"One-Pot" Synthesis of 4-Substituted 1,5-Diaryl-1*H*-pyrazole-3-carboxylic Acids via a MeONa/LiCl-Mediated Sterically Hindered Claisen Condensation–Knorr Reaction–Hydrolysis Sequence

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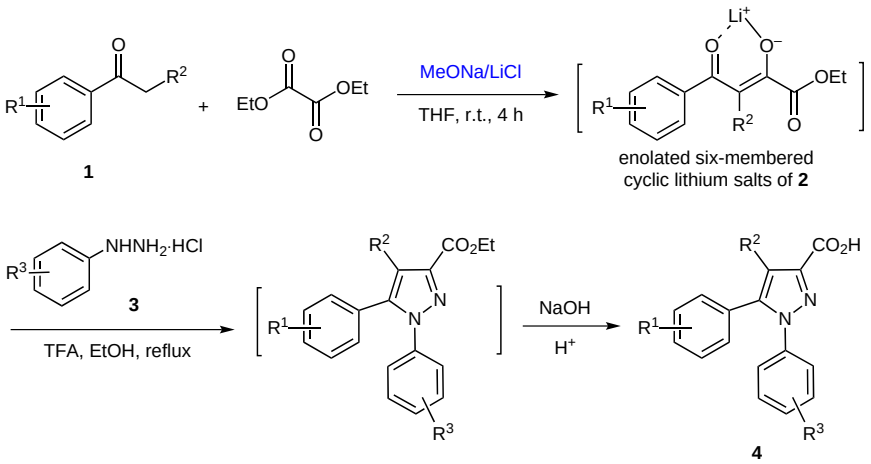
Abstract: A "one-pot" synthesis of 4-substituted 1,5-diaryl-1*H*-pyrazole-3-carboxylic acids was first reported in moderate to good yields. This concise procedure, featuring efficiency and green chemistry, was composed of MeONa/LiCl-mediated sterically hindered Claisen condensation, Knorr reaction and hydrolysis.

Key words: MeONa/LiCl, sterically hindered Claisen condensation, Knorr reaction, 4-substituted 1,5-diaryl-1*H*-pyrazole-3-carboxylic acids, "one-pot" synthesis

Among nitrogen-containing heterocycles, the pyrazole motif is a common core component of numerous biologically active molecules.[1] Notably, recent discoveries that 4-substituted 1,5-diaryl-1*H*-pyrazole-3-carboxylate derivatives can act as cannabinoid-1 (CB1) receptor antagonists,[2] Iκβ kinase β (IKKβ or IKK-2) inhibitors,[3] analgesics,[4] and anti-inflammatory agents[5] have attracted increasing attention and have led to the development of new syntheses of this class of compounds and further biological explorations.[2–6] With this background, the precursor 4-substituted 1,5-diaryl-1*H*-pyrazole-3-carboxylic acids have been a particular focus; these are generally prepared through application of the Knorr reaction of 3-substituted 4-aryl-2,4-diketo esters and arylhydrazines followed by basic hydrolysis.[2a,b,f,g,4] This classical preparation inevitably requires the use of commercially unavailable 2,4-diketo esters, which are usually synthesized from alkylphenones and diethyl oxalate by base-mediated sterically hindered Claisen condensation (SHCC). However, the SHCC reaction often suffers from low chemical yield in sodium ethoxide-mediated procedures,[2a,4] or troublesome and uneconomical operation in lithium hexamethyldisilazide (LiHMDS)-mediated procedures.[2b,f,g] Hence, there remains an urgent need for conceptually sustainable and versatile syntheses of 2,4-diketo esters as well as the fully substituted pyrazoles from easily available reactants. Toward this end, we became interested in the development of a mild SHCC using low-cost and robust base to efficiently generate the labile 2,4-diketo esters on both bench and industrial scales.

Our group had found that the use of an alkoxide/LiCl system could efficiently execute the SHCC of 4-chloropropiophenone and diethyl oxalate to generate an intermediate of Rimonabant, a listed CB1 receptor antagonist.[7] Thus, we formally turned our attention to the alkoxide/LiCl system, as a potentially green and competent surrogate for sodium ethoxide and LiHMDS, for preparing the 2,4-diketo esters efficiently and sustainably. Herein, we reported a



Scheme 1 "One-pot" synthesis of 4-substituted 1,5-diaryl-1*H*-pyrazole-3-carboxylic acids

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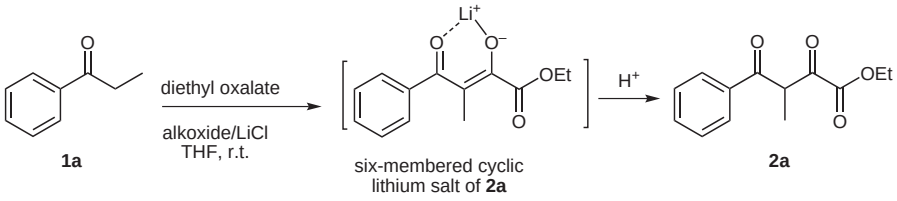
MeONa/LiCl-mediated SHCC of alkylphenones **1** with diethyl oxalate to afford the corresponding enolated lithium salts of 3-substituted 4-aryl-2,4-diketo esters **2**, which were trapped in situ by arylhydrazine hydrochlorides **3** upon addition of stoichiometric trifluoroacetic acid (TFA) in ethanol, followed by a sodium hydroxide mediated hydrolysis in situ to create structurally diverse 4-substituted 1,5-diaryl-1*H*-pyrazole-3-carboxylic acids **4** in a "one-pot" fashion (Scheme 1).

Our investigations began with the EtONa/LiCl-mediated SHCC of propiophenone (**1a**; 1.0 equiv) and diethyl oxalate (1.3 equiv, Table 1). Interestingly, when the SHCC was conducted with a pre-prepared mixture of EtONa (1.5 equiv) and LiCl (1.5 equiv) in tetrahydrofuran (THF) at room temperature for three hours, the expected 3-methyl 4-phenyl-2,4-diketo ester (**2a**) was isolated only in 74% yield, with two consistent contaminants being observed (entry 1).[8] The formation of unexpected contaminants promoted us to further optimize the reaction conditions. On increasing the amount of LiCl, the formation of undesired contaminants could be suppressed (entries 2–4), and the yield of **2a** was increased to 90–91% by utilizing 2.5 or 3.0 equiv LiCl (entries 3 and 4). It was further observed that the use of other alkoxides including *t*-BuOK and MeONa also proved to be equally effective for this transformation (entries 5 and 6), with the latter system being preferable in terms of cost. These results suggested that the presence of lithium could play a vital role in this SHCC to generate the enolated six-membered cyclic lithium salts;[2f,g] the advantage of using lithium in the reaction could stem from the stronger affinity of lithium towards oxygen compared with that of sodium and potassium.[9]

It should also be mentioned that, similar to sterically hindered 2-substituted 1,3-diketones,[10e–h] 2-substituted 3-keto esters,[10b,d,h] as well as 3-unsubstituted 2,4-diketo esters[10c] and 2-unsubstituted 1,3-diketones,[10a] compound **2a** is highly unstable. To avoid the need to isolate unstable **2**, we subsequently sought to combine the SHCC, the Knorr reaction, and the base-mediated hydrolysis into a "one-pot" process. Extensive studies led to an optimal process allowing a "one-pot" synthesis of highly valuable **4**.[11] First, a mixture of LiCl (2.5 equiv) and MeONa (1.5 equiv) in THF was heated at reflux for three hours,[12] to which was then added **1a** (1.0 equiv) and diethyl oxalate (1.3 equiv) and the reaction mixture was stirred for a further three hours at room temperature. After removal of THF, EtOH (solvent), TFA (2.0 equiv), and phenylhydrazine hydrochloride (**3a**; 1.0 equiv) were sequentially added to instigate the Knorr reaction of **2a** and **3a**, which was conducted at reflux for 12 hours. Subsequent addition of NaOH (4.0 equiv) to the reaction mixture and heating at reflux for four hours gave **4aa** in a good total yield of 73%. We realized that the use of an equimolar amount of **3a** (versus **1a**) was necessary to trap the freshly generated **2a** almost completely. Another key factor for this "one-pot" synthesis was direct introduction of NaOH to achieve **4** after completion of the Knorr reaction without any modification of the reaction mixture.

Having established the "one-pot" procedure, we then evaluated the generality of the approach with respect to substrate **3** (Table 2). By varying the substituent(s) R^3 of **3**, it became clear that electron-neutral **3a** (entry 1) and electron-deficient **3b**–**d**, bearing chlorine substituents on the benzene ring, was slightly beneficial, giving the corresponding products **4ab**–**ad** in yields of 74–76% (entries 2–4). We considered that the chlorine atom(s) could stabilize the hydrazinyl group, making the arylhydrazines more stable under reflux conditions. In contrast, the "one-pot" procedure gave the products **4af**–**ah** in lower yields of 70–72% with electron-rich substrates **3f**–**h** bearing electron-donating methyl group(s) on the benzene ring

Table 1 The Investigation of Alkoxid/LiCl-Mediated SHCC[a]

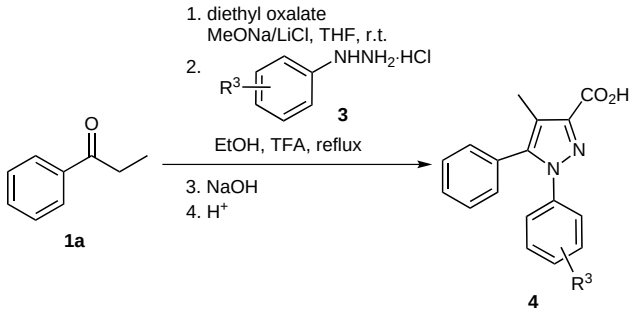


Entry	Alkoxide	LiCl (*n* equiv to **1a**)	Yield (%)[b]
1	EtONa	1.5	74
2	EtONa	2.0	83
3	EtONa	2.5	90
4	EtONa	3.0	91
5	*t*-BuOK	2.5	90
6	**MeONa**	**2.5**	**90**

[a] Performed with LiCl (*n* equiv), alkoxide (7.5 mmol), anhydrous THF (15 mL) at reflux for 3 h, then **1a** (5.0 mmol), diethyl oxalate (6.5 mmol) at room temperature for 3 h.
[b] Isolated yields.

(entries 6–8). This weakly detrimental effect was presumed to result from the increased oxidizability caused by the electron-donating group(s) for the hydrazinyl group. It should be noted that, irrespective of the electronic properties of R^3, the di-*ortho*-substituted steric hindrance of **3e** and **3i** had a remarkable impact on the yield of products **4ae** and **4ai**, with relatively low yields of 65 and 60%, respectively (entries 5 and 9). Thus, steric effects would be expected to significantly influence the efficiency of the "one-pot" procedure. As expected, isopropylhydrazine hydrochloride gave a good yield in the "one-pot" procedure as a representative alkylhydrazine (**3j**; entry 10), further demonstrating the utility and scope of this methodology.

Table 2 The Generality of Arylhydrazine Hydrochlorides **3**[a]



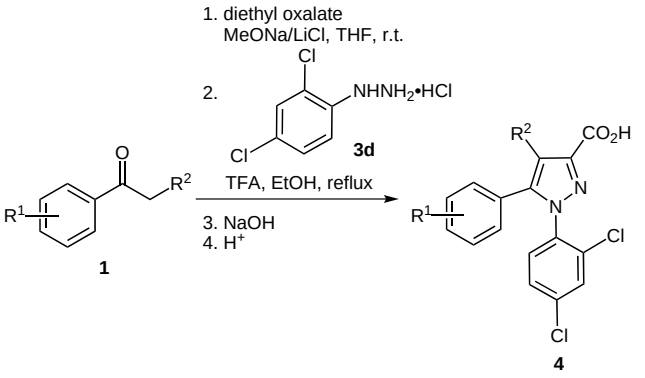
Entry	**3** (R^3)	Product	Yield (%)[b]
1	**3a** (R^3 = H)	**4aa**	73
2	**3b** (R^3 = 3-Cl)	**4ab**	74
3	**3c** (R^3 = 4-Cl)	**4ac**	74
4	**3d** (R^3 = 2,4-Cl_2)	**4ad**	76
5	**3e** (R^3 = 2,4,6- Cl_3)	**4ae**	65
6	**3f** (R^3 = 4-Me)	**4af**	72
7	**3g** (R^3 = 2,4-Me_2)	**4ag**	70
8	**3h** (R^3 = 2,5- Me_2)	**4ah**	72
9	**3i** (R^3 = 2,6-Me_2)	**4ai**	60
10	**3j** = *i*-PrNHNH$_2$·HCl	**4aj**[c]	79

[a] Performed with LiCl (12.5 mmol), MeONa (7.5 mmol), anhydrous THF (15 mL), **1a** (5.0 mmol), diethyl oxalate (6.5 mmo), anhydrous EtOH (15 mL), TFA (10.0 mmol), **3** (5.0 mmol) and NaOH (20.0 mmol) following the typical "one-pot" procedure.[11]
[b] Isolated yields.
[c] *N*-substituent as isopropyl group in the structure of **4aj**.

We then investigated the effect of substituents R^1 and R^2 of **1** by using **3d** as a representative in the "one-pot" procedure (Table 3). The substituent(s) R^1 could include not only electron-donating group(s) (**1b**–**d**) but also electron-withdrawing group(s) (**1e**–**h**), giving the corresponding products **4bd**–**hd** in good yields (66–72%; entries 1–7). Indeed, the best result was obtained for **4aa** with electron-neutral **1a** (Table 2, entry 4).

To test the limits of the procedure further, we synthesized more sterically challenging substrates **4** containing larger R^2 groups, which would be expected to be obtained with poor efficiency through the discrete protocol due to the extreme instability of the corresponding precursors **2**. By using *n*-butyrophenone (**1i**) and *n*-valerophenone (**1j**), as well as 2-phenyl-1-(*p*-tolyl)ethanone (**1k**), we were pleased to obtain **4id**–**kd** in respectable yields of 62, 56, and 45%, respectively (Table 3, entries 8–10).

Table 3 The Generality of Alkylphenones **1**[a]



Entry	**1** (R^1/R^2)	Product	Yield (%)[b]
1	**1b** (R^1 = 4-MeO, R^2 = Me)	**4bd**	70
2	**1c** (R^1 = 4-Me, R^2 = Me)	**4cd**	72
3	**1d** (R^1 = 2,4-Me_2, R^2 = Me)	**4dd**	70
4	**1e** (R^1 = 4-Cl, R^2 = Me)	**4ed**	72
5	**1f** (R^1 = 2,4-Cl_2, R^2 = Me)	**4fd**	67
6	**1g** (R^1 = 4-Br, R^2 = Me)	**4gd**	70
7	**1h** (R^1 = 2-F, R^2 = Me)	**4hd**	66
8	**1i** (R^1 = H, R^2 = Et)	**4id**	62
9	**1j** (R^1 = H, R^2 = *n*-Pr)	**4jd**	56
10	**1k** (R^1 = 4-Me, R^2 = Ph)	**4kd**	45

[a] Performed with LiCl (12.5 mmol), MeONa (7.5 mmol), anhydrous THF (15 mL), **1** (5.0 mmol), diethyl oxalate (6.5 mmo), anhydrous EtOH (15 mL), TFA (10.0 mmol), **3d** (5.0 mmol) and NaOH (20.0 mmol) following the typical "one-pot" procedure.[11]
[b] Isolated yields.

In summary, we have developed an efficient "one-pot" synthesis of highly valuable **4** from readily available reactants. This procedure, featuring green chemistry, was based on a MeONa/LiCl-mediated sterically hindered Claisen condensation/Knorr reaction/hydrolysis sequence. The low cost of the reagents MeONa and LiCl, good tolerance, and simple operation render the procedure particularly appealing for sustainable chemistry-oriented synthesis. The synthetic versatility of **2** and pharmaceutical importance of **4** underline the usefulness of this methodology. Studies are in progress to broaden the field of

application, in particular, for the synthesis of sterically overcrowded heterocyclic skeletons.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

References and Notes

(1) For selected reports, see: (a) de Paulis, T.; Hemstapat, K.; Chen, Y.; Zhang, Y.; Saleh, S.; Alagille, D.; Baldwin, R. M.; Tamagnan, G. D.; Conn, P. J. *J. Med. Chem.* **2006**, *49*, 3332. (b) Chimenti, F.; Fioravanti, R.; Bolasco, A.; Manna, F.; Chimenti, P.; Secci, D.; Befani, O.; Turini, P.; Ortuso, F.; Alcaro, S. *J. Med. Chem.* **2007**, *50*, 425. (c) Cavero, E.; Uriel, S.; Romero, P.; Serrano, J. L.; Gimenez, R. *J. Am. Chem. Soc.* **2007**, *129*, 11608. (d) Ye, C.; Gard, G. L.; Winter, R. W.; Syvret, R. G.; Twamley, B.; Shreeve, J. M. *Org. Lett.* **2007**, *9*, 3841. (e) Fustero, S.; Roman, R.; Sanz-Cervera, J. F.; Simon-Fuentes, A.; Bueno, J.; Villanova, S. *J. Org. Chem.* **2008**, *73*, 8545. (f) Wyatt, P. G.; Woodhead, A. J.; Berdini, V.; Boulstridge, J. A.; Carr, M. G.; Cross, D. M.; Davis, D. J.; Devine, L. A.; Early, T. R.; Feltell, R. E.; Lewis, E. J.; MsMenamin, R. L.; Navarro, E. F.; O'Brien, M. A.; O'Reilly, M.; Reule, M.; Saxty, G.; Seavers, L. A.; Smith, D.-M.; Squires, M.; Trewartha, G.; Walker, M. T.; Woolford, A. J.-A. *J. Med. Chem.* **2008**, *51*, 4986. (g) Fustero, S.; Sanchez-Rosell, M.; Barrio, P.; Simon-Fuentes, A. *Chem. Rev.* **2011**, *111*, 6984.

(2) For selected examples, see: (a) Zhang, Y.; Burgess, J. P.; Brackeen, M.; Gilliam, A.; Mascarella, S. W.; Page, K.; Seltzman, H. H.; Thomas, B. F. *J. Med. Chem.* **2008**, *51*, 3526. (b) Wu, C.-H.; Hung, M.-S.; Song, J.-S.; Yeh, T.-K.; Chou, M.-C.; Chu, C.-M.; Jan, J.-J.; Hsieh, M.-T.; Tseng, S.-L.; Chang, C.-P.; Hsieh, W.-P.; Lin, Y.; Yeh, Y.-N.; Chung, W.-L.; Kuo, C.-W.; Lin, C.-Y.; Shy, H.-S.; Chao, Y.-S.; Shia, K.-S. *J. Med. Chem.* **2009**, *52*, 4496. (c) Dow, R. L.; Carpino, P. A.; Hadcock, J. R.; Black, S. C.; Iredale, P. A.; DaSilva-Jardine, P.; Schneider, S. R.; Paight, E. S.; Griffith, D. A.; Scott, D. O.; O'Connor, R. E.; Nduaka, C. I. *J. Med. Chem.* **2009**, *52*, 2652. (d) Spivey, A. C.; Tseng, C.-C.; Jones, T. C.; Kohler, A. D.; Ellames, G. J. *Org. Lett.* **2009**, *11*, 4760. (e) Seo, H. J.; Kim, M. J.; Lee, S. H.; Lee, S.-H.; Jung, M. E.; Kim, M.-S.; Ahn, K.; Kim, J.; Lee, J. *Bioorg. Med. Chem.* **2010**, *18*, 1149. (f) Cooper, M.; Receveur, J.-M.; Bjurling, E.; Nørregaard, P. K.; Nielsen, P. A.; Sköld, N.; Högberg, T. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 26. (g) Yan, L.; Huo, P.; Debenham, J. S.; Madsen-Duggan, C. B.; Lao, J.; Chen, R. Z.; Xiao, J. C.; Shen, C.-P.; Stribling, D. S.; Shearman, L. P.; Strack, A. M.; Tsou, N.; Ball, R. G.; Wang, J.; Tong, X.; Bateman, T. J.; Reddy, V. B. G.; Fong, T. M.; Hale, J. J. *J. Med. Chem.* **2010**, *53*, 4028. (h) Lange, J. H. M.; Coolen, H. K. A. C.; Neut, M. A. W.; Borst, A. J. M.; Stork, B.; Verveer, P. C.; Kruse, C. G. *J. Med. Chem.* **2010**, *53*, 1338. (i) Donohue, S. R.; Dannals, R. F.; Halldin, C.; Pike, V. W. *J. Med. Chem.* **2011**, *54*, 2961.

(3) Xie, J.; Poda, G. I.; Hu, Y.; Chen, N. X.; Heier, R. F.; Wolfson, S. G.; Reding, M. T.; Lennon, P. J.; Kurumbail, R. G.; Selness, S. R.; Li, X.; Kishore, N. N.; Sommers, C. D.; Christine, L.; Bonar, S. L.; Venkatraman, N.; Mathialagan, S.; Brustkern, S. J.; Huang, H.-C. *Bioorg. Med. Chem.* **2011**, *19*, 1242.

(4) Abd-El Gawad, N. M.; Hassan, G. S.; Georgey, H. H. *Med. Chem. Res.* **2012**, *21*, 983.

(5) Nassar, E.; Abdel-Aziz, H. A.; Ibrahim, H. S.; Mansour, A. M. *Sci. Pharm.* **2011**, *79*, 507.

(6) (a) Selttman, H. H.; Carroll, F. I.; Burgess, J. P.; Wyrick, C. D.; Burch, D. F. *J. Chem. Soc., Chem. Commun.* **1995**, 1549. (b) Vazquez, N.; Gomez-Vallejo, V.; Llop, J. *Tetrahedron Lett.* **2012**, *53*, 4743.

(7) Ji, Y.-F.; Zhang, P.-Z.; Wan, H.; Duan, M.-L.; Xu, X.; Wang, Y. CN Patent 101585810A (101585810B), **2009**; *Chem. Abstr.* **2009**, *152*: 57302

(8) Two contaminants were detected: ethyl benzoate and ethyl 2-hydroxy-3-methyl-4,5-dioxohept-2-enoate, which were presumed to be byproducts derived from **2a.**

(9) (a) Sannigrahi, A. B.; Kar, T.; Niyogi, B. G.; Hobza, P.; Schleyer, P. v. R. *Chem. Rev.* **1990**, *90*, 1061. (b) Izatt, R. M.; Bradshaw, J. S.; Dalley, N. K. *Chem. Rev.* **1991**, *91*, 137. (c) Paquette, L. A.; Ra, C. S.; Gallucci, J. C.; Kang, H.-J.; Ohmori, N.; Arrington, M. P.; David, W.; Brodbelt, J. S. *J. Org. Chem.* **2001**, *66*, 8629.

(10) (a) Dejaegher, Y.; Kuz'menok, N. M.; Zvonok, A. M.; de Kimpe, N. *Chem. Rev.* **2002**, *102*, 29. (b) Cvetovich, R. J.; Pipik, B.; Hartner, F. W.; Grabowski, E. J. J. *Tetrahedron Lett.* **2003**, *44*, 5867. (c) Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A.; Petrini, M. *Chem. Rev.* **2005**, *105*, 933. (d) Kawata, A.; Takata, K.; Kuninobu, Y.; Takai, K. *Angew. Chem. Int. Ed.* **2007**, *46*, 7793. (e) Veitch, G. E.; Bridgwood, K. L.; Ley, S. V. *Org. Lett.* **2008**, *10*, 3623. (f) Rao, C. B.; Rao, D. C.; Babu, D. C.; Venkateswarlu, Y. *Eur. J. Org. Chem.* **2010**, 2855. (g) Biswas, S.; Maiti, S.; Jana, U. *Eur. J. Org. Chem.* **2010**, 2861. (h) Grenning, A. J.; Tunge, J. A. *J. Am. Chem. Soc.* **2011**, *133*, 14785.

(11) **Typical "one-pot" procedure for 4:** An oven-dried vial was charged with LiCl (0.53 g, 12.5 mmol) and MeONa (0.41 g, 7.5 mmol) in anhydrous THF (15 mL). The mixture was stirred and heated at reflux for 3 h and then cooled to 0 °C, and alkylphenone **1** (5.0 mmol) and diethyl oxalate (0.95 g, 6.5 mmol) were added. The resulting mixture was stirred at r.t. for 3 h and then concentrated to remove THF. Anhydrous EtOH (15 mL), TFA (1.14 g, 10.0 mmol) and arylhydrazine hydrochloride **3** (5.0 mmol) were added at r.t., and the mixture was heated to reflux for 12 h. A solution of NaOH (0.8 g, 20.0 mmol) in H_2O (2 mL) was then added to the reaction solution, which was stirred and heated to reflux for a further 4 h. The solution was then concentrated in vacuo to remove EtOH, affording a residue, to which was added H_2O (15 mL), CH_2Cl_2 (15 mL), and 10% HCl (ca. 10 mL) until pH 3–4 to make the solution partition into organic and aqueous layers. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic phase was washed with H_2O (2 × 20 mL), dried over anhydrous sodium sulfate, and concentrated to give the crude product, which was purified by recrystallization (petroleum ether–EtOAc, 5:1 v/v; 6 mL) to give the corresponding product **4**. Representative compound **4aa**: yellow solid; Yield: 1.01 g (73%); mp 158–160 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.37 (m, 3 H), 7.37–7.25 (m, 5 H), 7.25–7.15 (m, 2 H), 2.38 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.4, 142.8, 141.2, 139.4, 130.1 (2C), 129.3, 128.9 (2C), 128.7, 128.6 (2C), 128.1, 125.2 (2C), 120.3, 9.6; HRMS (ESI): *m*/*z* [M – H^+] calcd for $C_{17}H_{13}N_2O_2$: 277.0977; found: 277.0974.

(12) When the mixture of LiCl and MeONa was used directly, the SHCC of **1a** with diethyl oxalate gave unsatisfactory results.

