EurJOC European Journal of Organic Chemistry

SHORT COMMUNICATION

DOI: 10.1002/ejoc.201200267

Reactions of Arylpropynehydrazides with Substituted Malonyl Chlorides: A Route to Pyrazolo-Condensed 1,3-Oxazines

Olga A. Petina,*[a] Igor P. Yakovlev,[b] and Detlef Geffken[a]

Keywords: Hydrazides / Heterocycles / Cycloaddition / Cyclization / Pyrazoles

Reaction of phenylpropynehydrazide with dimethylmalonyl chloride furnished the corresponding 4,4-dimethyl-1-(3-phenylprop-2-ynoyl)pyrazolidine-3,5-dione, which upon thermolysis underwent a 6-*endo*-*dig* cyclization to a pyrazolo[5,1-*b*][1,3]oxazine. The corresponding reaction of arylpropynehydrazides with monosubstituted malonyl chlorides furnished pyrazolo[5,1-*b*][1,3]oxazine-7-ones via intermediates that could not be isolated.

Introduction

It is well known that hydrazines react with 1,3-dicarbonyl compounds to yield a pyrazole ring with an NH–NH group.[1] The pyrazole nucleus plays an important role in medicinal chemistry.[2] Several pyrazolidinediones[3] are used as nonsteroidal anti-inflammatory drugs, for example, phenylbutazone, sulfinpyrazone, kebuzone, feprazone, and mofebutazone (Figure 1).[4]

Phenylbutazone: R = n-C_4H_9
Sulfinpyrazone: R = $(CH_2)_2SOPh$
Kebuzone: R = $(CH_2)_2COCH_3$
Febrazone: R = $CH_2CH{=}C(CH_3)_2$

Mofebutazone

Figure 1. Pyrazolidinedione derivatives with anti-inflammatory effect.

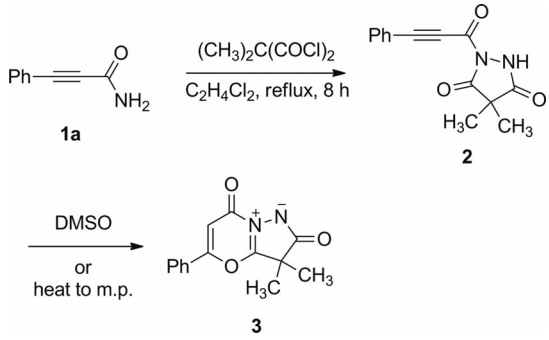
In addition, pyrazole-condensed heterocycles obtainable from the reaction of hydrazides with malonic esters have been shown to be effective as anti-Alzheimer[5] and antitumor[6] agents, analgesic and anti-inflammatory[7] agents, as well as Farnesoid X receptor (FAX) antagonists.[8]

The aim of the present work was to investigate the reaction of arylpropynehydrazides with malonyl chlorides, which we expected to deliver novel fused pyrazolo[1,3]oxazines of type **3**/**5**.

Alkynes with an activated triple bond have been proven as valuable organic intermediates in heterocyclic chemistry. For instance, acceptor-substituted alkynes can serve as Michael acceptors, as dienophiles in Diels–Alder reactions, or as dipolarophiles in 1,3-dipolar cycloaddition reactions. Although these reactions are well documented in the literature,[9] very few publications are dedicated to the corresponding reactivity of α-alkynehydrazides.

Results and Discussion

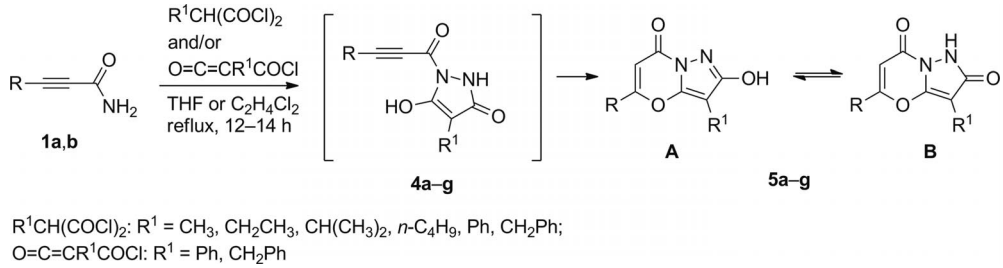
The reaction of 3-phenylprop-2-ynehydrazide (**1a**) with dimethylmalonyl chloride led to the formation of expected 4,4-dimethyl-1-(3-phenylprop-2-ynoyl)pyrazolidine-3,5-dione (**2**, Scheme 1). Unambiguous structural assignment of **2**, which crystallizes as the (*NH*)-tautomer, was achieved by X-ray crystal structure analysis (see the Supporting Information). Interestingly, when heated to its melting point or when left in DMSO, pyrazolidinedione **2** undergoes 6-*endo*-*dig* cyclization to 3,3-dimethyl-2,7-dioxo-5-phenyl-3,7-dihydro-2*H*-pyrazolo[5,1-*b*][1,3]oxazin-8-ium-1-ide (**3**, Scheme 1).



Scheme 1. Synthesis of **2** and its cyclization to **3**.

The reaction of arylpropynehydrazides **1a** and **1b** with monosubstituted malonyl chlorides or (chlorocarbonyl)ethylketene[10] produced pyrazolo[1,3]oxazines **5a**–**g** in 57–70% yield (Table 1), presumably by 6-*endo*-*dig* cyclization of intermediates **4a**–**g**, which cannot be isolated (Scheme 2).

[a] Institute of Pharmacy, University of Hamburg, Bundesstrasse 45, 20146 Hamburg, Germany
E-mail: petina@chemie.uni-hamburg.de
[b] St Petersburg State Chemical Pharmaceutical Academy, ul. Professora Popova 14, 197376 St. Petersburg, Russia
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201200267.



Scheme 2. Synthesis of pyrazolo[5,1-*b*][1,3]oxazine-7-ones (**5**).

Table 1. Synthesis of pyrazolo[5,1-*b*][1,3]oxazine-7-ones **5a**–**g**.

Entry	Product	R	R^1	Yield [%]
1	**5a**	Ph	CH_3	65
2	**5b**	Ph	CH_2CH_3	61
3	**5c**	Ph	$CH(CH_3)_2$	70
4	**5d**	Ph	$(CH_2)_3CH_3$	59
5	**5e**	Ph	Ph	68
6	**5f**	Ph	CH_2Ph	64
7	**5g**	4-ClC_6H_4	Ph	57

Pyrazolo[5,1-*b*][1,3]oxazine-7-ones **5**, which were found to exist in a tautomeric equilibrium between **5A** and **5B**, are of special interest to medicinal chemistry because of their bioisosteric relationship to flavones, which are widely spread bioactive natural compounds.[11]

Only a few related compounds with the same basic ring structure but with other substituents, especially at the 2- and 5-positions, have been reported.[12] For example, 2-alkylpyrazolo[5,1-*b*][1,3]oxazines have been synthesized by treating the corresponding substituted 2-pyrazolin-5-ones with Fisher carbene analogues of the 3-phenylpropiolyl group and further oxidative demetalation.[12d] Although this synthetic pathway leads to a compound mixture in which the pyrazolooxazines are present only as minor products (yield < 20%), we have successfully obtained pyrazolo[5,1-*b*][1,3]oxazine-7-ones **5** in a one-pot synthesis in good yields. In contrast, antimicrobial 5-amino-2-methylpyrazolo[5,1-*b*][1,3]oxazine-7-one was prepared by multistep synthesis and utilizes ethyl acetate and cyanoacetohydrazide as starting materials.[12c]

The structures of compounds **5a**–**g** were determined by mass spectrometry, IR, ^{1}H NMR, and ^{13}C NMR spectroscopy, and elemental analysis. The ^{1}H NMR spectrum of **5a** in DMSO shows the presence of methyl protons (s, δ = 1.97 ppm, 3 H), aromatic protons (m, δ = 8.05 ppm, 2 H; m, δ = 7.58 ppm, 3 H; s, δ = 6.82 ppm, 1 H) and mobile protons of the NH- or OH group (br. s., δ = 11.42 ppm, 1 H). In accordance with the ^{1}H NMR spectrum, the corresponding ^{13}C NMR spectrum shows the presence of 10 C atoms. The ^{1}H NMR and ^{13}C NMR spectra of **5b**–**g** are similar to those of **5a**. Unfortunately, the ^{1}H NMR and ^{13}C NMR spectroscopic data do not give unambiguous information about the structure of the obtained compounds, as they could match structure **4** or **5**. However, the absence of a characteristic triple bond absorption band in the IR spectrum allowed structure **4** to be excluded.

Additional detailed NMR spectroscopic investigations of **5e** in [D_6]DMSO solution provided important information about its structure and tautomerism. The NOESY spectrum (see the Supporting Information) unmistakably revealed the structure of **5e** as the reaction product isolated, because its spectrum shows a clear positive NOE peak between H2′–H2′′ and H2′–H6, which cannot occur in the case of pyrazole **4e**. The observation of an NOE peak between the H2′ protons and the proton at δ = 11.42 ppm provides evidence of the spatial proximity of these protons and proof that 2-hydroxy-3,5-diphenyl-7*H*-pyrazolo[5,1-*b*]-[1,3]oxazine-7-one (**5e**) mainly exists as the OH-tautomer (Figure 2). In contrast, the corresponding phenyl protons and the NH proton in the case of the NH-tautomer were too far apart for an NOE to be detected.

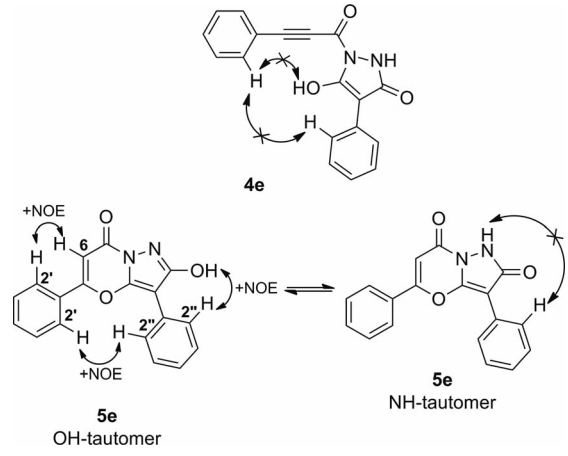


Figure 2. Structure determination of **5e** by NOE.

The same tautomeric form was detected for 2-hydroxy-3-methyl-5-phenyl-7*H*-pyrazolo[5,1-*b*][1,3]oxazine-7-one (**5a**) by X-ray crystal structure analysis (Figure 3).

The acetylation of **5a** and **5e** by using acetyl chloride furnished exclusively O-acylated products **6a** and **6b** (Scheme 3), characterized by three sharp IR absorption bands at 1780–1785 (C=O, ester), 1700–1710 (C=O, oxazinone), and 1640–1650 cm^{-1} (C=N).

When **5a** was treated with diazomethane no reaction took place. However, reaction of **5a** with iodomethane in boiling DMSO in the presence of potassium carbonate furnished a mixture of compounds **7** (27%) and **8** (43%, Scheme 4), which could be separated easily by column chromatography on silica gel.

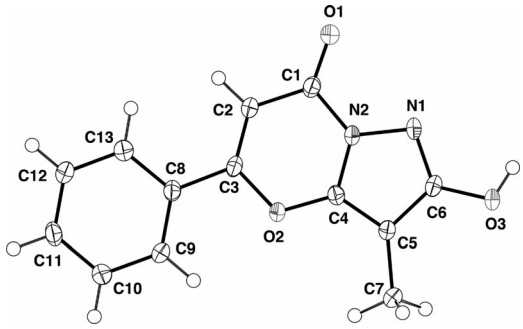
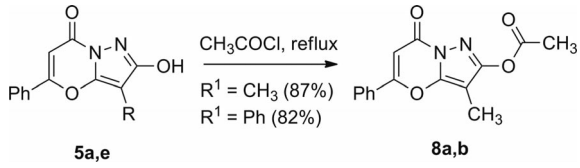
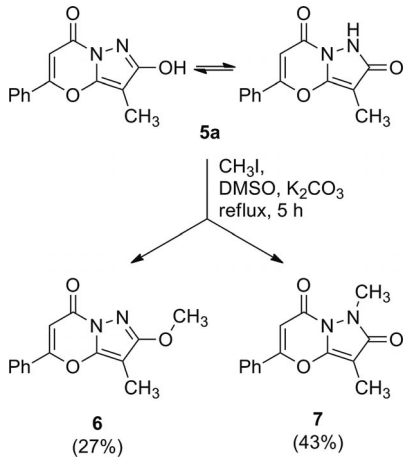


Figure 3. Molecular structure of compound **5a**.



Scheme 3. Acetylation of pyrazolo[5,1-*b*][1,3]oxazine-7-ones **5a** and **5e**.



Scheme 4. Methylation of compound **5a**.

Conclusions

In conclusion, we have developed a simple and efficient one-pot synthesis of 2-hydroxypyrazolo[5,1-*b*][1,3]oxazine-7-ones (**5**). Furthermore, thermolysis of 4,4-dimethyl-1-(3-phenylprop-2-inoyl)pyrazolidine-3,5-dione (**2**), obtained from the reaction of phenylpropynehydrazide with dimethylmalonyl chloride, produced mesoionic pyrazolo[5,1-*b*]-[1,3]oxazine **3**.

Experimental Section

4,4-Dimethyl-1-(3-phenylprop-2-ynoyl)pyrazolidine-3,5-dione (2): Dimethylmalonyl dichloride (3.1 mmol, 0.36 mL) was added to a stirred solution of **1a** (3 mmol, 0.44 g) in absolute dichloroethane (30 mL) at room temperature. The reaction mixture was heated at reflux for 8 h and then allowed to cool to room temperature. The solid product formed was filtered and recrystallized from acetonitrile or dichloromethane. To increase the yield, the mother liquor was placed into the freezer for additional crystallization. Yield: 0.64 g (83%); colorless crystals; m.p. 223–225 °C (acetonitrile). IR (KBr): $\tilde{\nu}$ = 2217 (C≡C), 1785 (C=O), 1710 (C=O), 1664 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 12.22 (br. s, 1 H, OH), 7.69 (m, 2 H, 2,6-Ph), 7.68 (m, 1 H, 4-Ph), 7.53 (m, 2 H, 3,5-Ph), 1.32 (s, 6 H, CH$_3$) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 171.4 and 170.6 (C-3 and C-5), 143.0 (C-1′), 132.9 (2,6-Ph), 131.6 (4-Ph), 129.3 (3,5-Ph), 119.1 (1-Ph), 92.2 (C-3′), 81.7 (C-2′), 45.1 (C-4), 21.0 (CH$_3$) ppm. MS: *m*/*z* (%) = 256 (5) [M]$^+$, 130/129 (13/100) [PhC≡CCO]$^+$, no other peaks >10%. $C_{14}H_{12}N_2O_3$ (256.26): calcd. C 65.62, H 4.72, N 10.93; found C 65.62, H 4.84, N 11.02.

3,3-Dimethyl-2,7-dioxo-5-phenyl-3,7-dihydro-2*H*-pyrazolo[5,1-*b*]-[1,3]oxazin-8-ium-1-ide (3): 4,4-Dimethyl-1-(3-phenylprop-2-ynoyl)-pyrazolidin-3,5-dione (**2**; 0.26 g, 1 mmol) was heated to its melting point for 5 min. After cooling, the resulting product was recrystallized from toluene.

General Procedure for the Preparation of 5-Aryl-2-hydroxy-7*H*-pyrazolo[5,1-*b*][1,3]oxazine-7-ones 5a–g: The corresponding malonyl dichloride [(chlorocarbonyl)ethylketene] (3.1 mmol) was added to a stirred solution of **4a**,**b** (3 mmol) in absolute dichloroethane or THF (30 mL) at room temperature. The reaction mixture was heated at reflux for 12–14 h. During this time, a white solid deposited. The solid separated upon cooling and was filtered off and recrystallized from either dimethylformamide (for **5a**–**d** and **5g**) or DMSO (for **5e** and **5f**) to give analytically pure products.

2-Hydroxy-3-methyl-5-phenyl-7*H*-pyrazolo[5,1-*b*][1,3]oxazin-7-one (5a): Yield: 0.47 g (48%); colorless solid; m.p. >300 °C (dimethylformamide). IR (KBr): $\tilde{\nu}$ = 1715 (C=O), 1664 (C=N) cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 11.42 (br. s, 1 H, OH), 8.05 (m, 2 H, 2,6-Ph), 7.58 (m, 3 H, 4-Ph and 3,5-Ph), 6.82 (s, 1 H, 6-H), 1.97 (s, 3 H, CH$_3$) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 163.3 (C-2), 160.0 (C-5), 152.8 (C-7), 137.7 (C-3a), 132.0 (4-Ph), 129.5 (1-Ph), 129.1 (3,5-Ph), 126.1 (2,6-Ph), 96.8 (C-6), 84.9 (C-3), 4.5 (CH$_3$) ppm. MS: *m*/*z* (%) = 243/242 (13/85) [M]$^+$, 146 (10), 130/129 (11/100) [PhC≡CHCO]$^+$, 105 (39), 102 (37) [PhC≡CH]$^+$, 83 (57), 77 (32) [Ph]$^+$, 76 (11), 69 (12), 56 (11), 51 (19) [C$_4$H$_3$]$^+$, 44 (13), 40 (41), no other peaks >10%. $C_{13}H_{10}N_2O_3$ (242.23): calcd. C 64.46, H 4.16, N 11.56; found C 64.40, H 4.16, N 11.48.

CCDC-867859 (for **2**) and -867860 (for **5a**) contain 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.

Supporting Information (see footnote on the first page of this article): Characterization data for all compounds, copies of the ^{1}H NMR and ^{13}C NMR spectra, and selected crystallographic data.

[1] Selected recent papers: a) J.-Y. Yoon, S. Lee, H. Shin, *Curr. Org. Chem.* **2011**, *15*, 657–674; b) A. Schmidt, A. Dreger, *Curr. Org. Chem.* **2011**, *15*, 2897–2970; c) L. Yet in *Comprehensive Heterocyclic Chemistry III* (Ed.: J. Elguero), Elsevier Science, Oxford, **2008**, vol. 4, pp. 74–83.

[2] Selected recent papers: a) A. Schmidt, A. Dreger, *Curr. Org. Chem.* **2011**, *15*, 2897–2970; b) A. A. Bekhit, A. Hymete, A. E.-D. A. Bekhit, A. Damtew, H. Y. Aboul-Enein, *Mini Rev. Med. Chem.* **2010**, *10*, 1014–33; c) L. Yet, in *Comprehensive Heterocyclic Chemistry III* (Ed.: J. Elguero), Elsevier Science, Oxford, **2008**, vol. 4, pp. 113–119.

[3] N. R. El-Rayyes, N. A. Al-Awadi, *Synthesis* **1985**, 1028.

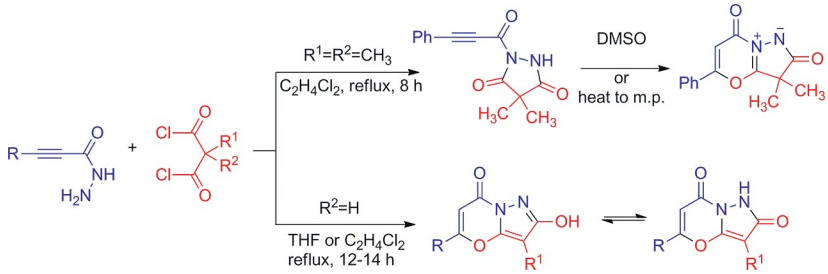
[4] M. J. O'Neil (Ed.), *The Merck Index*, 14th ed., Merck, Whitehouse Station, NJ, **2006**.

[5] F. A. Attaby, A. M. Abdel-Fattah, L. M. Shaif, M. M. Elsayed, *Phosphorus Sulfur Silicon Relat. Elem.* **2010**, *185*, 129.
[6] a) M. M. F. Ismail, H. S. Rateb, M. M. M. Hussein, *Eur. J. Med. Chem.* **2010**, *45*, 3950; b) S. A. F. Rostom, *Bioorg. Med. Chem.* **2010**, *18*, 2767.
[7] a) H. N. Hafez, A. B. A. El-Gazzar, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5222; b) V. Sharma, M. S. Y. Khan, *Pharmazie* **2003**, *58*, 99; c) H. H. Fahmy, G. A. Soliman, *Arch. Pharmacal. Res.* **2001**, *24*, 180.
[8] G. Deng, W. Li, J. Shen, H. Jiang, K. Chen, H. Liu, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5497.
[9] a) G. V. Boyd in *The Chemistry of Triple-Bonded Functional Groups* (Ed.: S. Patai), Wiley, Chichester **1994**, pp. 287–374; b) J. Bastide, O. Henri-Rousseau in *The Chemistry of the Carbon-Carbon Triple Bond* (Ed.: S. Patai), Wiley, Chichester, **1978**, Vol. 1, pp. 447–522; c) E. Winterfeldt, *Angew. Chem.* **1967**, *79*, 389; *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 423.
[10] a) S. Nakanishi, K. Butler, *Org. Prep. Proced. Int.* **1975**, *7*, 155; b) W. Friedrichsen, E. Kujath, G. Liebezeit, *Z. Naturforsch. B* **1982**, *37*, 222.
[11] a) J. B. Harborne in *The Flavonoids: Advances in Research [since 1982]*, Chapman & Hall, London, **1982**; b) C. A. Rice-Evans, L. Packer, *Flavonoids in Health and Disease*, 2nd ed., Dekker, New York, **2003**.
[12] a) F. P. Dubau, G. Zinner, *Chem. Ber.* **1975**, *108*, 2189–2201; b) H. J. Gais, K. Hafner, *Heterocycles* **1976**, *4*, 1921–1932; c) A. W. Erian, S. El-Gohary, F. M. Mahni, F. A. Ali, *Pharmazie* **1998**, *53*, 748–751; d) Z. Zheng, Z. Yu, N. Luo, X. Han, *J. Org. Chem.* **2006**, *71*, 9695–9700; e) I. Tetsuya, O. Hideki, JP 2007–2135 [*Chem. Abstr.* **2008**, *149*, 235338].

Received: March 5, 2012
Published Online: ■

EurJOC European Journal of Organic Chemistry

Cyclization



The reaction of arylpropynehydrazides with monosubstituted malonyl chlorides leading to pyrazolo[5,1-*b*][1,3]oxazines is reported. This method can also be extended to the synthesis of pyrazolidine-3,5-dione, which subsequently can be converted by thermolysis into a pyrazolo[5,1-*b*][1,3]oxazine.

Keywords: Hydrazides / Heterocycles / Cycloaddition / Cyclization / Pyrazoles

