Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 6506

www.rsc.org/obc

COMMUNICATION

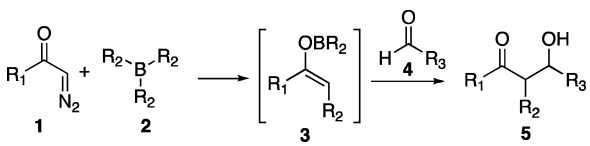
Base-free two-step synthesis of 1,3-diketones and β-ketoesters from α-diazocarbonyl compounds, trialkylboranes, and aromatic aldehydes†‡

Miguel A. Sanchez-Carmona, David A. Contreras-Cruz and Luis D. Miranda*

Received 27th January 2011, Accepted 29th July 2011
DOI: 10.1039/c1ob05150d

We describe a convergent, base-free two-step synthesis of 1,3-diketones and β-ketoesters from α-diazocarbonyl compounds, trialkylboranes, and aromatic aldehydes in a three-component process. The synthetic potential of this protocol was underscored by the synthesis of several symmetrical 1,3,5-triaryl-4-alkyl and 1,3,4,5-tetraryl substituted pyrazoles in a three-step sequence.

Pyrazoles, which are five-membered aromatic heterocyclic compounds, are synthetic targets of considerable importance in both the pharmaceutical and agrochemical industries.[1] The pyrazole nucleus is frequently present in natural products and synthetic molecules, some of which display a range of pharmacological activities, including inhibition of antitumor cyclin-dependent kinase,[2] monoamine oxidase-B, and inflammation, and also are potential atypical antipsychotics.[2] Some noteworthy commercially successful pyrazole containing compounds are Viagra,[3] used for the treatment of erectile dysfunction; Celebrex, used as a potent anti-inflammatory agent;[4] and Acomplia,[5] used for the treatment of obesity. Undoubtedly, the most general method for preparing pyrazoles is the condensation of hydrazines and 1,3-dicarbonyl compounds.[6] Nevertheless, the scope of this synthesis is limited by the availability of the 1,3-dicarbonyl compounds. The usual methodology for generating these building blocks typically involves acylation of an enolate with an acid chloride. This process usually requires the use of strongly basic conditions and low temperatures.[7] Furthermore, the generation of 2-alkyl-1,3-diketones, which are used for the preparation of polysubstituted pyrazoles, also requires the use of a strong base, and dialkylation often is a competing reaction. Interestingly, 40 years ago, Hooz and coworkers[8] reported that the aldols **5** could be efficiently prepared in a three component reaction involving a trialkylborane **2**, a diazocarbonyl compound **1**, and an aldehyde **4** (Scheme 1). Mechanistically, the formation of **5** was interpreted as proceeding *via* the boron enolate **3**, resulting from the transfer of an alkyl substituent of the borane **2** to the diazocarbonyl compound **1**, which was then trapped by the aldehyde.[8] Electrophiles such as dimethylethylenammonium iodide,[9] NBS and NCS[10] and nitriles could also be used as trapping agents of **3**.[11] It is noteworthy that α-diazocarbonyl compounds are usually easily prepared from readily accessible precursors generally under relatively mild conditions.[12] The acylation of diazomethane with an acid chloride (Arndt–Eistert synthesis of diazo ketones)[12a–c] and also with a carboxylic acid,[12d] remains the single most important methodology to obtain acyclic α-diazo ketones. In addition, the diazo group transfer technique introduced by Regitz and coworkers,[12e,f] is useful for the preparation of cyclic and acyclic α-diazocarbonyl containing systems.



Scheme 1 Hooz three-component reaction.

Although the Hooz reaction allows efficient construction of two C–C bonds under metal-free conditions (Scheme 1), its application in synthetic organic chemistry has remained largely unexplored. We reasoned that this process might be a versatile source of 1,3-dicarbonyl compounds (**6**), by simply oxidizing the corresponding aldol adduct **5** (Table 1). This report describes the use of the Hooz reaction/oxidation sequence as the source of the various 1,3-dicarbonyl compounds, and the subsequent use thereof for the preparation of various polysubstituted pyrazoles.

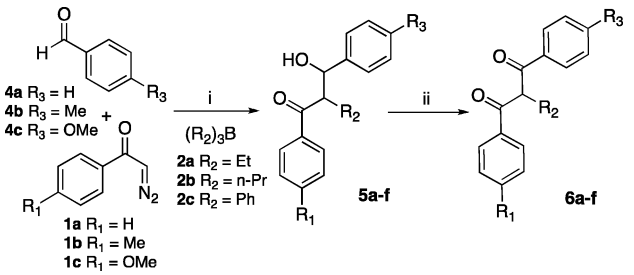
First, to optimize the reaction conditions, we studied the condensation of α-diazoacetophenone **1a**[12d] (Table 1, entry 1), the commercially available triethylborane, and benzaldehyde. However, when a 1 M solution of Et_3B in hexane was utilized, a low yield of the desired aldol **5a** was obtained (Table 1, entry 1). In contrast, when a solution of **1a** in a THF solution was added dropwise to a solution of the aldehyde and Et_3B in THF, at room temperature, a moderate yield of **5a** was obtained (Table 1, entry 2). Under these optimized conditions, the use of *p*-OMe-, *p*-tolyl α-diazoacetophenone and *p*-Me, and *p*-methoxybenzaldehyde in combination with Et_3B resulted in excellent yields of the corresponding aldols **5c–d** (Table 1, entries 3–4). Similarly, n-Pr_3B[13] afforded good yields of the expected aldol **5e**. Furthermore, we confirmed that a phenyl group could be introduced into the enol derivative by simply using the corresponding Ph_3B.[13] It is worth

Instituto de Química, Universidad Nacional Autónoma de México, Circuito Exterior, Ciudad Universitaria, Coyoacán México, D. F. 04510, México. E-mail: lmiranda@servidor.unam.mx; Tel: +52 5556224440

† We thank CONACYT (82643) for financial support and Dr Joseph M. Muchowski for many helpful discussions. We also thank R. Patiño, J. Pérez, L. Velasco, H. Rios, E. Huerta, A. Peña, and I. Chavez for technical support.

‡ Electronic supplementary information (ESI) available. See DOI: 10.1039/c1ob05150d

Table 1 Synthesis of 1,3-diketones



entry	substrates	R_1	R_2	R_3	Aldol, yield (%)	Diketone, yield (%)
1	**1a**, **2a**, **4a**	H	Et	H	**5a** (41)	**6a** (58)
2	**1b**, **2a**, **4a**	H	Et	Me	**5b** (56)	**6b** (73)
3	**1b**, **2a**, **4b**	Me	Et	Me	**5c** (96)	**6c** (60)
4	**1c**, **2a**, **4c**	OMe	Et	OMe	**5d** (98)	**6d** (56)
5	**1c**, **2b**, **4c**	OMe	n-Pr	OMe	**5e** (75)	**6e** (63)
6	**1b**, **2c**, **4b**	Me	Ph	Me	**5f** (72)	**6f** (65)

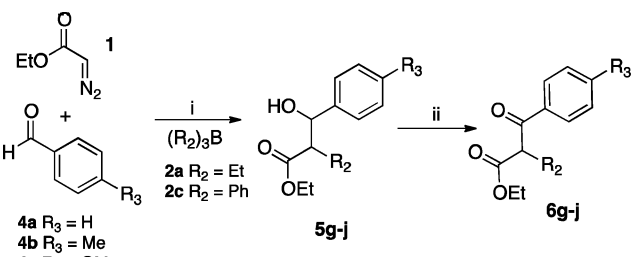
Conditions: i) diazoketone (1 eq.), aldehyde (1 eq.), trialkylborane (3 eq.), THF, r. t. 1 h. ii) PCC, CH_2Cl_2, molecular sieves 4 Å, r. t. 4 h.

noting that this sort of transformation typically entails the use of transition metal-catalyzed conditions.

Next, we focused our efforts on finding efficient oxidation conditions for transforming the aldols **5a–f** into the corresponding diketones **6a–f**. After testing several conditions, we found that treating the corresponding aldol (**5a–f**) with an excess of PCC, in the presence of molecular sieves, afforded the diketones **6a–f** in moderate yields. In order to avoid the generation of regioisomeric pyrazole mixtures, symmetrical diketones were prepared, in all but one case (**6b**, Table 1, entry 2).

We then explored the utility of this approach for the preparation of β-ketoesters. Straightforwardly, the reaction of the commercially available ethyl diazoacetate with benzaldehydes **4a–c** and boranes **2a–c** afforded the corresponding aldols **5g–j**, which were transformed into the expected β-ketoesters **6g–j** in moderate yields (Table 2). Both triphenylborane and triethylborane both gave moderate to good product yields in this variation of the three-

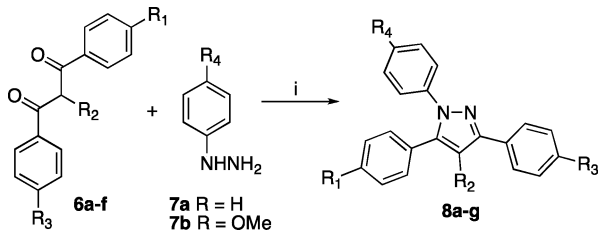
Table 2 Synthesis of substituted β-ketoesters



entry	substrates	R_2	R_3	Aldol, yield (%)	Ketoesters, yield (%)
1	**1**, **2a**, **4a**	Et	H	**5g** (51)	**6g** (35)
2	**1**, **2a**, **4b**	Et	Me	**5h** (75)	**6h** (30)
3	**1**, **2a**, **4c**	Et	OMe	**5i** (74)	**6i** (35)
4	**1**, **2c**, **4a**	Ph	H	**5j** (38)	**6j** (40)
5	**1**, **2c**, **4b**	Ph	Me	**5k** (40)	**6k** (41)

Conditions: i) diazoketone (1 eq.), aldehyde (1 eq.), trialkylborane (3 eq.), THF, r. t. 1 h. ii) PCC, CH_2Cl_2, molecular sieves 4 Å, r. t. 4 h.

Table 3 Synthesis of tetrasubstituted pyrazoles

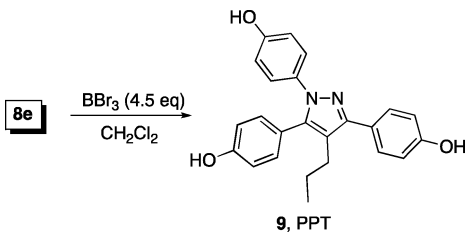


entry	Substrates		R_1	R_2	R_3	R_4	Pyrazole, yield (%)
1	**6b**	**7b**	H	Et	Me	OMe	**8a** (60)[a]
2	**6a**	**7b**	H	Et	H	OMe	**8b** (98)
3	**6c**	**7a**	Me	Et	Me	H	**8c** (54)
4	**6d**	**7a**	OMe	Et	OMe	H	**8d** (49)
5	**6e**	**7b**	OMe	n-Pr	OMe	OMe	**8e** (74)
6	**6f**	**7a**	Me	Ph	Me	H	**8f** (90)
7	**6f**	**7b**	Me	Ph	Me	OMe	**8g** (64)

Conditions: i) Method A: For **7a**, 1,3-diketone (1 eq.), hydrazine (1.4 eq.), CAN (3 mol%), MeCN, reflux, 3 h. Method B: For **7b**·**HCl** (3 eq.) DMF/THF (3 : 1) 120 °C.[a] As a 1 : 1 mixture of regioisomers.

component Hooz reaction. Unfortunately, attempts to carry out the same reaction protocol using aliphatic aldehydes failed to obtain the expected aldols.

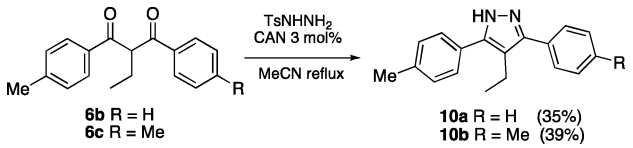
With the diketones **6a–f** (Table 1) in hand, we next explored their reactions with phenylhydrazine and p-methoxyphenylhydrazine hydrochloride (Table 3). In reactions with the free hydrazines **7a–b** (Table 3), we employed ceric ammonium nitrate (CAN), which was recently reported to improve yields in this transformation.[14] The reaction with the unsymmetrical diketone **6b** produced the expected 1 : 1 (determined by ^{1}H NMR) mixture of regioisomeric pyrazoles **8a**, (Table 3, entry 1). However, when symmetrical diketones **6a,c–f** were employed, several symmetrical tetrasubstituted pyrazoles **8a–f** were obtained in moderate to excellent yields (Table 3, entries 2–7). It is worth noting that the 1,2,3,4-tetraaryl pyrazoles **8f–g** (Table 3, entries 6 and 7) were efficiently constructed in three steps from readily available starting materials in a convergent, base-free, synthetic sequence that did not require expensive Pd-catalyst-mediated protocols. Interestingly, the 1,3,5-triaryl-4-alkyl substituted pyrazoles, exemplified by propylpyrazole triol (PPT) **9** (Scheme 2), are selective estrogen receptor modulator compounds (SERMs), which display a broad spectrum of agonist and antagonist actions at different target tissues.[15,16] In this context, the data collected in Table 3 demonstrate that several structurally diverse 1,3,5-triaryl-4-alkyl substituted pyrazoles (*i.e.*, **8b–e**) can be readily available using the protocol reported in the present letter. Indeed, PPT was obtained in good yield



Scheme 2 Synthesis of propylpyrazole triol (PPT), a selective estrogen receptor modulator.

after demethylation of **8e** with BBr_3, as reported previously (Scheme 2).[16]

The N-unsubstituted 2,4-diaryl-3-ethyl pyrazoles **10a** and **10b** were also prepared when diketones **6b** and **6c** were reacted with tosylhydrazine in refluxing acetonitrile (Scheme 3).[17]



Scheme 3 Synthesis of 2,4-diaryl-3-ethyl pyrazole.

Conclusions

In conclusion, we have described a highly convergent, two-step synthesis of 1,3-diketones and β-ketoesters from α-diazocarbonyl compounds, trialkylboranes, and aldehydes in a three-component process. The synthetic potential of this protocol was underscored by the synthesis of several symmetrical 1,3,5-triaryl-4-alkyl and 1,2,3,4-tetraryl substituted pyrazoles in a three-step protocol. This protocol precludes the use of strong bases and expensive Pd-catalysis-mediated conditions. Furthermore, it offers a modular approach for easily introducing different substituents by simply varying the substituents in the starting materials.

Notes and references

1 I. Shinkai, In: *Comprehensive Heterocyclic Chemistry II*, Vol. 3; I. Shinkai, Ed., Pergamon: Oxford UK, 1996, 1–75.
2 R. Lin, G. Chiu, Y. Yu, P. J. Connolly, S. Li, Y. Lu, M. Adams, A. R. Fuentes-Pesquera, S. L. Emanuel and L. M. Greenberger, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 4557–4561.
3 P. Dunn, *Org. Process Res. Dev.*, 2005, **9**, 88.
4 T. D. Penning, J. J. Talley, S. R. Bertenshaw, J. S. Carter, P. W. Collins, S. Docter, M. J. Graneto, L. F. Lee, J. W. Malecha, J. M. Miyashiro, R. S. Rogers, D. J. Rogier, S. S. Yu, G. D. Anderson, E. G. Burton, J. N. Cogburn, S. A. Gregory, C. M. Koboldt, W. E. Perkins, K. Seibert, A. W. Veenhuizen, Y. Y. Zhang and P. C. Isakson, *J. Med. Chem.*, 1997, **40**, 1347.
5 M. Rinaldi-Carmona, F. Barth, M. Héaulme, D. Shire, B. Calandra, C. Congy, S. Martinez, J. Maruani, G. Néliat, D. Caput, P. Ferrara, P. Soubrié, J. C. Breliére and G. Le Fur, *FEBS Lett.*, 1994, **350**, 240.
6 (*a*) L. Knorr, *Ber.*, 1883, **16**, 2587; (*b*) M. V. Patel, R. Bell, S. Majest, R. Henry and T. Kolasa, *J. Org. Chem.*, 2004, **69**, 7058; (*c*) S. Peruncheralathan, T. A. Khan, H. Ila and H. Junjappa, *J. Org. Chem.*, 2005, **70**, 10030.
7 (*a*) T. T. Dang, C. Fischer, H. Görls and P. Langer, *Tetrahedron*, 2008, **64**, 2207; (*b*) Z. Turgut and N. Öcal, *Russ. J. Org. Chem.*, 2002, **38**, 602; (*c*) S. R. Stauffer, Y. Huang, C. J. Coletta, R. Tedesco and J. A. Katzenellenbogen, *Bioorg. Med. Chem.*, 2001, **9**, 141.
8 (*a*) J. Hooz and S. Linke, *J. Am. Chem. Soc.*, 1968, **90**, 5936–37; (*b*) J. Hooz and D. M. Gunn, *Tetrahedron Lett.*, 1969, 3455–56; (*c*) J. Hooz and G. F. Morrison, *Can. J. Chem.*, 1970, **48**, 868–70; (*d*) J. Hooz, J. Oudenes, J. L. Roberts and A. Benderly, *J. Org. Chem.*, 1987, **52**, 1347–49.
9 J. Hooz and J. Bridson, *J. Am. Chem. Soc.*, 1973, **95**, 602–603.
10 J. Hooz and J. Bridson, *Can. J. Chem.*, 1972, **50**, 2387–2390.
11 J. Hooz and J. Oudenes, *Synth. Commun.*, 1982, **12**, 189–194.
12 (*a*) F. Anrdt, B. Eistert and W. Part de, *Ber. Dtsch. Chem. Ges.*, 1927, **60B**, 1364; (*b*) F. Amdt and J. Amende, *Ber. Dtsch. Chem. Ges.*, 1928, **61B**, 1122; (*c*) F. Arndt, B. Eistert and J. Amende, *Ber. Dtsch. Chem. Ges.*, 1928, **61B**, 1949; (*d*) E. Cuevas-Yañez, M. A. García, M. A. de la Mora, J. M. Muchowski and R. Cruz-Almanza, *Tetrahedron Lett.*, 2003, **44**, 4815–4817; (*e*) M. Regitz, *Angew. Chem., Int. Ed. Engl.*, 1967, **6**, 733; (*f*) M. Regitz, *Synthesis*, 1972, 351.
13 H. C. Brown and U. S. Racherla, *J. Org. Chem.*, 1986, **51**, 427–432.
14 R. Flowers, J. Devery, P. Mohanta and B. Casey, *Synlett*, 2009, 1490.
15 B. E. Fink, D. S. Mortensen, S. R. Stauffer, Z. D. Aron and J. A. Katzenellenbogen, *Chem. Biol.*, 1999, **6**, 205–219.
16 S. R. Stauffer, C. J. Coletta, R. Tedesco, G. Nishigushi, K. E. Carlson, J. Sun, B. S. Katzenellenbogen and J. A. Katzenellenbogen, *J. Med. Chem.*, 2000, **43**, 4934–4947.
17 A. Padwa, *J. Org. Chem.*, 1965, **30**, 1274–1275.

