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α-Diazo-β-oxosulfones as Partners in the Wolff 1,2,3-Triazole Synthesis and the Wolff Rearrangement in the Presence of Aromatic Amines

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ABSTRACT

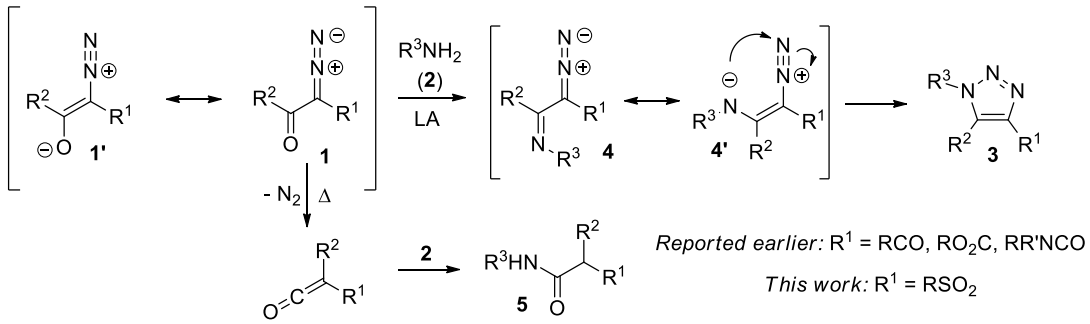
The readily available α-diazo-β-oxosulfones have been employed, for the first time, in the Wolff cyclocondensation with aromatic amines promoted by 1.5-fold excess of $TiCl_4$. The reaction was found to be general (as illustrated by 15 product examples) and resulted in moderate yields of medicinally relevant sulfonyl 1,2,3-triazoles. Excluding the Lewis acid promoter resulted in a clean and high-yielding formation of α-sulfonyl acetanilides resulting from the thermal Wolff rearrangement and trapping of the ketene intermediate with an aniline molecule.

Introduction

The Wolff 1,2,3-triazole synthesis from α-diazo carbonyl compounds **1** and primary amines **2**[1] constitutes a valuable alternative to the currently much exploited Huisgen ('click') cycloaddition of alkynes and azides.[2] Unlike the latter, the former method is regiochemically unambiguous when delivering 1,4,5-trisubstituted 1*H*-1,2,3-triazoles **3**, doesn't rely on transition metal catalysts (a favorable feature from the pharmaceutical process chemistry standpoint[3]) and is rooted in two densely populated reagent areas: those of the primary amines and of α-C-H carbonyl compounds from which α-diazo carbonyl compounds can be easily prepared[4]. The innate deactivation of the carbonyl group in such compounds by the diazo group (due to the contribution of resonance structure **1′**) reduces the electrophilicity of the former,[5] particularly and requires that stoichiometric amounts of a Lewis acid promoter (most commonly, $TiCl_4$[6]) are employed, along with elevated reaction temperatures. It is unsurprising, therefore, that electron-withdrawing groups R^1 promote this process by increasing both the electrophilicity of the carbonyl group in **1** toward reaction with amine **2** (to give imine **4**). This is the likely reason why

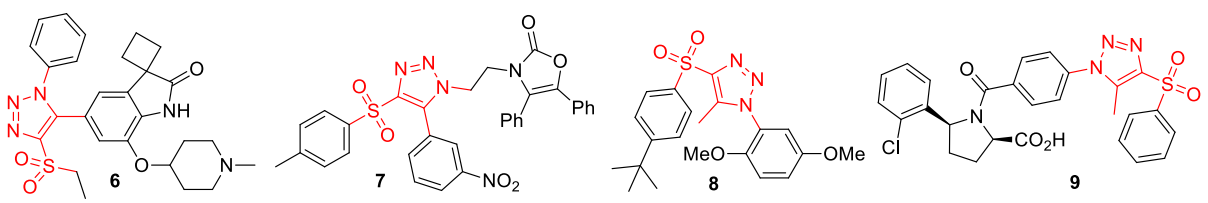
the variety of Wolff cyclization-derived 1,2,3-triazoles **3** is well represented by 4-carbonyl derivatives such as 4-acyl-[7], 4-(alkoxycarbonyl)-[8] and, to a lesser extent[5,9], 4-(aminocarbonyl)-1,2,3-triazoles. Surprisingly, 4-sulfonyl derivatives **1** ($R^1 = SO_2R$) have not been reported as partners in the Wolff cyclization, possibly due to less efficient conjugation to the carbonyl group in question (Figure 1). These compounds, however, are easily accessible from the respective β-keto sulfones by diazotransfer reaction[10] and have been reported to undergo such transformations as the thermal Wolff rearrangement with the trapping of the respective ketene intermediate with nitrogen nucleophiles (giving rise to amides **5**)[11] and imines (producing β-lactams).[12]

Figure 1. The Wolff 1,2,3-triazole synthesis and electron-withdrawing R^1 substituent variations reported to-date and investigated in this work.



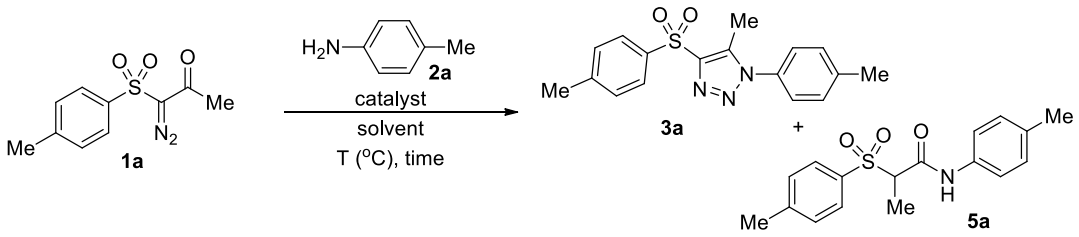
Puzzled by the lack of reports in the literature on the involvement of α-sulfonyl α-diazocarbonyl compounds **1** ($R^1 = SO_2R$) in the Wolff 1,2,3-triazoles synthesis, we decided to investigate this possibility. Filling this methodology void, we reasoned, would provide a streamlined entry in the 1,5-disubstituted 4-sulfonyl 1,2,3-triazole core which is featured in a range of biologically active compounds such as bromodomain inhibitor **6**,[13] antifungal compound **7**,[14] pregnane X receptor antagonist **8** for attenuation of drug metabolism[15] and anti-inflammatory GPR43 receptor agonist **9**[16] (Figure 2). Notably, such an approach would complement the earlier reported synthesis of similarly substituted 1,2,3-triazoles by the Dimroth cyclocondensation of β-keto sulfones with aryl azides.[17]

Figure 2. Examples of biologically active compounds bearing a 1,5-disubstituted 4-sulfonyl 1,2,3-triazole moiety.



Results and Discussion

Table 1. Conditions screening for the reaction of **1a** and **2a**.



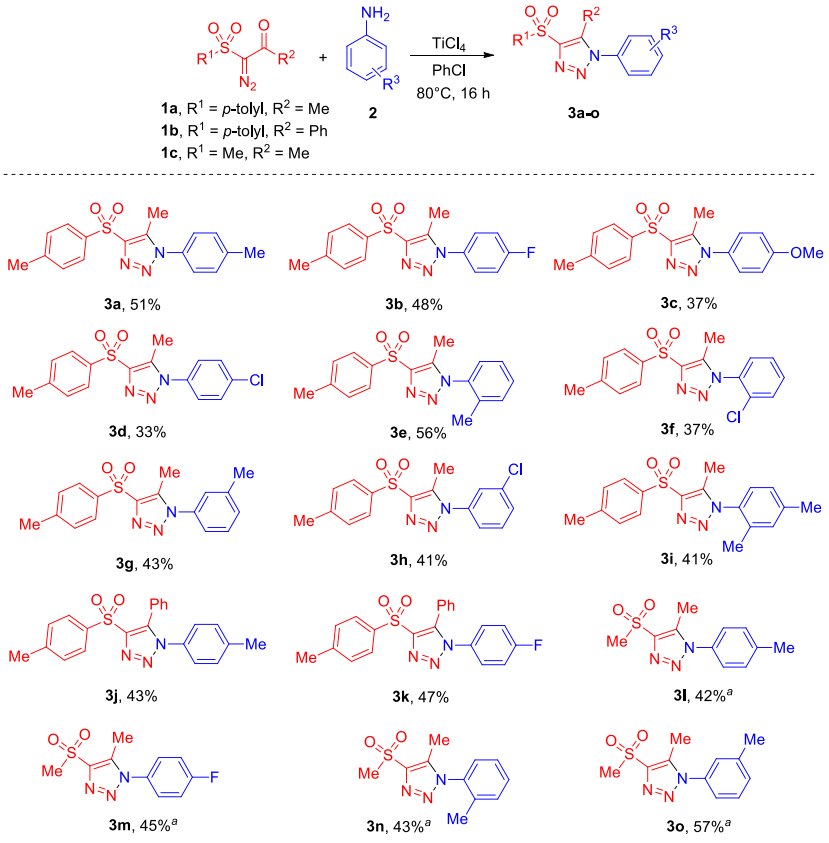
Entry	Solvent	T (°C)	Time (h)	Catalyst (equiv.)	Yield of **3a** (%)	Yield of **5a** (%)
1	PhMe	80	16	$TiCl_4$ (1.0)	35	13
2	DMF	80	16	$TiCl_4$ (1.0)	13	2
3	PhCl	80	16	$TiCl_4$ (1.0)	38	3
4	DCE	80	16	$TiCl_4$ (1.0)	35	3
5	1,4-dioxane	80	16	$TiCl_4$ (1.0)	22	10
6	PhCl	80	16	$Zn(OTf)_4$ (0.1)	0	42
7	PhCl	80	16	$BF_3{\cdot}Et_2O$ (0.2)	0	43
8	PhCl	80	16	$ZnCl_2$ (0.2)	0	50
9	PhCl	80	16	$AlCl_3$ (0.2)	5	38
10	PhCl	80	16	$Ti(O\textit{i}Pr)_4$ (1.0)	3	35
11	PhCl	80	16	$SnCl_4$ (1.0)	1	37
12	PhCl	80	16	$FeCl_2$ (1.0)	1	27
13	PhCl	110	16	–	0	52
14	PhCl	110	3	–	0	77
15	PhCl	80	16	$TiCl_4$ (1.5)	51	0
16	PhCl	80	8	$TiCl_4$ (1.5)	22	0
17	PhCl	80	40	$TiCl_4$ (1.0)	38	4
18	PhCl	110	16	$TiCl_4$ (1.5)	40	0
19	PhCl	80	40	$TiCl_4$ (1.5)	36	0
20	$PhCF_3$	80	16	$TiCl_4$ (1.5)	48	0

In order to find suitable conditions for the efficient cyclocondensation of β-keto-α-diazo sulfones with primary amines, we investigated the reaction of diazo compound **1a**[18] with *p*-toluidine (**2a**) (Table 1). The initial reaction conducted in toluene at 80 ºC for 16 h in the presence of equimolar amount of titanium(IV) chloride gave 35% yield of the desired triazole **3a** along with a substantial quantity (13%) of amide **5a** resulting from the Wolff rearrangement and

trapping of the ketene intermediate with the amine (Table 1, entry 1). While lowering the temperature led to no conversion at all (not shown), our goal became to screen for solvents and Lewis acid catalysts/promoters which would direct the reaction toward the formation of the desired product (**3a**). As it follows from the data presented in Table 1, $TiCl_4$ turned out to be the most efficient promoter to cause the formation of **3a** (the best yield of 51% was achieved with 1.5 equiv. of $TiCl_4$, entry 15) while in other cases, **5a** dominated in the product mixture. Interestingly, excluding Lewis acid altogether, raising the temperature to 110 ºC and shortening reaction time to 3 h resulted in 77% isolated yield of **5a** (Table 1, entry 14).

While the yield of the target product (**3a**) was rather moderate, we attributed it to the limited ability of substrates like **1a** to enter the Wolff cyclocondensation (thereby justifying the absence of any examples of such reaction in the literature to-date, *vide supra*). This was confirmed by the preliminary scope investigation of the newly developed 4-sulfonyl 1,2,3-triazole synthesis undertaken with the use of substrates **1a**,[18] **1b**[19] and **1c**[19-20] as well as a set of substituted anilines **2** (Scheme 1).

Scheme 1. Synthesis of triazoles **3a-o**.

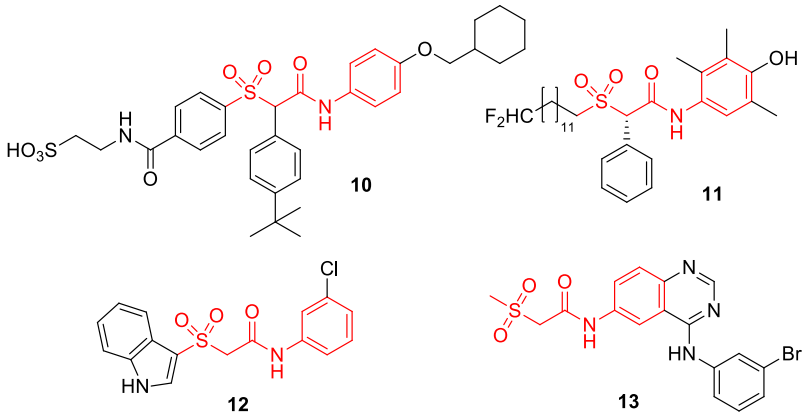


[a] Reaction was conducted over 40 h.

It was apparent that the moderate yields of these cyclocondensations were virtually independent of substrates employed and are, again, likely a corollary of a difficult reactivity. Interestingly, neither the nature of the ketone nor that of the sulfone portion (aromatic *vs.* aliphatic) in substrates **1a-c** appeared to affect the yield of the reaction. However, methyl sulfone **1c** required substantially longer reaction time to achieve full conversion and the isolated yields of the respective products (**3l-o**). It should be noted that aliphatic amines have been tried in this reaction and led to no appreciable 1,2,3-triazole formation.

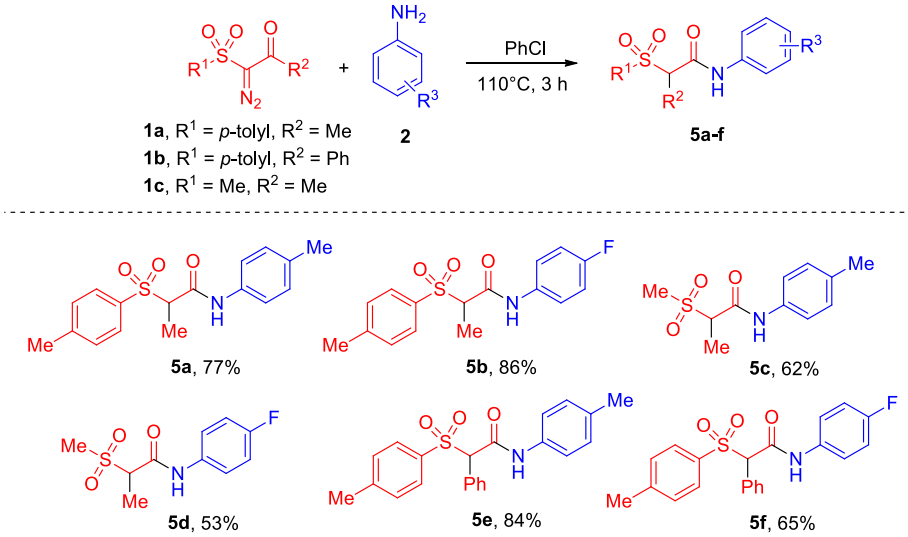
Compounds **3a-o** indeed represent the first examples of compounds bearing a sulfonyl 1,2,3-triazole core of high medicinal relevance assembled in one step *via* the Wolff cyclocondensation. At the same time, the Wolff rearrangement product **5a** obtained in respectable 77% yield (*vide supra*) is also a representative of a useful class of compounds. This notion is attested to by such examples as glucagon receptor antagonist **10**,[21] cholesterol *O*-acyl transferase inhibitor **11**,[22] antiviral compound **12**[23] as well as compound **13**, an inhibitor of enzymes containing redox-sensitive cysteines[24] (Figure 3). Considering that examples of the Wolff rearrangement of α-diazo-β-oxo sulfones reported in the literature are limited to those of trifluoromethyl sulfones (triflones),[11-12] establishing the generality of transformation 1→5 appeared a worthy undertaking.

Figure 3. Examples of biologically active compounds bearing the α-sulfonyl acetanilide moiety.



As it follows from the data presented in Scheme 2, the thermal Wolff rearrangement of diazo compounds **1a-c** with subsequent nucleophilic trapping of the ketene intermediate proceeded with markedly higher isolated yields of compounds **5a-f** compared to the respective $TiCl_4$-promoted cyclocondensation into 1,2,3-triazoles **3a-o** (*vide supra*). In this case, however, methyl sulfones appeared to give somewhat lower product yields compared to their aryl sulfone counterparts. At the same time, with the latter, migration of methyl (**1a**) and phenyl (**1b**) groups proceeded with similar efficiency as reflected, for instance, in comparable yields of **5a** and **5e**.

Scheme 2. Synthesis of α-sulfonyl acetanilides **5a-f**.



Conclusion

We have described the first example of involving α-diazo-β-oxo sulfones in the Wolff cyclocondensation with aromatic amines. The reaction is promoted by 1.5-fold excess of titanium(IV) chloride and, while rather clean, gives moderate yields of the target medicinally relevant sulfonyl 1,2,3-triazoles. Exclusion of $TiCl_4$ from the reaction leads to thermal Wolff rearrangement of the same substrates providing, at higher temperature and over shorter period of time, products of trapping of the ketene intermediates with anilines.

ASSOCIATED CONTENT

Supporting Information

Synthetic procedures, analytical data, copies of the ^{1}H and ^{13}C NMR spectra.

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Notes

The authors declare no competing financial interest.

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KEYWORDS: α-diazo-β-oxosulfones; 1,2,3-triazoles, α-sulfonyl acetanilides; Wolff cyclocondensation; Wolff rearrangement

REFERENCES

1. (a) L. Wolff, *Justus Liebigs Ann. Chem.* **1902**, *325*, 129; (b) L. Wolff, *Justus Liebigs Ann. Chem.* **1912**, *394*, 23.
2. M. Meldal and C. W. Tornøe, *Chem. Rev.* **2008**, *108*, 2952.
3. Flahive, E.; Ewanicki, B.; Yu, S.; Higginson, P.D.; Sach, N.W.; Morao, I. *QSAR Comb. Sci.* **2007**, *26*, 679.
4. W. Regitz, *Angew. Chem., Int. Ed.* **1967**, *6*, 733.
5. Z. Wang, X. Bi, P. Liao, R. Zhang, Y. Liang, D. Dong, *Chem. Commun.* **2012**, *48*, 7076.
6. M. Ohno, M. Itoh, T. Ohashi and S. Eguchi, *Synthesis* **1993**, 793.
7. L. L. Fershtat, M. R. Radzhabov, A. A. Romanova, I. V. Ananyev, N. N. Makhova, *ARKIVOC* **2017**, *iii*, 140
8. A. C. Tome, *Sci. Synth.* **2004**, *13*, 415.
9. Z. Wang, Y. Tao, Z. Wang, J. Yan, *Polym. Chem.* **2016**, *7*, 3172.
10. C.-K. Chan, H.-S. Wang, R.-T. Hsu, M.-Y. Chang, *Synthesis* **2017**, *49*, 2423.
11. Z. Huang, S. Jia, C. Wang, E. Tokunaga, Y. Sumii, N. Shibata, *J. Fluorine Chem.* **2017**, *198*, 61.
12. Z. Huang, C. Wang, E. Tokunaga, Y. Sumii, N. Shibata, *Org Lett.* **2015**, *17*, 5610.
13. C. Abbineni, T. Linnanen, S. Mukherjee, S. Samajdar, O. Tormakangas, G. Wohlfahrt, PCT Int. Appl. WO2018109271; *Chem. Abstr.* **2018**, *169*, 112993.
14. A. Ramirez-Villalva, D. Gonzalez-Calderon, R. I. Rojas-Garcia, C. Gonzalez-Romero, J. Tamariz-Mascarua, M. Morales-Rodriguez, N. Zavala-Segovia, A. Fuentes-Benites, *MedChemComm* **2017**, *8*, 2258.
15. T. Chen, W. Lin, Y. Wang, PCT Int. Appl. WO2017165139; *Chem. Abstr.* **2017**, *167*, 444968.

16. H. Hoveyda, D. Schils, L. Zoute, J. Parcq, J. Bernard, G. Fraser, PCT Int. Appl. WO2015078949; *Chem. Abstr.* **2015**, *163*, 51674.

17. N. T. Pokhodylo, V. S. Matiychuk, M. D. Obushak, *Synthesis* **2009**, 2321.

18. D. Dar'in, G. Kantin, M. Krasavin, *Chem. Commun.* **2019**, *55*, 5239.

19. S. Ahamad, R. K. Patidar, A. Kumar, R. Kant, K. Mohanan, *ChemistrySelect* **2017**, *2*, 11995.

20. F. G. Ady, K. O. Marichev, J. A. Jensen, H. Arman, M. P. Doyle, *Org. Lett.* **2019**, *21*, 40.

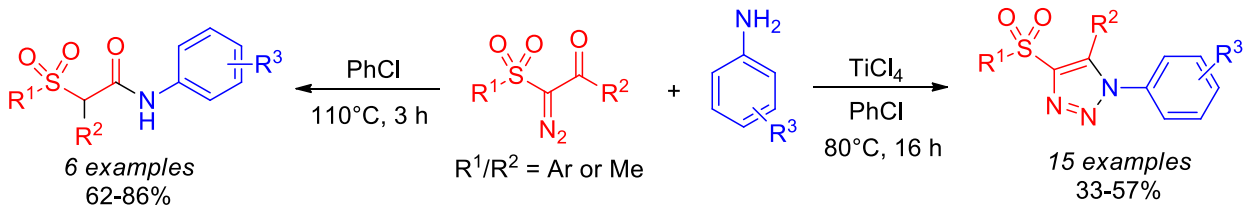
21. J. E. Gomez-Galeno, R. K. Reddy, P. D. Van Poelje, R. H. Lemus, T. H. Nguyen, M. P. Grote, Q. Dang, S. J. Hecker, V. R. Mali, M. Chen, Z. Sun, S. H. Boyer, H. Li, W. Craigo, PCT Int. Appl. WO 2008098244; *Chem. Abstr.* **2008**, *149*, 267757.

22. J. F. Patoiseau, J. M. Autin, A. Delhon, D. Junquero, Didier, French Patent FR 2845991; *Chem. Abstr.* **2004**, *140*, 339074.

23. J. He, Y. Wang, Y. Fu, G. Zhang, Z. Xu, Q. Li, Y. Zheng, J. Wang, X. Peng, x Bai, Cninese Patent CN 108276323; *Chem. Abstr.* **2018**, *169*, 283369.

24. K. S. Carrol, PCT Int. Appl. WO 2014089546; *Chem. Abstr.* **2014**, *161*, 94456.

Graphical abstract



TOC text:

α-Diazo-β-oxosulfones have been shown to undergo a $TiCl_4$-promoted Wolff cyclocondensation with anilines to give moderate yields of medicinally relevant sulfonyl 1,2,3-triazoles. If $TiCl_4$ is omitted, a thermal Wolff rearrangement occurs, leading to α-sulfonyl acetanilides formed via trapping of the respective ketene intermediate.

Key topic:

Diazo compounds