Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 8761–8764

Recyclable supported catalysts in microwave-assisted reactions: first Diels–Alder cycloaddition of a triazole ring

Ángel Díaz-Ortiz,* Abel de Cózar, Pilar Prieto,* Antonio de la Hoz and Andrés Moreno

Dpto. Q. Inorgánica, Q. Orgánica y Bioquímica, Facultad de Química, Universidad de Castilla-La Mancha, E-13071 Ciudad Real, Spain

Received 23 August 2006; revised 29 September 2006; accepted 2 October 2006
Available online 20 October 2006

Abstract—We describe here the first example in which a 1,2,3-triazole ring acts as a diene towards DMAD in microwave-assisted solvent-free Diels–Alder cycloadditions. The extrusion of a molecule of a nitrile affords pyrazole derivatives as the products. The yields can be markedly increased by using a recyclable supported Lewis acid catalyst, which can be reused at least five times without a decrease in the yield.

The intermolecular Diels–Alder reactions of heterocyclic compounds are the basis for the synthesis of a wide range of target molecules.[1]

Dimethyl acetylenedicarboxylate (DMAD) undergoes Diels–Alder cycloaddition reactions with several heterocyclic systems with subsequent extrusion of a small molecule (through retro-Diels–Alder cleavage). DMAD reacts with: (i) 3-arylsydnones to afford pyrazole-3,4-dicarboxylates and CO_2;[2] (ii) oxazoles leading to furans and a nitrile;[3] (iii) furan[4] and pyrrole[5] derivatives to give furan- or pyrrole-3,4-dicarboxylates and ethylene or an alkyne, respectively; (iv) methoxythiophenes to yield dimethyl phthalates and sulfur;[6] (v) dimesityl-1,2,4-oxadiphosphole to give a 1,2-oxaphosphole and mesitylphosphaacetylene;[7] (vi) 2-(1*H*)-pyrazinones to afford 2-(1*H*)-pyridinone-4,5-dicarboxylates and cyanogen chloride or pyridine-3,4-dicarboxylates and an isocyanate.[8]

1,2,3-Triazole is the essential structural unit in a number of drugs and some of these materials are also potent HIV-1 inhibitors,[9] antimicrobial agents[10] or selective β_3-adrenergic receptor agonists.[11] 1,2,3-Triazole can be easily built by a 1,3-dipolar cycloaddition using an azide derivative.[12] However, its reactivity, particularly in Diels–Alder reactions, has barely been studied in comparison with other heterocyclic systems.

Typically, a Lewis acid catalyst such as aluminium chloride is used in Diels–Alder reactions. However, in recent years, following a drive for simplified work-ups, solid acids have become increasingly considered for these reactions, albeit with limited success. These solid acids were shown to be capable of facilitating the same reactions as the unsupported reagents, with the advantage of recovery by filtration for a subsequent reuse.[13]

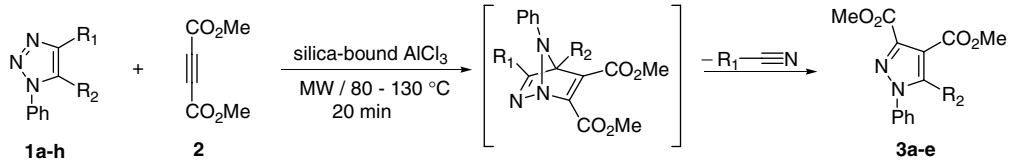
In the last decade, we have often demonstrated the utility of microwave irradiation in cycloaddition reactions.[14] The combination of supported reagents and microwave irradiation can be used to carry out a wide range of Diels–Alder reactions in short times and with high conversions and selectivity, without the need for solvents.

As a continuation of our studies, we report here that 1,2,3-triazoles undergo a Diels–Alder cycloaddition with DMAD under solvent-free conditions and microwave irradiation within 20 min to afford pyrazole-3,4-dicarboxylates with extrusion of the substituent on position 4 of the triazole as a nitrile (Scheme 1). Yields can be increased significantly by using silica-bound $AlCl_3$ as a catalyst[15] (0.1 mol %) (Table 1).[16]

The silica-bound Lewis acid catalyst could be reused five times in the cycloaddition of **1f** under microwaves without a decrease in the product yield. This result shows the utility and enhances the environmentally benign applications of this catalyst.[17]

* Corresponding authors. Tel.: +34 926 295300; fax: +34 926 295318 (Á.D.-O.); e-mail: Angel.Diaz@uclm.es

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.10.006



Scheme 1. Reaction of 1,2,3-triazoles **1a**–**h** with DMAD under microwave irradiation.

Table 1. Product yield obtained in the reaction of 1,2,3-triazoles **1a**–**h** with DMAD by classical heating or under microwaves

Entry	Substrate	R_1	R_2	Product	Power (W)[c]	Temperature (°C)	Product yield[a,b] (%)	
							Classical heating[d]	Microwaves
1	**1a**	H	H	**3a**	60	120	15 (8)	40 (14)
2	**1b**	C_6H_5	H	**3a**	80	120	34 (5)	58 (18)
3	**1c**	CHO	H	**3a**	80	130	7 (4)	35 (15)
4	**1d**	CO_2Me	H	**3a**	80	120	12 (5)	38 (12)
5	**1e**	C_6H_5	CH_3	**3b**	60	120	30 (11)	57 (20)
6	**1f**	CH_3CH_2	CH_3CH_2	**3c**	40	80	46 (25)	89 (56)
7	**1g**	CH_3OCH_2	CH_3OCH_2	**3d**	60	100	62 (12)	94 (20)
8	**1h**	$CH_3(CH_2)_3$	$CH_3(CH_2)_3$	**3e**	80	100	48 (21)	86 (34)

[a] Isolated products.
[b] Yields of uncatalyzed reactions are given in brackets.
[c] Starting power in the microwave-assisted reactions.
[d] No significative increase of the yields is observed at higher reaction times.

To the best of our knowledge, this reaction represents the first example of a Diels–Alder cycloaddition involving a 1,2,3-triazole ring. The importance of these results particularly relates to: (i) the transformation of a very unreactive and scarcely studied heterocyclic system, which extends the scope of its reactivity and (ii) the environmentally friendly and sustainable reaction conditions used, that is, absence of solvent, microwave irradiation and recyclable supported catalyst.

The reactivity of heterocyclic compounds as dienes in Diels–Alder reactions is a subject of extensive study from two points of view: (i) in terms of synthetic applications leading to valuable compounds and (ii) from a theoretical point of view because, as aromatic compounds, these are at the limit of reactivity as dienes.

Five-membered heterocyclic systems with one heteroatom have been reacted as dienes, with furan being the most reactive and thiophene the least. The introduction of a second heteroatom decreases the reactivity of these systems as dienes. In azoles only 1,3-diazoles and—almost exclusively—oxazoles (2-azadienes) show reactivity as dienes, whereas 1,2-azoles (1-azadienes) do not react at all.

In this regard, of the five-membered heterocyclic compounds with three heteroatoms only 1,3,4-oxadiazole (2,3-diazadiene) reacts as a diene and a large number of papers have been published in this area. In contrast, 1-substituted 1,2,3-triazole is one of the least reactive heterocyclic systems (1,2-diazadiene) and reports on its use as a diene have not been published.[18]

As a consequence, our methodology opens new possibilities for a large number of heterocyclic compounds to act as dienes and these, in principle, should be more reactive than 1-substituted 1,2,3-triazoles.

In the absence of microwaves and catalyst, and under similar reaction conditions (time and temperature), the yields of the products decrease dramatically (4–25%). This fact explains why 1,2,3-triazole and/or its cycloaddition reactions have not been studied previously.

5-Phenyl-1,2,3-triazoles, such as 1,5-diphenyl- and 1,4,5-triphenyl-1,2,3-triazoles **1i** and **1j**, respectively, do not react with DMAD under prolonged irradiation at high temperatures and in these cases only decomposition of the reagents was observed. In order to have a higher knowledge on the mechanism of this reaction, we decided to compute the structure of the 4-phenyl- and 5-phenyl-1,2,3-triazoles at the B3LYP/6-31G* level of theory (Fig. 1). These structures show that the steric hindrance is crucial in this reaction. Thus, the 4-phenyl group is coplanar with the triazole ring. The driedral angle between the 4-phenyl and the triazole is −2.89° in compound **1b** and −26.86° in compound **1e**. In contrast, the 5-phenyl substituent is more perpendicular to the triazole (43.66° in the case of **1i** and −57.31 in **1j**) and, for this reason, the approach of DMAD is unfavoured on both sides of the triazole ring.

On the other hand, the reaction of (1*H*)-1,2,3-triazole (**4**) and DMAD under microwave irradiation in the absence of catalyst led to a mixture of products **5** (as the *E* stereoisomer) and **6** (as a *E*/*Z* mixture, 7:3 ratio) through a Michael addition (Scheme 2).[19] The overall yield increased from 57% to 91% in the presence of silica-bound $AlCl_3$ without modification of the isomer ratio. Tentatively, in the absence of a protic solvent, protonation of the Michael intermediate must occur mainly from

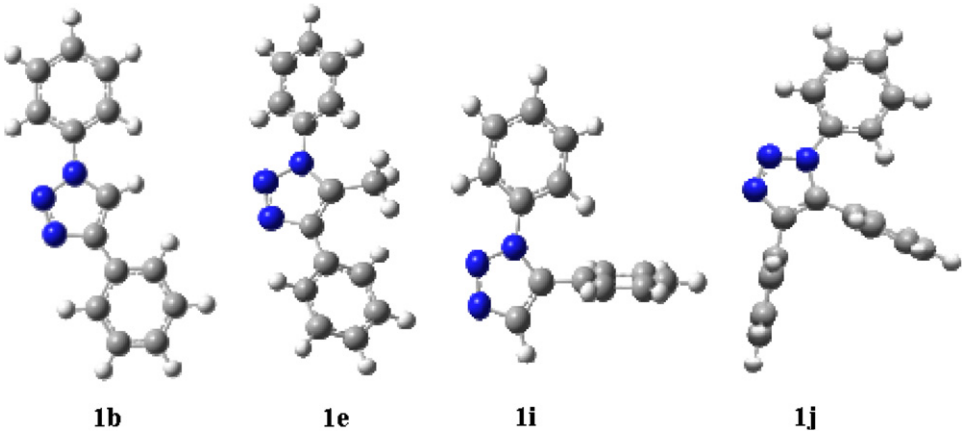
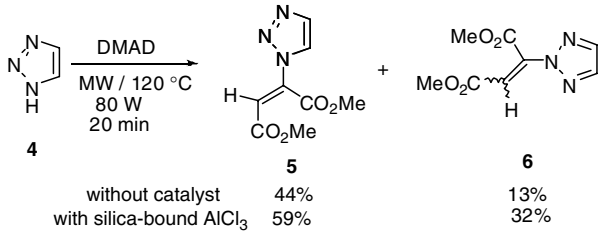


Figure 1. Fully optimized [B3LYP/6-31G+d level of theory] structures of 1,2,3-triazoles **1b,e,i,j**.



Scheme 2. Reaction between (1*H*)-1,2,3-triazole (**4**) and DMAD.

the triazole side leading to the *E* stereoisomer as the only or main product. This stereochemical assignment was confirmed by comparison of the olefinic proton chemical shifts in **5** and **6** with its pyrazole analogue.[20]

In conclusion, we have described the first microwave-assisted Diels–Alder reaction in which a 1,2,3-triazole ring acts as a diene. The use of a recyclable silica gel functionalized Lewis acid in the absence of solvent not only improves the product yields dramatically but makes this reaction into an environmentally friendly process. Further studies to expand the scope of this reaction to other uninvestigated heterocyclic systems will be the subject of future publications.

Acknowledgements

Financial support from the Spanish DGCyT (Project CTQ2004-01177/BQU) and Junta de Comunidades de Castilla-La Mancha (Projects PAI05-019 and PBI06-0020) is gratefully acknowledged. We would like to thank Juan de M. Muñoz for technical support.

References and notes

1. Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press: Oxford, UK, 1990.
2. (a) Gottardt, H.; Reiter, F. *Chem. Ber.* **1979**, *112*, 1206; (b) Hunnur, R. K.; Latthe, P. R.; Badami, B. V. *J. Chem. Res.* **2005**, 592.
3. See, for example: (a) Grigg, R.; Hayes, R.; Jackson, J. L. *J. Chem. Soc., Chem. Commun.* **1969**, 1167; (b) Potts, K. T.; Marshall, J. *J. Chem. Soc., Chem. Commun.* **1972**, 1000.
4. (a) Cook, M. J.; Forbes, E. J. *Tetrahedron* **1968**, *24*, 4501; (b) Mavoungon-Gomès, L.; Bruneton, J.; Aicart, M. *J. Heterocycl. Chem.* **1985**, *22*, 1233.
5. Noland, W. E.; Lee, C. K. *J. Org. Chem.* **1980**, *45*, 4573.
6. (a) Corral, C.; Lissavetzky, J.; Manzanares, I. *Synthesis* **1997**, 29; (b) Loupy, A.; Maurel, F.; Sabatié-Gogová, A. *Tetrahedron* **2004**, *60*, 1683.
7. Mack, A.; Bergsträßer, U.; Reiß, G. J.; Regitz, M. *Eur. J. Org. Chem.* **1999**, 587.
8. (a) Kaval, N.; Van der Eycken, J.; Caroen, J.; Kappe, C. O.; Dehaen, W.; Strohmeier, G. A.; Van der Eycken, E. *J. Comb. Chem.* **2003**, *5*, 560; (b) Kaval, N.; Ermolat'es, D.; Appukkuttan, P.; Dehaen, W.; Kappe, C. O.; Van der Eycken, E. *J. Comb. Chem.* **2005**, *7*, 490.
9. Ölgen, S.; Chung, K. C. *Z. Naturforsch., B: Chem. Sci.* **2001**, *56*, 804.
10. Genin, M. J.; Alwine, D. A.; Anderson, D. J.; Barbachyn, M. R.; Emmert, D. E.; Garmon, S. A.; Graber, D. R.; Grega, K. C.; Hester, J. B.; Hutchison, D. K.; Morris, J.; Reischer, R. J.; Ford, C. W.; Zurenko, G. E.; Hamel, J. C.; Schaadt, R. D.; Staper, D.; Yagi, B. H. *J. Med. Chem.* **2000**, *43*, 953.
11. Brockunier, L. L.; Parmee, E. R.; Ok, H. O.; Candelore, M. R.; Cascieri, M. A.; Colwell, L. F.; Deng, L.; Feeney, W. P.; Forrest, M. J.; Hom, G. J.; MacIntyre, D. E.; Tota, L.; Wyvratt, M. J.; Fisher, M. H.; Weber, A. E. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2111.
12. (a) Huisgen, R. *Proc. Chem. Soc.* **1961**, 357; (b) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem.* **2002**, *114*, 2708; (c) Amantini, D.; Fringuelli, F.; Piermatti, O.; Pizzo, F.; Zunino, E.; Vaccaro, L. *J. Org. Chem.* **2005**, *70*, 6526.
13. (a) McKillop, A.; Young, K. W. *Synthesis* **1979**, 401 and 481; (b) Laszlo, P. *Preparative Chemistry using Supported Reagents*; Academic Press: San Diego, USA, 1987; (c) Smith, K. *Solid Supports and Catalyst in Organic Synthesis*; Ellis Horwood: Chichester, 1992; (d) Clark, J. H.; Rhodes, C. N. *Clean Synthesis using Porous Inorganic Solid Acid Catalysts and Supported Reagents*; RSC Clean Technology Monographs: Cambrigde, UK, 2000.
14. See, for example: (a) Díaz-Ortiz, A.; Díez-Barra, E.; de la Hoz, A.; Prieto, P.; Moreno, A.; Langa, F.; Prangé, T.; Neuman, A. *J. Org. Chem.* **1995**, *60*, 4160; (b) Díaz-Ortiz, A.; Langa, F.; de la Hoz, A.; Moreno, A. *Eur. J. Org. Chem.* **2000**, *4*, 3659; (c) De la Hoz, A.; Díaz-Ortiz, A.; Langa, F. In *Microwaves in Organic Synthesis*; Loupy, A.,

Ed.; Wiley-VCH: Weinheim, Germany, 2002; pp 295–344.

15. Aluminium chloride functionalized silica gel (particle size 70–120 mesh, extent of labeling: 1.5 mmol/g) was supplied by Sigma–Aldrich Co.
16. *Experimental procedure:* A mixture of 1,2,3-triazole (1 equiv), DMAD (3 equiv) and silica-bound aluminium chloride (0.1 mol %) in an open vessel was irradiated in a Discover® microwave reactor (CEM) at the power and temperature indicated in Table 1 for 20 min. The crude reaction mixture was extracted with dichloromethane (2×25 mL) and the product was purified by flash column chromatography (silica gel) using hexane/ethyl acetate as the eluent.
Dimethyl 1-phenylpyrazole-3,4-dicarboxylate (**3a**): mp 76–77 °C (lit. 75–76 °C, Claisen L. *Liebigs Ann. Chem.* **1897**, *295*, 311). ^{1}H NMR δ (ppm) 8.4 (s, 1H, H-5); 7.72–7.52 (m, 2H, H Ph); 7.5–7.48 (m, 2H, H Ph); 7.46–7.31 (m, 1H, H Ph); 4.0 and 3.9 ($2 \times$ s, 6H, $2 \times CH_3$).
Dimethyl 5-methyl-1-phenylpyrazole-3,4-dicarboxylate (**3b**): colorless oil. ^{1}H NMR δ (ppm) 7.52–7.47 (m, 3H, H Ph); 7.42–7.4 (m, 2H, H Ph); 3.95 and 3.88 ($2 \times$ s, 6H, $2 \times OCH_3$); 2.49 (s, 3H, CH_3). ^{13}C NMR δ (ppm) 163.3 and 162.7 (CO); 144.18; 144.13; 138.11 (*ipso*-C Ph); 129.3 (*o*-C Ph); 129.2 (*m*-C Ph); 125 (*p*-C Ph); 112.0 (C-5); 52.5 and 51.8 (OCH_3); 11.9 (CH_3). ESI-HRMS $C_{14}H_{14}N_2O_4$ $(M+H)^+$: calcd: 274.0954. Found: 274.0949.
Dimethyl 5-ethyl-1-phenylpyrazole-3,4-dicarboxylate (**3c**): colorless oil. ^{1}H NMR δ (ppm) 7.5–7.48 (m, 3H, H Ph); 7.3 (m, 2H, H Ph); 3.93 and 3.87 ($2 \times$ s, 6H, $2 \times OCH_3$); 2.86 (q, $J = 7.3$ Hz, 2H, CH_2); 1.12 (t, $J = 7.4$ Hz, 3H, CH_3). ^{13}C NMR δ (ppm) 163.25 and 162.89 (CO); 149.89 (*ipso*-C Ph); 144.2 (C-3); 138.3 (C-4); 129.6 (*o*-C Ph); 129.4 (*p*-C Ph); 126.29 (*m*-C Ph); 112.09 (C-5); 52.7 and 52.0 (OCH_3); 19.06 (CH_2); 13.89 (CH_3). ESI-HRMS $C_{15}H_{16}N_2O_4$ $(M+H)^+$: calcd: 288.1110. Found: 288.1118.
Dimethyl 5-methoxymethyl-1-phenylpyrazole-3,4-dicarboxylate (**3d**): colorless oil. ^{1}H NMR δ (ppm) 7.7–7.6 (m, 2H, *o*−H Ph); 7.5–7.48 (m, 3H, *m*- and *p*-H Ph); 4.5 (s, 2H, CH_2); 3.96 and 3.9 ($2 \times$ s, 6H, $2 \times COOCH_3$); 3.4 (s, 3H, CH_3). ^{13}C MR δ (ppm) 162.8 and 162.6 (CO); 145; 143.2; 138.4 (*ipso*-C Ph); 129.6 (*o*-C Ph); 129.5 (*m*-C Ph); 125.6 (*p*-C Ph); 115.2 ; 62.3 (CH_2); 59.2 (OCH_3); 52 and 52.8 ($COOCH_3$). ESI-HRMS $C_{15}H_{16}N_2O_5$ $(M+H)^+$: calcd: 304.1059. Found: 304.1053.
Dimethyl 5-butyl-1-phenylpyrazole-3,4-dicarboxylate (**3e**): yellow oil. ^{1}H NMR δ (ppm) 7.46 (m, 3H, H Ph); 7.37 (m, 2H, H Ph); 3.91 and 3.84 ($2 \times$ s, 6H, $2 \times CH_3$); 2.82 (m, 2H, H-1′ butyl); 1.43 (m, 2H, H-2′ butyl); 1.2 (m, 2H, H-3′ butyl); 0.76 (t, $J = 7.2$ Hz, 3H, CH_3 butyl). ^{13}C NMR δ (ppm) 163.5 and 163.1 (CO); 149.1 (*ipso*-C); 144.4 (C-3); 138.5 (C-4); 129.7 (*p*-C Ph); 129.5 (*o*-C Ph); 126.5 (*m*-C Ph); 112.5 (C-5); 52.7 and 52.0 (OCH_3); 31.3 (C-2′ butyl); 25.0 (C-1′ butyl); 22.5 (C-3′ butyl); 13.7 (CH_3 butyl). ESI-HRMS $C_{17}H_{20}N_2O_4$ $(M+H)^+$: calcd: 316.1423. Found: 316.1429.
17. Silica-bound $AlCl_3$ was recovered by filtration and drying at 80 °C under reduced pressure for 2 h. The use of this recycled catalyst for five consecutive experiments in the cycloaddition of **1f** with DMAD afforded **3c** in 89%, 89%, 88%, 88% and 89% yield, respectively.
18. (a) Boger, D. L.; Weinreb, S. M. *Hetero Diels–Alder Methodology in Organic Synthesis*; Academic Press: London, UK, 1987; (b) Tietze, L. F.; Kettschau, G. Hetero Diels–Alder Reactions in Organic Chemistry. In Topics in Current Chemistry, 1998; 190, 1–121.
19. *Dimethyl (1,2,3-triazol-1-yl)maleate* (**5**): mp 84–84.5 °C. ^{1}H NMR δ (ppm) 7.85 and 7.8 ($2 \times$ d, $J = 0.9$ Hz, 2H, H-4 and -5); 6.79 (s, 1H, =CH); 4.0 and 3.8 ($2 \times$ s, 6H, $2 \times CH_3$). ^{13}C NMR δ (ppm) 165.0 and 162.6 (CO); 138.0 and 134.6 (C maleate); 123.0 and 122.5 (C-4 and -5): 55.0 and 53.0 (CH_3). ESI-HRMS $C_8H_9N_3O_4$ $(M+H)^+$: calcd: 211.0593. Found: 211.0590.
Dimethyl (1,2,3-triazol-2-yl)maleate (*E*-**6**): mp 76–77 °C. ^{1}H NMR δ (ppm) 7.85 (s, 2H, H-4 and -5); 6.77 (s, 1H, =CH); 4.0 and 3.8 ($2 \times$ s, 6H, $2 \times CH_3$). ^{13}C NMR δ (ppm) 165.1 and 162.2 (CO); 143.1 and 137.9 (C fumarate); 107.4 (C-4 and -5): 53.0 and 52.0 (CH_3). ESI-HRMS $C_8H_9N_3O_4$ $(M+H)^+$: calcd: 211.0593. Found: 211.0600.
Dimethyl (1,2,3-triazol-2-yl)fumarate (*Z*-**6**): Colorless oil. ^{1}H NMR δ (ppm) 7.76 (s, 2H, H-4 and -5); 7.01 (s, 1H, =CH); 3.8 and 3.6 ($2 \times$ s, 6H, $2 \times CH_3$). ^{13}C NMR δ (ppm) 163.5 and 162 (CO); 137.0 and 136.4 (C maleate); 126.7 (C-4 and -5); 54.0 and 52.0 (CH_3). ESI-HRMS $C_8H_9N_3O_4$ $(M+H)^+$: calcd 211.0593. Found: 211.0601.
20. Elguero, J.; de la Hoz, A.; Pardo, C. *J. Chem. Soc., Perkin Trans 2* **1985**, 427.