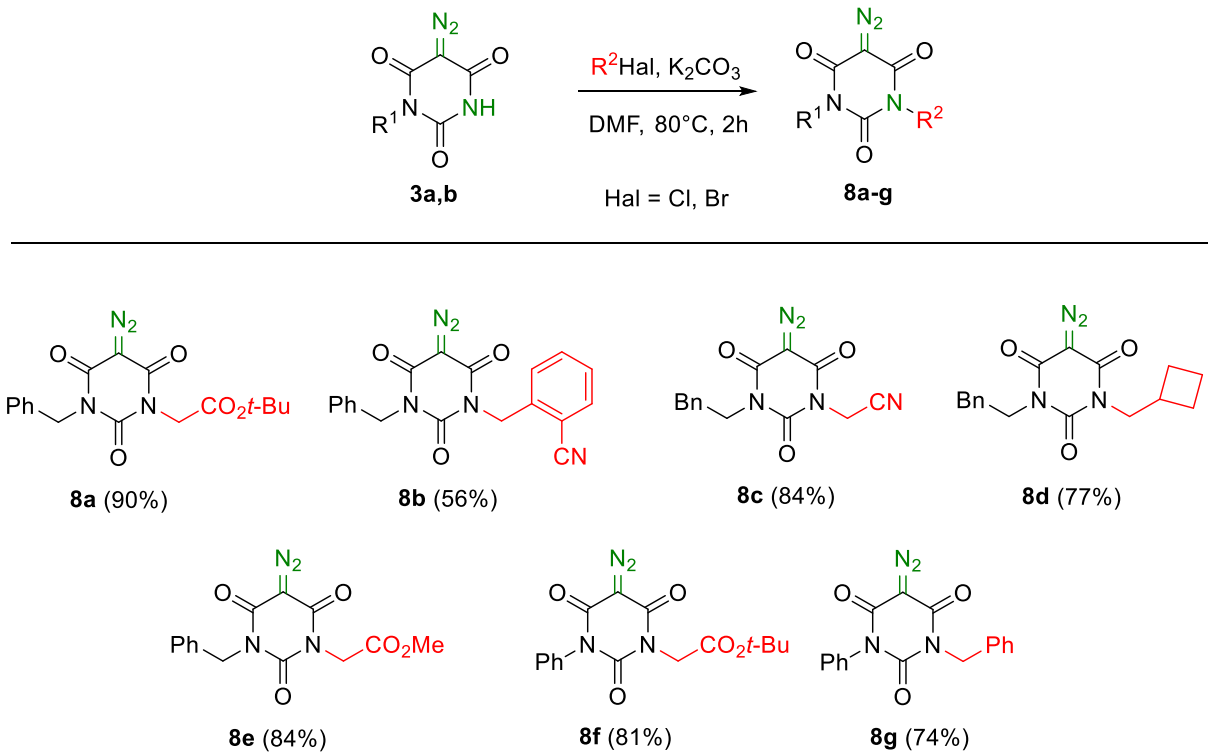
Scheme 1: Alkylation of diazo homophthalimide **1** with alkyl bromides.

We next focused on *N*-alkylation of diazo arylidene succinimides **2a**,**b** (Scheme 2). It was found that alkylation with alkyl bromides proceeded smoothly under milder conditions and was completed in 2 h, yielding substituted diazo compounds **7a-e** in moderate to good yields. In contrast to the homophthalimide analogue, compounds **2** showed higher reactivity, yielding alkylated derivatives with less reactive bromides such as (bromomethyl)cyclobutane or 1,5-dibromopentane (products **7c,d**) albeit in decreased yields. Secondary alkyl bromides could be also involved into reaction, although it gave a low yield (compound **7b**). The low yield of diazo imide **7d** can be attributed to the formation of unidentified by-products. When chloroacetonitrile was used as alkylating agent decomposition of the reaction mixture was observed.



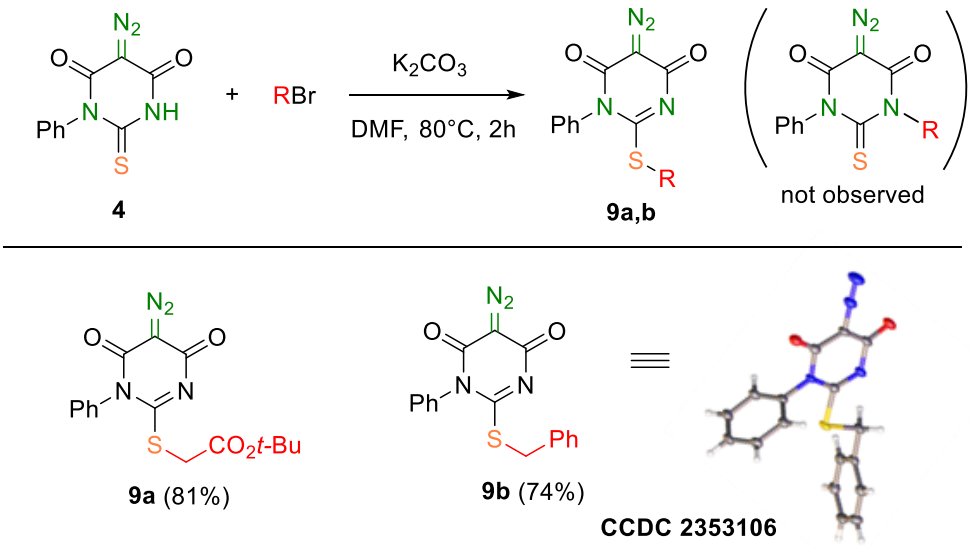
Scheme 2: Alkylation of diazo arylidenesuccinimides **2** with alkyl bromides.

Non-symmetrically substituted barbituric acid fragment is present in some biologically active compounds [26, 27]. Besides, previously we showed that monosubstituted diazo barbituric acid did not undergo metal-catalyzed decomposition with the formation of oxazole in acetonitrile [28]. Therefore, methods for the preparation of diversely substituted (including mono-*N*-protected) diazo barbituric acids are in demand. Barbituric acids **3a**,**b** readily reacted with alkyl bromides giving corresponding derivatives in moderate to high yields (Scheme 3). In contrast to aforementioned diazo imides, compound **3a** smoothly reacted with chloroacetonitrile to give corresponding derivative **8c** in 84% yield.



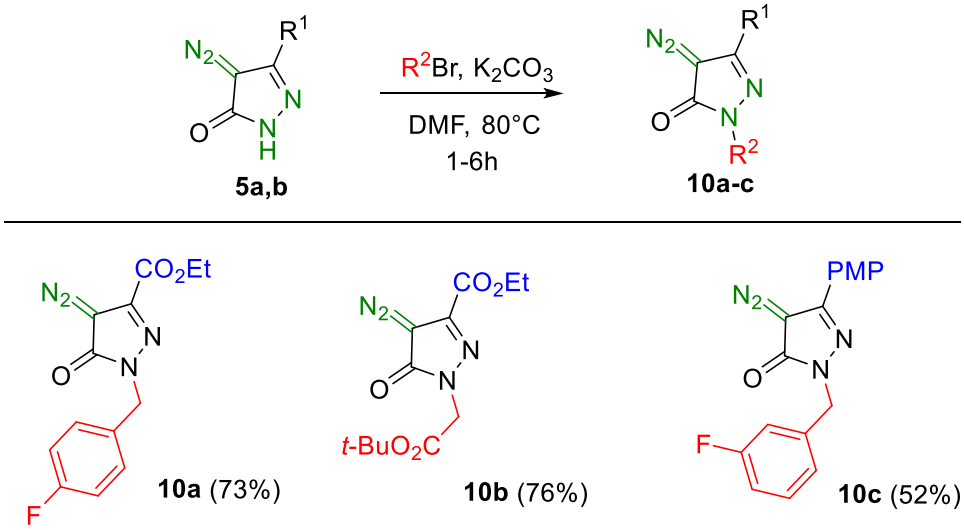
Scheme 3: Alkylation of diazo barbituric acids **3** with alkyl halides.

Thiobarbituric acid **4** has two reaction centers, which can undergo alkylation. It was found that heating diazo compound **4** with alkyl bromides in DMF at 80 °C for 2 h resulted in the formation of *S*-alkylated derivatives only (Scheme 4). The structure of product **9b** was unambiguously confirmed by the X-ray analysis data. The obtained compounds **9** are representatives of a class of diazo pyrimidines hitherto not described in the literature. Their chemical behavior and possible application in synthesis remain to be investigated.



Scheme 4: Alkylation of diazo diazo thiobarbituric acid **4** with alkyl bromides.

The reactivity of diazo pyrazolones **5a**,**b** in *N*-alkylation reaction with alkyl halides was found to be dependent on the substituent at C-3 position (Scheme 5). The electron withdrawing ester group provoked higher reactivity and the reaction was finished in 1 h in DMF at 80 °C in the presence of potassium carbonate as a base. When *p*-methoxyphenyl substituted diazo pyrazolone **5b** was used instead, the reaction was completed in 6 h and gave a lower yield. The higher temperature did not improve the yield, but rather caused degradation.



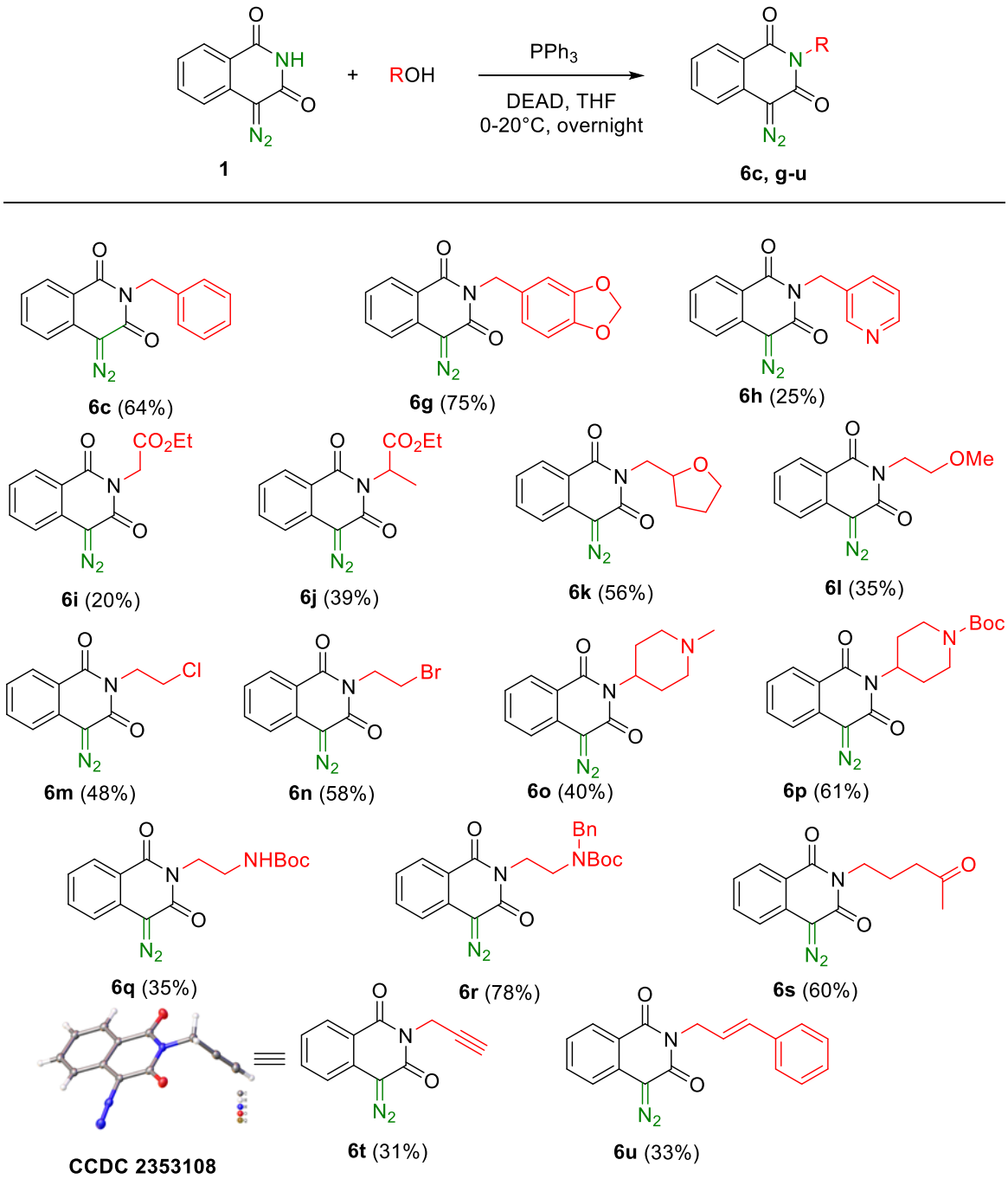
Scheme 5: Alkylation of diazo pyrazolones **5** with alkyl bromides.

Since the alkylation of selected diazo heterocycles with alkyl halides was limited mostly by the use of alkyl bromides and turned out to be dependent on both the halide reactivity and the electronic nature of substituents in the diazo molecule, we next focused on the use of alcohols as alkylating agents for the functionalization of diazo NH-heterocycles. We assumed Mitsunobu reaction would serve well for this purpose.

To test the feasibility of *N*-alkylation of diazo imides with alcohols in terms of Mitsunobu reaction we reproduced the synthesis of derivative **6c** using benzyl alcohol. To our delight, the interaction underwent smoothly at room temperature yielding target *N*-benzyl diazo homophthalimide in comparable yield (64% vs 69%). The low solubility of the starting compound was not an obstacle in this case, the diazo imide **1** fully dissolved during the curse of the reaction.

In order to evaluate the scope and limitations of the method we synthesized a series of *N*-alkyl diazo homophthalimides **6c-r** (Scheme 6). In contrast to alkyl bromides, primary and secondary alcohols proved to be the alkylating agents of choice for diazo homophthalimide **1** yielding wide scope of diversely functionalized diazo derivatives. The order of the reagent loading had no effect on the reaction outcome.

Intriguingly, ethyl 2-hydroxyacetate was less effective comparing to methyl 2-bromoacetate, giving compound **6f** in 20% yield (83% for bromoacetate).

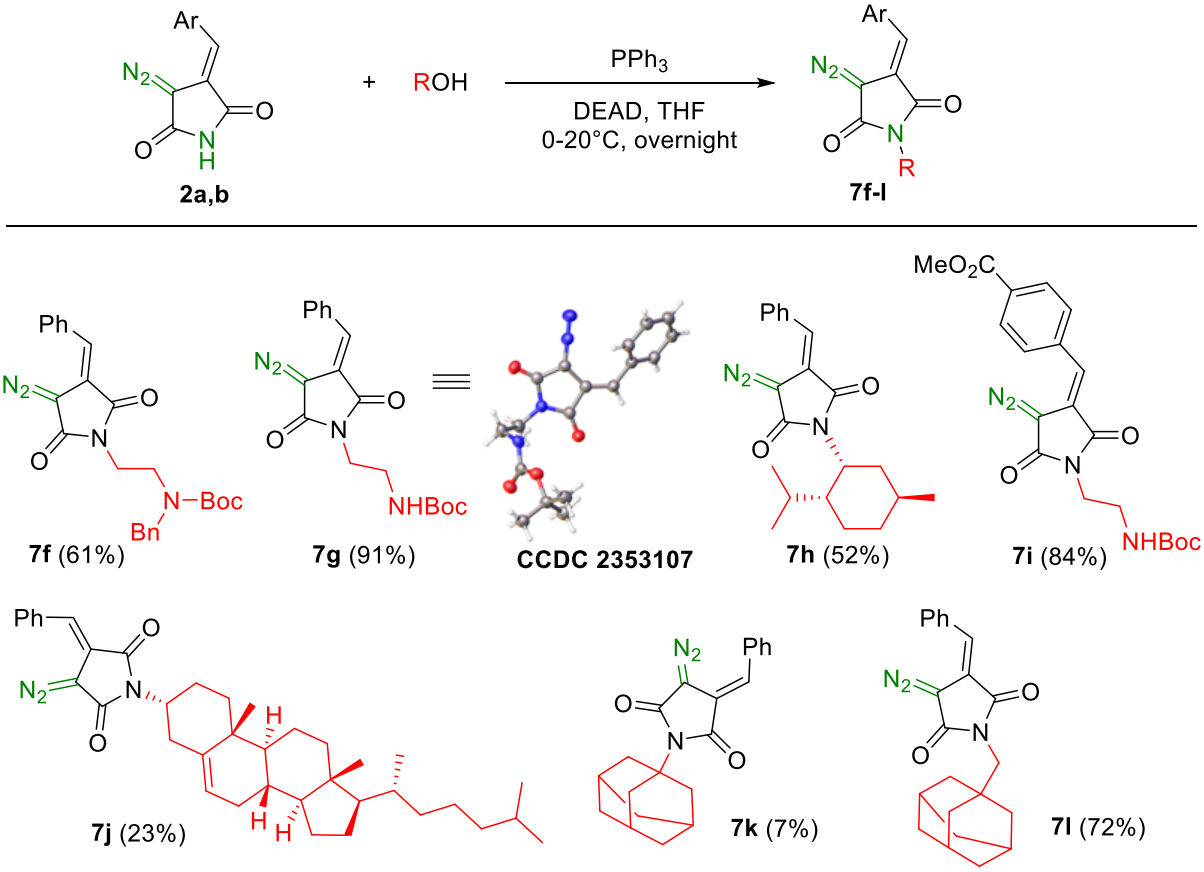


Scheme 6: Alkylation of diazo homophthalimide **1** with alcohols.

Diazo arylidene succinimides **2a**,**b** likewise smoothly underwent alkylation with alcohols (Scheme 7). It was found that the order of the reagent adding played a crucial role in this case. When triphenylphosphine was pre-stirred with DEAD before diazo NH-heterocycle and alcohol adding (reverse order) the yields were twice higher compared to addition of DEAD to a pre-stirred mixture of PPh_3, diazo imide, and alcohol (direct order). A possible reason for this may be the side process of

phosphazene formation during the interaction of the diazo group with triphenylphosphine.

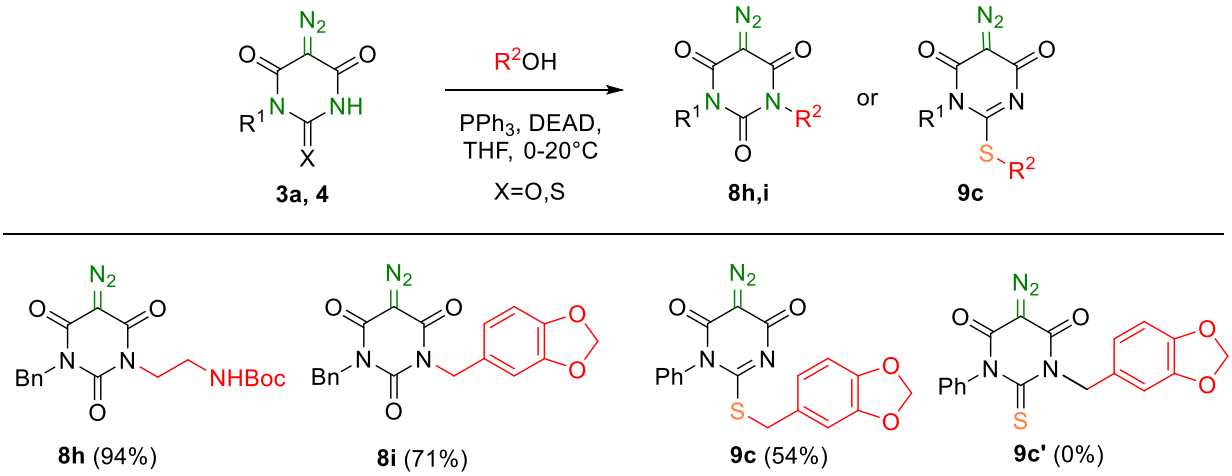
Taking into account that Mitsunobu alkylation proceeds via S_N2 mechanism with the formation of carbon-heteroatom bond with a stereoselective outcome, we performed a reaction of **2a** with menthol and cholesterol. In both cases, the inversion of stereocenter configuration was observed (products **7h**, **7j**). When diazo **2a** was involved into the reaction with 1-adamantanol, the target product **7k** was obtained only in 7% yield.



Scheme 7: Alkylation of diazo arylidenesuccinimide **2** with alcohols.

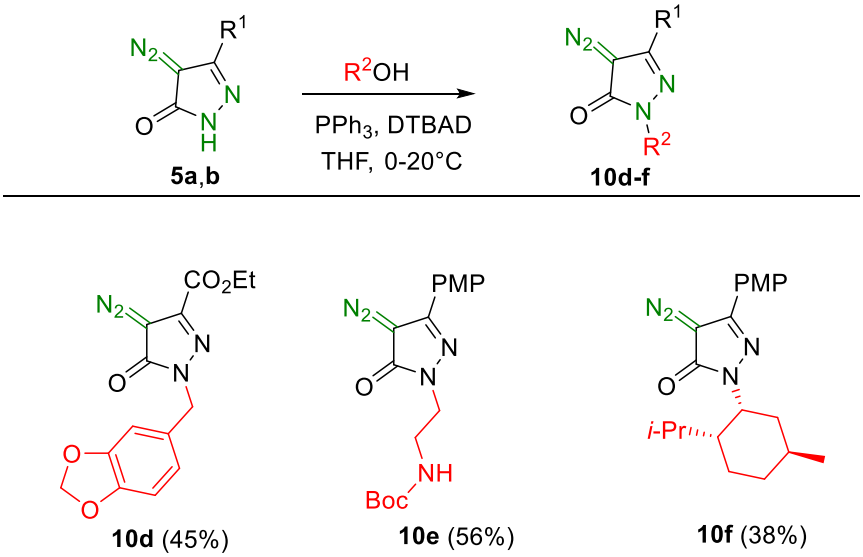
Diazo barbituric acid **3a** was readily alkylated with alcohols to give compounds **8h**,**i** in high yields (Scheme 8). The reagent loading order had almost no impact on the reaction outcome. In contrast to the *N*-alkylation of 5,5-dimethyl thiobarbituric acid derivative previously described in the literature [29], Mitsunobu reaction of diazo

thiobarbituric acid **4** proceeded exclusively as *S*-alkylation, yielding only the product **9c** (Scheme 8).



Scheme 8: Alkylation of diazo (thio)barbituric acids **3a** and **4** with alcohols.

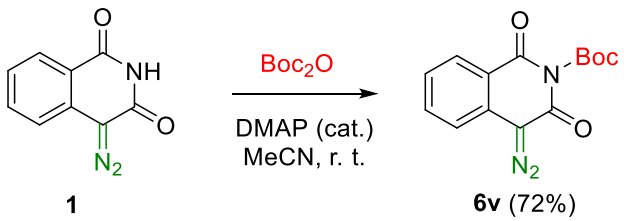
Alkylation of diazo pyrazolones **5a**,**b** with alcohols was slightly less effective than alkylation with alkyl bromides, resulting in moderate yields of the corresponding products **10d,e** (Scheme 9). At the same time, the use of the Mitsunobu reaction allowed the introduction of a sterically demanding *sec*-alkyl substituent into the diazo heterocycle (**10f**). Diethyl azadicarboxylate was replaced by di-*tert*-butyl azadicarboxylate due to the fact that formed in the course of reaction diethyl hydrazine-1,2-dicarboxylate has close chromatographic mobility with the target compounds and could not be separated from them. The reverse order of reagents adding was required.



Scheme 9: Alkylation of pyrazolones **5** with alcohols.

It is noteworthy that despite the known ability of diazocarbonyl compounds to react with triphenylphosphine to form phosphazenes,[30,31] the alkylation of diazo heterocycles under Mitsunobu reaction conditions can be carried out with high chemoselectivity, avoiding this side reaction (also by using the reverse order of mixing reagents).

In order to improve the solubility profile and to introduce a substituent that can be easily removed afterwards, we performed a reaction of diazo homophthalimide **1** with Boc_2O (Scheme 10). The *N*-Boc-protected derivative **6v** was isolated in high yield.



Scheme 10: Preparation of *N*-Boc diazo homophthalimide **6v**.

Conclusion

In conclusion, we expanded the scope of alkyl halides, which can be employed for alkylation of diazo NH-heterocycles and demonstrated the utility of the Mitsunobu

reaction in the synthesis of *N*-funcionalized diazo derivatives with maintaining the diazo function. The efficiency of both *N*-alkylation methods using halides and alcohols has been compared for a series of diazo heterocyclic substrates. The Mitsunobu reaction-based approach exhibits a wide substrate scope with regards to alcohol and diazo pattern. The undoubted advantages of the method are mild conditions, the use of less hazardous alkylating agents and insertion of important for medicinal chemistry substituents. The developed method allows introduction of menthyl and cholesteryl motifs in a stereoselective manner. The diazo thiobarbituric acid selectively gave *S*-alkylated product under both protocols, providing a hitherto undescribed type of diazo pyrimidine. These synthetic findings are expected to significantly boost the research in the field of diazo chemistry and its application to the synthesis of valuable structures.

Supporting Information

Supporting Information File 1

File Name: General experimental information, synthetic procedures, analytical data, X-ray crystallographic data.

File Format: pdf

[https://www.beilstein-journals.org/bjoc/content/supplementaryxxxx-xxxx-xx-xx-S1.pdf]

Supporting Information File 2:

File Name: Copies of NMR and IR spectra for the reported compounds.

File Format: pdf

[https://www.beilstein-journals.org/bjoc/content/supplementaryxxxx-xxxx-xx-xx-S2.pdf]

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