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Convenient preparation of (*E*)-3-arylidene-4-diazopyrrolidine-2,5-diones in array format

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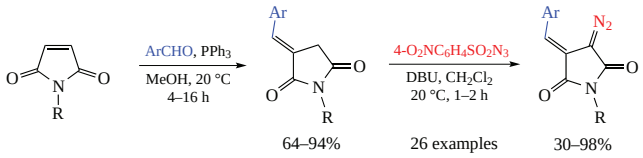
A practically convenient synthesis of (*E*)-3-arylidene-4-diazopyrrolidine-2,5-diones from N-substituted maleimides *via* the Wittig reaction and the Regitz diazo transfer has been developed. In all 26 cases studied, only one chromatographic purification was required with no need for aqueous workup, which makes this protocol amenable to producing the emerging class of diazo compounds in parallel format.



Keywords: privileged structures, maleimides, Wittig reaction, Michael acceptors, diazo transfer, diazo compounds, parallel synthesis.

Besides their notoriety as potential sources of false-positives in biological assays,[1] the so-called Michael acceptors (electron-deficient olefins capable of undergoing 1,4-conjugate nucleophilic addition) have found significant utility in medicinal chemistry. Michael addition of cysteine residues has been successfully exploited in the design of targeted covalent inhibitors.[2] Many natural products endowed with anticancer activity possess Michael acceptor motifs[3] which are essential pharmacophoric elements of these compounds.[4]

Recently, 3-arylidene pyrrolidine-2,5-diones **1** have drawn our attention as a potential source of tunable-reactivity Michael acceptors. Not only have such compounds displayed various biological activity documented in the literature (such as antiviral,[5] anticancer[6] and vasorelaxant[7]), they have been recently termed 'exocyclic methylidene maleimides' and employed in the study on bioconjugation to cysteines.[8] Moreover, the unsubstituted methylene group in **1** has recently been shown to be sufficiently acidic to allow for direct Regitz diazo transfer as demonstrated by Bhat and co-workers who prepared several 3-arylidene-4-diazopyrrolidine-2,5-diones **2** and used them in [2+1] cycloaddition with aldehydes.[9] Our own expertise in diazo chemistry inspired us to consider diazo succinimides **2** as promising templates for introducing various new elements of diversity at position 4 of 3-arylidene pyrrolidine-2,5-diones **1** (Figure 1). In particular, we have been able to involve them in Rh^{II}-catalyzed X–H insertion reactions with alcohols, thiols and carboxylic acids.[10] This even more encouraged us to cover as large chemical space of 3-arylidene-4-diazopyrrolidine-2,5-diones **2** as possible, preferably in parallel format. Synthetic procedure reported by Bhat and co-workers[9] was not amenable to array synthesis as it involved an aqueous extractive workup operation. Hence, we aimed to develop such a synthesis of compounds **2** which would exclude aqueous workup and thus allow for the preparation of these compounds in fairly large cohorts in parallel. Herein, we report a successful realization of this goal.

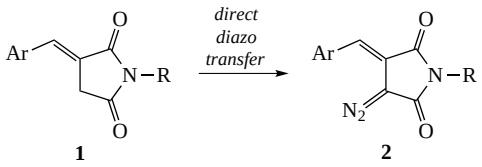


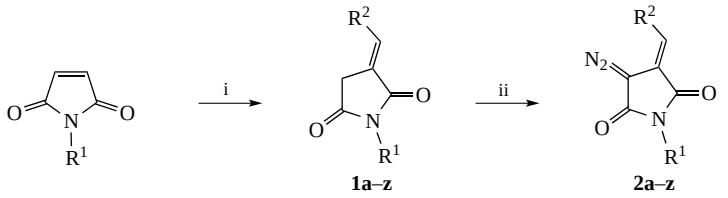
Figure 1 Compounds **1** and **2** explored as templates for a new medicinally important Michael acceptor design.

(*E*)-Configured 3-arylidene pyrrolidine-2,5-diones **1a–z** were prepared in parallel from *N*-aryl maleimides using a reported approach based on the conjugate addition of triphenylphosphine and the subsequent Wittig reaction of the resulting phosphonium ylide with aromatic aldehydes (Scheme 1).[11] However, unlike noted recently, the reaction was remarkably efficient, clean and high-yielding at room temperature in methanol.[†] Crystalline 3-arylidene succinimides **1a–z** thus obtained did not require further purification and were directly used in the diazo transfer step.

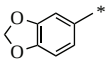
As to the latter, we considered the relatively high lipophilicity of substrates **1a–z** (for instance, LogP value for **1t** was calculated[12] as 2.64) and deemed them unsuitable substrates for the recently developed 'sulfonyl-azide-free' (SAFE) diazo transfer protocol in aqueous medium.[13] Moreover, the SAFE protocol would not allow avoiding the extractive workup operation which was our initial goal. Hence, the diazo transfer step was conducted using 4-nitrophenylsulfonyl azide and DBU in dichloromethane for all substrates.[‡] Considering that both

[†] *General procedure for the preparation of compounds* **1a–z** *via the Wittig reaction*. To a solution of N-substituted maleimide (10 mmol) in methanol (50 ml), triphenylphosphine (11 mmol) was added, and the mixture was stirred for 20 min followed by the addition of an aromatic aldehyde (10.5 mmol). In several minutes, precipitation was observed, and the mixture was stirred at ambient temperature for 4–16 h. Upon cooling in ice bath, the thick precipitate was filtered off, washed with methanol (20 ml) and air-dried to afford benzylidene succinimides **1a–z**.

[‡] *General procedure for the preparation of compounds* **2a–z** *via the Regitz diazo transfer*. To a stirred solution/suspension of imide **1** (2 mmol) in CH_2Cl_2 (15 ml), 4-$O_2NC_6H_4SO_2N_3$ (479 mg, 2.1 mmol) and DBU (313 μl, 2.1 mmol) were added, and the mixture was stirred at ambient temperature for 1–2 h (TLC control). The resulting mixture was loaded on a silica gel column eluted with CH_2Cl_2 to afford pure diazo compounds **2a–z**.



	R^1	R^2	Yield (%) **1**	Yield (%) **2**
a	4-$MeOC_6H_4$	4-$F_3CC_6H_4$	74	81
b	Ph	3,4,5-$(MeO)_3C_6H_2$	93	92
c	Ph	4-$MeO_2CC_6H_4$	89	87
d	Bn	Ph	84	83
e	Ph	2-FC_6H_4	93	98
f	4-MeC_6H_4	Ph	85	91
g	piperonyl	3,4-$(MeO)_2C_6H_3$	94	95
h	4-FC_6H_4	Ph	87	59
i	4-ClC_6H_4	3,4-$(MeO)_2C_6H_3$	86	89
j	4-MeC_6H_4	CH=CHPh-(*E*)	72	84
k	Bn	4-ClC_6H_4	84	94
l	4-FC_6H_4	4-$O_2NC_6H_4$	64	54
m	4-$MeOC_6H_4$	2-thienyl	69	88
n	Ph	4-$Me_2NC_6H_4$	84	92
o	Ph	4-$MeOC_6H_4$	85	96
p	Ph	3-MeC_6H_4	82	88
q	Ph	2-$MeOC_6H_4$	78	84
r	Ph	4-MeC_6H_4	87	89
s	Ph	2-MeC_6H_4	80	87
t	Ph	Ph	82	84
u	Ph	4-FC_6H_4	86	81
v	Ph	3-FC_6H_4	81	76
w	Ph	4-ClC_6H_4	90	77
x	Ph	4-$F_3CC_6H_4$	81	75
y	Ph	4-$O_2NC_6H_4$	90	33
z	Ph	3-$O_2NC_6H_4$	93	30


(piperonyl)

Scheme 1 *Reagents and conditions*: i, R^2CHO, PPh_3, MeOH, 20 °C, 4–16 h; ii, 4-$O_2NC_6H_4SO_2N_3$, DBU, CH_2Cl_2, 20 °C, 1–2 h.

DBU and 4-nitrobenzenesulfonamide (the secondary reaction product) were significantly more polar compared to compounds **2a**–**z**, the latter were easily purified chromatographically by loading the reaction mixture directly on a silica gel column. Thus, the aqueous workup step was avoided altogether, which facilitated performing the 26 reactions as well as the purification of the resulting yellow to orange crystalline products **2a**–**z** in parallel format (see Scheme 1).

Several observations could be made regarding the scope of the syntheses of compounds **1a**–**z** and their transformations into diazo counterparts **2a**–**z**. Firstly, the yields and product purities were uniformly high in the first step (the Wittig reaction) for all substituent combinations on the succinimide core (the crude products obtained in these reactions were sufficiently pure to be directly used in the next step). The same could be noted for the second (the Regitz diazo transfer) step, except for the markedly lower yields obtained with substrates containing nitrobenzylidene moiety (*cf.* **2l**, **2y**–**z**). While the reasons for this remain unclear, one could speculate that the nitrobenzylidene group could over-stabilize the enolate intermediate formed before the diazo transfer event and thus lower the effectiveness of the latter.

While the (*E*)-configuration of the Wittig products **1a**–**z** had been established previously,[11] we were curious to see if it was possibly changed in the diazo transfer step. However, as shown for two representative products (**2f** and **2j**)[§] for which we managed to obtain a single-crystal X-ray diffraction structure, the double bond in question retained its (*E*)-configuration with respect to the imide carbonyl group (Figure 2).

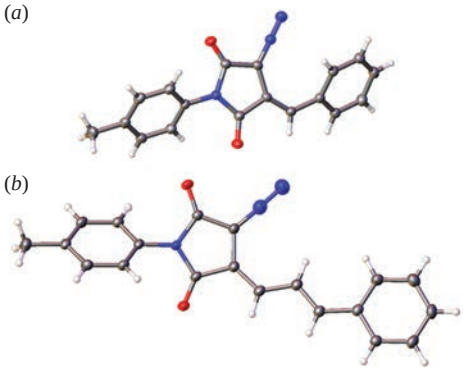


Figure 2 Single-crystal X-ray crystallographic structure of compounds (*a*) **2f** and (*b*) **2j**.

In summary, we have described a practically convenient synthesis of the recently reported 3-arylidene-4-diazopyrrolidine-2,5-diones. The 26 representative examples were produced in generally high yields over two steps, the Wittig reaction of a succinimide phosphonium ylide generated *in situ*, and the Regitz diazo transfer reaction using 4-$O_2NC_6H_4SO_2N_3$ and DBU. In all cases, only one chromatographic purification was employed with no need for aqueous workup. This makes this method amenable to producing compounds of such chemotype in parallel format. With the new, broad arsenal of these reactants in hand, we will proceed studying their transformations in the classical reactions of diazo compounds.

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[§] *Crystal data for* **2f**. $C_{18}H_{13}N_3O_2$ (M = 303.32), monoclinic, space group $P2_1$, a = 9.34450(10), b = 13.38360(10) and c = 23.8971(2) Å, β = 99.4670(10)°, V = 2947.94(5) Å^3, Z = 2, T = 100.0(10) K, μ = 0.747 mm^{-1}, d_{calc} = 1.367 g cm^{-3}, 60289 reflections measured, 12289 independent reflections (R_{int} = 0.0347, R_σ = 0.0269) which were used in all calculations. The final R_1 was 0.0446 [$I > 2\sigma(I)$] and wR_2 was 0.1259 (all data).

Crystal data for **2j**. $C_{20}H_{15}N_3O_2$ (M = 329.35), triclinic, space group $P\bar{1}$, a = 6.21290(10), b = 9.2395(2) and c = 14.5466(3) Å, α = 79.089(2)°, β = 85.627(2)°, γ = 76.324(2)°, V = 796.26(3) Å^3, Z = 2, T = 100.0(10) K, μ = 0.737 mm^{-1}, d_{calc} = 1.374 g cm^{-3}, 8190 reflections measured, 3031 independent reflections (R_{int} = 0.0298, R_σ = 0.0309) which were used in all calculations. The final R_1 was 0.0525 [$I > 2\sigma(I)$] and wR_2 was 0.1583 (all data).

CCDC 2014276 and 1999007 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2021.01.010.

References

1 J. B. Baell and J. W. M. Nissink, *ACS Chem. Biol*., 2018, **13**, 36.
2 (*a*) P. A. Jackson, J. C. Widen, D. A. Harki and K. M. Brummond, *J. Med. Chem*., 2017, **60**, 839; (*b*) R. A. Bauer, *Drug Discovery Today*, 2015, **20**, 1061.
3 J. B. Baell and M. A. Walters, *Nature*, 2014, **513**, 481.
4 X. Deng, L. Kong, Y. Zhao, J. He, L.-Y. Peng, Y. Li and Q.-S. Zhao, *Nat. Prod. Bioprospect*., 2012, **2**, 210.
5 K. Luo, Y. Bao, F. Liu, C. Xiao, K. Li, C. Zhang, R. Huang, J. Lin, J. Zhang and Y. Jin, *Eur. J. Med. Chem*., 2019, **179**, 805.
6 E. M. Shalaby, A. S. Girgis, H. Farag, A. F. Mabied and A. N. Fitch, *RSC Adv*., 2016, **6**, 112950.
7 G. Maga, F. Falchi, M. Radi, L. Botta, G. Casaluce, M. Bernardini, H. Irannejad, F. Manetti, A. Garbelli, A. Samuele, S. Zanoli, J. A. Este, E. Gonzalez, E. Zucca, S. Paolucci, F. Baldanti, J. De Rijck, Z. Debyser and M. Botta, *ChemMedChem*, 2011, **6**, 1371.
8 D. Kalia, P. V. Malekar and M. Pathasarathy, *Angew. Chem., Int. Ed*., 2016, **55**, 1432.
9 D. Laha and R. Bhat, *Asian J. Org. Chem*., 2020, **9**, 918.
10 E. Chupakhin, M. Gecht, A. Ivanov, G. Kantin, D. Dar'in and M. Krasavin, *Synthesis*, in press.
11 (*a*) E. Hedaya and S. Theodoropulos, *Tetrahedron*, 1968, **24**, 2241; (*b*) J. H. Kim, S. H. Jung and J. H. Lee, *Bull. Korean Chem. Soc*., 2004, **25**, 1088; (*c*) K. P. Haval and N. P. Argade, *Tetrahedron*, 2006, **62**, 3557.
12 https://www.molinspiration.com/
13 P. A. Zhmurov, D. V. Dar'in, O. Yu. Bakulina and M. Krasavin, *Mendeleev Commun*., 2020, **30**, 311.

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