Huisgen Zwitterions

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A Novel Reaction of the "Huisgen Zwitterion" with Chalcones and Dienones: An Efficient Strategy for the Synthesis of Pyrazoline and Pyrazolopyridazine Derivatives**

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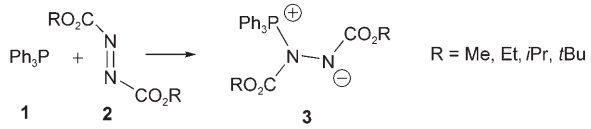
Dedicated to Professor C. N. R. Rao

The formation of a zwitterion by the reaction of triphenylphosphane and a dialkyl azodicarboxylate was first observed by Cookson and Locke,[1] although the correct structure was subsequently assigned by Huisgen.[2] This zwitterion, commonly known as the "Huisgen zwitterion" (Scheme 1), plays a crucial role in the Mitsunobu reaction, which is a powerful and widely used protocol for the inversion of the configuration of alcohols.[3] Apart from this, however, the chemistry of Huisgen zwitterions has received little attention.



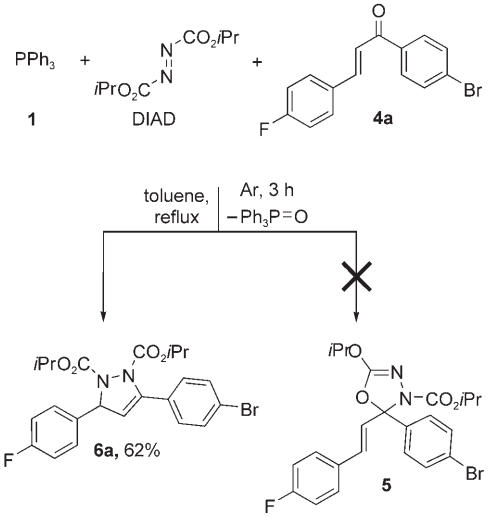
Scheme 1. Formation of Huisgen zwitterions.

The most noteworthy reactions of these zwitterions include the formation of oxadiazolines and vinyl hydrazine dicarboxylates as side products in the attempted Mitsunobu reaction of α-hydroxyesters,[4] and the conversion of acetophenones to ene–hydrazine dicarboxylates[5] and of salicylaldehydes to hydrazones.[6] Recently, Lee and co-workers have reported that the reaction of the zwitterion **3** (R = *i*Pr) with carbonyl compounds affords various products.[7] Contemporaneous investigations in our laboratory showed that the reaction of **3** (R = Et) with diaryl 1,2-diones proceeds by a novel rearrangement to afford *N*,*N*-dicarboethoxy monohydrazones.[8] Very recently, we reported the facile synthesis of dihydro-1,2,3-benzoxadiazoles[9a] and functionalized pyrazole derivatives[9b] by the interception of **3** (R = Et, *i*Pr) with 1,2-benzoquinones and allenic esters, respectively.

In this context,[8,9] and in view of our general interest in employing zwitterions in carbon–carbon and carbon–nitrogen bond-forming reactions,[10] we were intrigued by the possibility of intercepting the zwitterion derived from triphenylphosphane and a dialkyl azodicarboxylate with chalcones and dienones. The results of our studies, which led to an unprecedented synthesis of pyrazoline and pyrazolopyridazine derivatives, are presented herein. To the best of our knowledge, pyrazolo[4,3-*c*]pyridazine derivatives have not been described before, and there are no obvious methods to synthesize them. It should be noted that the present protocol utilizes only common laboratory chemicals.

Our investigations were initiated by treating the chalcone **4a** with diisopropyl azodicarboxylate (DIAD) in the presence of a stoichiometric amount of triphenylphosphane. The reaction afforded a product that was subsequently characterized as the pyrazoline derivative **6a** (Scheme 2; 62% yield). Surprisingly, the expected oxadiazoline **5** was not formed. The structure of **6a** was assigned on the basis of spectroscopic analysis and was subsequently confirmed unequivocally by single-crystal X-ray analysis.[11]

The reaction was found to be general with respect to various substituted chalcones; the functionalized pyrazoline



Scheme 2. Reaction of the Huisgen zwitterion obtained from DIAD and triphenylphosphane with a chalcone.

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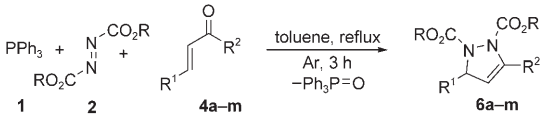
derivatives were obtained in good yields. Analogous results were obtained with diethyl azodicarboxylate (DEAD) and di-*tert*-butyl azodicarboxylate (DTAD). The results are summarized in Table 1. It should be mentioned that functionalized pyrazoles are an important class of heterocycles because of their biological properties being relevant to the pharmaceutical and agrochemical industries.[12]

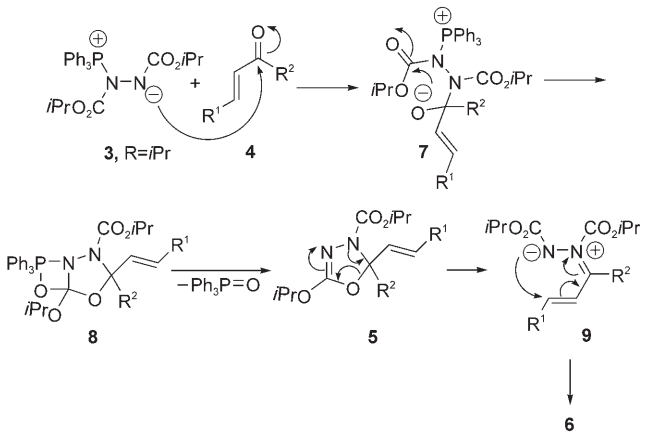
Table 1: Synthesis of functionalized pyrazolines.



R	R^1	R^2	Product	Yield [%]
*i*Pr	4-fluorophenyl	4-bromophenyl	**6a**	62
*i*Pr	2-chlorophenyl	4-nitrophenyl	**6b**	93
*i*Pr	4-methoxyphenyl	4-methoxyphenyl	**6c**	60
*i*Pr	4-chlorophenyl	phenyl	**6d**	63
*i*Pr	4-(trifluoromethyl)phenyl	4-bromophenyl	**6e**	72
*i*Pr	3-chlorophenyl	4-bromophenyl	**6f**	68
*i*Pr	phenyl	phenyl	**6g**	70
*i*Pr	naphthyl	4-chlorophenyl	**6h**	95
*i*Pr	9-anthryl	4-chlorophenyl	**6i**	96
Et	4-chlorophenyl	phenyl	**6j**	63
Et	2-chlorophenyl	4-nitrophenyl	**6k**	60
Et	2-furyl	4-chlorophenyl	**6l**	54
*t*Bu	4-fluorophenyl	4-bromphenyl	**6m**	94

The mechanism shown in Scheme 3 may be invoked to rationalize the reaction. The Huisgen zwitterion **3** formed from triphenylphosphane and the diisopropyl azoester could add to the carbonyl group of the chalcone to give a tetrahedral intermediate **7**, which then gives the oxadiazoline **5**, presumably by elimination of triphenylphosphane oxide in a process resembling the aza-Wittig/Staudinger reaction. This oxadiazoline then undergoes ring fragmentation to form **9**, which itself undergoes ring closure to give the final product.

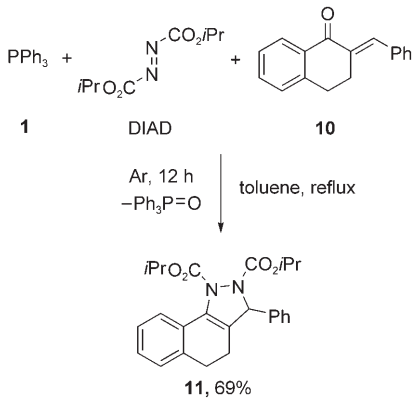
Interestingly, the reaction of benzylidene tetralone (**10**) with triphenylphosphane and DIAD affords the tricyclic



Scheme 3. Proposed mechanism for the reaction of the Huisgen zwitterion with a chalcone.

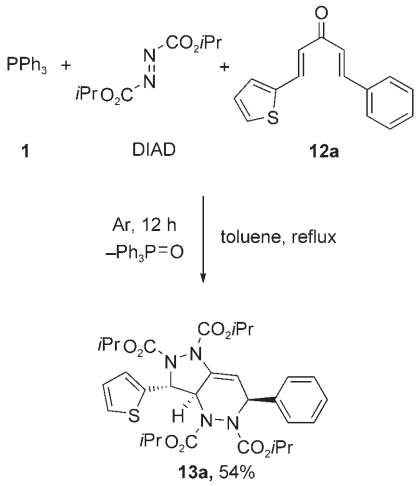
pyrazoline derivative **11** in 69% yield, thus opening up a route to polycyclic pyrazolines (Scheme 4).

In view of the interesting results obtained from the reaction of **3**, R = *i*Pr, with chalcones, we decided to apply the



Scheme 4. Synthesis of a polycyclic pyrazoline.

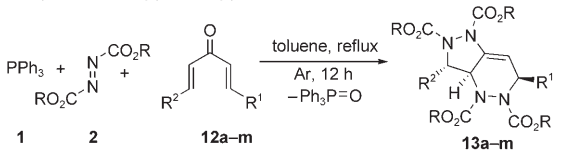
reaction to dienones. In a preliminary experiment, treatment of the dienone **12a** with DIAD (2.5 equiv) and triphenylphosphane (1.2 equiv) furnished the pyrazolopyridazine derivative **13a** in 54% yield (Scheme 5). This pyrazolopyridazine was characterized by spectroscopic analysis, and definitive confirmation of the structure and configuration of the compound was obtained by single-crystal X-ray analysis.[13] The complete stereoselectivity of the reaction is noteworthy.



Scheme 5. Reaction of the Huisgen zwitterion obtained from DIAD and triphenylphosphane with a dienone.

The scope of the reaction was investigated further with a number of dienones; the pyrazolopyridazine derivatives were obtained in good yields in all cases. Analogous results were obtained with DEAD and DTAD. The results are summarized in Table 2. It is noteworthy that certain pyrazolopyridazine derivatives show antimicrobial, anti-inflammatory, or analgesic activities.[14]

Table 2: Synthesis of pyrazolopyridazines.

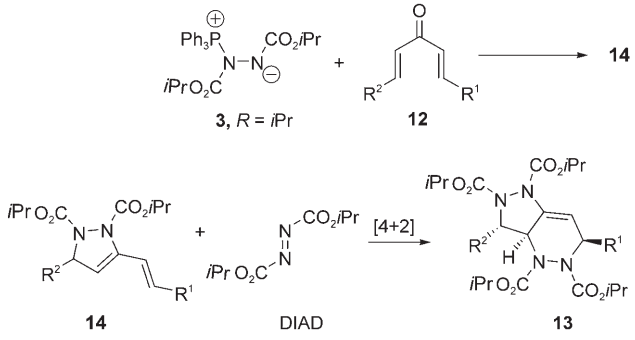


R	R^1	R^2	Product	Yield [%]
*i*Pr	phenyl	thienyl	**13a**	54
*i*Pr	2-(trifluoromethyl)-phenyl	2-(trifluoromethyl)-phenyl	**13b**	72
*i*Pr	2-fluorophenyl	2-fluorophenyl	**13c**	85
*i*Pr	phenyl	4-fluorophenyl	**13d**	57
*i*Pr	4-fluorophenyl	4-fluorophenyl	**13e**	57
*i*Pr	2-thienyl	2-thienyl	**13f**	62
*i*Pr	phenyl	3-chlorophenyl	**13g**	58
*i*Pr	2-bromophenyl	2-bromophenyl	**13h**	63
*i*Pr	2,6-difluorophenyl	2,6-difluorophenyl	**13i**	84
*i*Pr	phenyl	4-(trifluoromethyl)-phenyl	**13j**	57
Et	2-fluorophenyl	2-fluorophenyl	**13k**	63
Et	2-(trifluoromethyl)-phenyl	2-(trifluoromethyl)-phenyl	**13l**	74
*t*Bu	2-(trifluoromethyl)-phenyl	2-(trifluoromethyl)-phenyl	**13m**	83

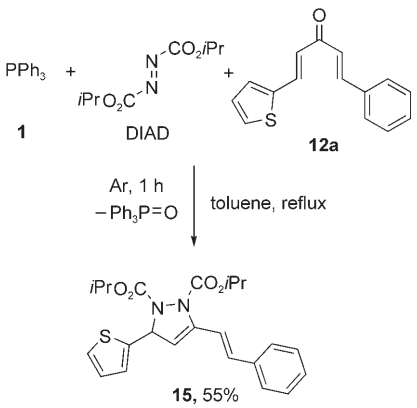
A mechanistic rationalization for the reaction may be advanced along the following lines. Interception of the zwitterion with the dienone initially generates the vinyl pyrazoline derivative **14**. This compound, which contains a diene moiety, undergoes an intermolecular Diels–Alder reaction with the excellent dienophile DIAD present in the reaction mixture to afford the pyrazolopyridazine (Scheme 6). It should be mentioned that if R^1 and R^2 are not identical the regioselectivity depends on their relative electronegativities.

To establish the intermediacy of the vinyl pyrazoline derivative, we treated dienone **12a** with 1.2 equivalents of DIAD and triphenylphosphane. The intermediacy of a vinyl pyrazoline derivative was ascertained by the isolation of **15** in 55% yield (Scheme 7). A small amount of the pyrazolopyridazine derivative was also isolated from the reaction mixture.

An attempt to trap the vinyl pyrazoline derivative with external dienophile was also successful: The reaction of

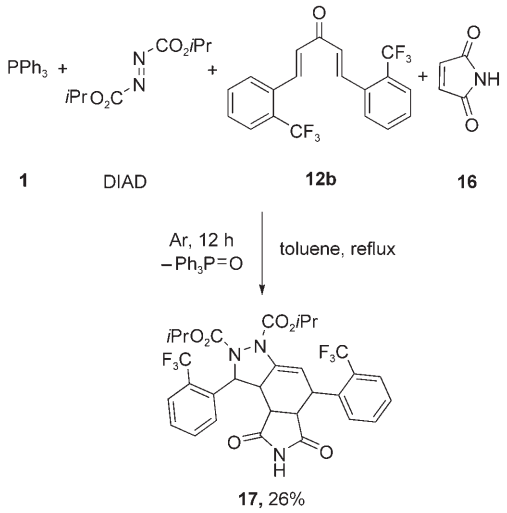


Scheme 6. Proposed mechanism for the reaction of the Huisgen zwitterion obtained from DIAD and triphenylphosphane with a dienone.



Scheme 7. Isolation of a vinyl pyrazoline.

dienone **12b** with DIAD (1.0 equiv) and maleimide (**16**) in the presence of a stoichiometric amount of triphenylphosphane afforded the indazole derivative **17**, albeit in low yield (Scheme 8).



Scheme 8. Synthesis of an indazole derivative.

In conclusion, we have discovered a novel synthesis of functionalized pyrazoline and pyrazolopyridazine derivatives that involves interception of a Huisgen zwitterion with chalcones and dienones, respectively. The pyrazolopyridazine derivatives result from the Diels–Alder reaction of the initially formed vinyl pyrazoline derivatives with excess DIAD.

Experimental Section

Synthesis of functionalized pyrazolines: DIAD (99 mg, 0.49 mmol) was added to a stirred solution of chalcone **4a** (100 mg, 0.33 mmol) in toluene (5 mL) under argon and the reaction mixture was stirred at reflux temperature. A solution of triphenylphosphane (128 mg, 0.49 mmol) in toluene (2 mL) was then added dropwise and the reaction mixture was stirred at reflux for 3 h. The reaction mixture was cooled and the solvent removed under reduced pressure on a rotary evaporator. The residue was subjected to column chromatog-

raphy on silica gel (100–200 mesh) with petroleum ether/ethyl acetate (85/15) as eluent to afford the functionalized pyrazoline **6a** as a colorless, crystalline solid (101 mg, 62%).

Synthesis of pyrazolopyridazines: DIAD (202 mg, 1.0 mmol) was added to a stirred solution of dienone **12a** (100 mg, 0.42 mmol) in toluene (5 mL) under argon and the reaction mixture was stirred at reflux temperature. A solution of triphenylphosphane (151 mg, 0.58 mmol) in toluene (2 mL) was then added dropwise and the reaction mixture was stirred under reflux for 12 h. The reaction mixture was cooled and the solvent removed under reduced pressure on a rotary evaporator. The residue was subjected to column chromatography on silica gel (100–200 mesh) with petroleum ether/ethyl acetate (70/30) as eluent to afford the pyrazolopyridazine **13a** as a colorless, crystalline solid (141 mg, 54%).

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[1] R. C. Cookson, J. M. Locke, *J. Chem. Soc.* **1963**, 6062–6064.
[2] a) E. Brunn, R. Huisgen, *Angew. Chem.* **1969**, *81*, 534–536; *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 513–515; b) R. Huisgen in *The Adventure Playground of Mechanisms and Novel Reactions: Profiles, Pathways and Dreams* (Ed.: J. I. Seeman), American Chemical Society, Washington DC, **1994**, p. 62.
[3] Reviews: a) O. Mitsunobu, *Synthesis* **1981**, 1–28; b) D. L. Hughes, *Org. Prep. Proced. Int.* **1996**, *28*, 127–164; c) T. Watanabe, I. D. Gridnav, T. Imamoto, *Chirality* **2000**, *12*, 346–351.
[4] T. Kolasa, M. J. Miller, *J. Org. Chem.* **1987**, *52*, 4978–4984.
[5] Y. Liu, C. Xu, L. Liu, *Synthesis* **2003**, 1335–1338.
[6] M. Girard, P. Murphy, N. N. Tsou, *Tetrahedron Lett.* **2005**, *46*, 2449–2452.
[7] R. D. Otte, T. Sakata, I. A. Guzei, D. Lee, *Org. Lett.* **2005**, *7*, 495–498.
[8] V. Nair, A. T. Biju, K. G. Abhilash, R. S. Menon, E. Suresh, *Org. Lett.* **2005**, *7*, 2121–2123.
[9] a) V. Nair, A. T. Biju, A. U. Vinod, E. Suresh, *Org. Lett.* **2005**, *7*, 5139–5142; b) V. Nair, A. T. Biju, K. Mohanan, E. Suresh, *Org. Lett.* **2006**, *8*, 2213–2216.
[10] V. Nair, R. S. Menon, A. R. Sreekanth, N. Abhilash, A. T. Biju, *Acc. Chem. Res.* **2006**, *39*, 520–530.
[11] CCDC-616377 (**6a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. See the Supporting Information for further details.
[12] Reviews: a) J. Elguero in *Comprehensive Heterocyclic Chemistry*, *Vol. 5* (Eds.: A. R. Katritzky, C. W. Rees, K. T. Potts), Pergamon, Oxford, **1984**, p. 167; b) J. Elguero in *Comprehensive Heterocyclic Chemistry II*, *Vol. 3* (Eds.: A. R. Katritzky, C. W. Rees, E. F. V. Scriven), Pergamon, Oxford, **1996**, p. 1.
[13] CCDC-616376 (**13a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. See the Supporting Information for further details.
[14] a) M. F. Braña, M. Cacho, M. L. García, E. P. Mayoral, B. López, B. Pascual-Teresa, A. Ramos, N. Acero, F. Llinares, D. Muñoz-Mingarro, O. Lozach, L. Meijer, *J. Med. Chem.* **2005**, *48*, 6843–6854; b) J. Witherington, V. Bordas, D. Haigh, D. M. B. Hickey, R. J. Ife, A. D. Rawlings, B. P. Slingsby, D. G. Smith, R. W. Ward, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1581–1584; c) A. K. Tewari, A. Mishra, *Bioorg. Med. Chem.* **2001**, *9*, 715–718.

