CAN-Mediated Oxidation of Electron-Deficient Aryl and Heteroaryl Hydrazines and Hydrazides

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Received 21 January 2008

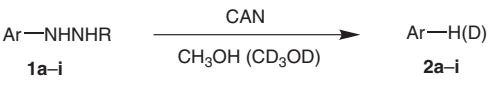
Dedicated to the memory of the late Professor Ljubo Golič

Abstract: Aryl and heteroaryl hydrazines and hydrazides were successfully oxidised using CAN, deriving dehydrazinated products. The reaction pathway strongly depends on the nature of the substrate, resulting in the formation of hydrocarbons or alkoxy derivatives. When deuterated solvents such as methanol-d_4 or acetonitrile-d_3 were used, a regiospecific incorporation of deuterium was achieved.

Key words: deuteration, CAN, oxidation, hydrazines, hydrazides

Among the various methods for bond formation and bond cleavage, single-electron transfer (SET) reactions occupy a prime position. Various procedures involving chemical, electrochemical, and photochemical methods are known for SET processes. Chemical methods for electron-transfer oxidations involve the use of salts of high-valent metals, among which one can find Ce(IV) salts. Cerium is a member of the lanthanides, whose [Xe]$4f^1 5d^1 6s^2$ electronic configuration means that cerium can exist in both tri- and tetrapositive states. As a result of its high charge, the Ce(IV) ion tends to hydrate, and very frequently coordinates with counterions. This last aspect provides a rationale for the Ce(IV)/Ce(III) potential dependence on the nature of the medium.[1] Accordingly, the strong oxidising power of the cerium(IV) ion has been recognised for many decades; however, its synthetic potential for organic chemists has only been explored in the past few decades. The synthesis of new cerium salts has meant that oxidation can take place under less vigorous conditions, and procedures employing catalytic amounts of various cerium(IV) salts have emerged as well. The most extensively used cerium(IV) reagent in organic chemistry is cerium(IV) ammonium nitrate (CAN). The reason for its common usage is its large reduction potential value of +1.61 V vs. normal hydrogen electrode (NHE), its low toxicity, the ease with which it can be handled, and its solubility in a number of organic solvents. Its consumption during a reaction can be judged by the fading of its orange colour to pale yellow, providing the substrate or the product is not strongly coloured. Accordingly, CAN plays an important role as an efficient reagent in numerous organic transformations.[2]

In the course of our studies that involve CAN as an oxidant, we revealed that hydrazides were readily oxidised by the use of CAN.[3] Despite wide applications of CAN for C–C, C–O, C–N bond-formation reactions and functional-group oxidation,[2,4] to the best of our knowledge, CAN has not been used to oxidise hydrazines. It was, however, reported that arylhydrazines were oxidatively converted into diimides,[5] using a series of arylsulfonyl peroxides. For example, when arylhydrazines were reacted with NO in THF in the presence of oxygen, benzene derivatives were obtained, accompanied by arylazides.[6] Cu(II) salts are competent oxidants of hydrazines; in the case of arylhydrazines resulting in the formation of aryl halides and hydrocarbons.[7] Waldmann and Lowe studied the oxidations of hydrazines and hydrazides in the context of protecting groups and traceless linkers for solid-phase synthesis using *N*-bromosuccinimide and Cu(II) salts.[8] Here, we wish to discuss the use of CAN as an efficient reagent for the oxidation of hydrazines and *N*′-acetylhydrazines (Scheme 1) so as to produce hydrocarbons in good yields. Initial experiments employing 2,4-dinitrophenylhydrazine were carried out in various solvents (alcohols, MeCN, Me_2CO, and EtOAc) and at different reaction temperatures. Thus, the addition of 2,4-dinitrophenylhydrazine (**1a**) to a CAN solution at room temperature resulted in the rapid formation of 2,4-dinitrobenzene. MeOH was found to be a superior solvent for the oxidation, yielding hydrocarbons as the sole products. For instance, significantly different results were obtained when $(NH_4)_2Ce(SO_4)_4 \cdot 2H_2O$ was employed for the oxidation of **1a** in MeOH, giving only a 25% conversion in 24 hours. When the above experiment using CAN was repeated in deuterated solvents such as CD_3OD or CD_3CN, a complete incorporation of the deuterium was achieved.[9] A similar result was obtained when CD_3OD–H_2O (1:1) was used, which led to the incorporation of 98% deuterium. On the other hand, there was no deuteration when CH_3OD was used as a solvent.



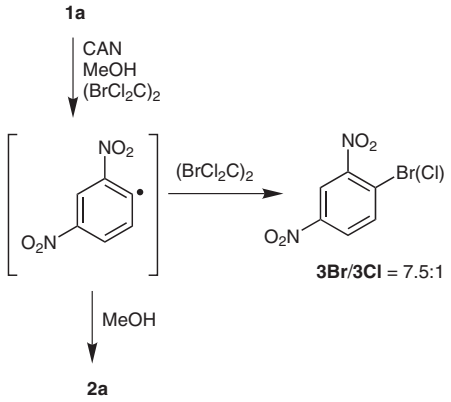
Scheme 1

Regarding the mechanism of the reaction, radical intermediates could, in principle, be expected due to the strong oxidant properties of CAN. In the 1970s Baciocchi et al.

SYNLETT 2008, No. 9, pp 1279–1282
Advanced online publication: 07.05.2008
DOI: 10.1055/s-2007-1072749; Art ID: D01708ST

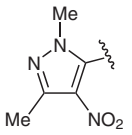
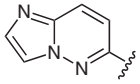
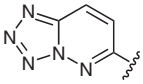
reported on oxidative acetoxylation of anisole by CAN where they proposed the formation of radical cation as an intermediate.[10] However, an experiment involving the addition of CBr_4 (1–4 equiv) to the CAN solution followed by addition of **1a**, led to 15–20% of bromo product, as is evident from the ^1H NMR spectra and the HPLC analysis of the crude reaction mixture. Additionally, the presence of 1,2-dibromotetrachloroethane (4 equiv) resulted in the formation of the corresponding bromo **3Br** and chloro **3Cl** co-products in the ratio of 7.5:1 (Scheme 2).[11] These experiments additionally support the idea of a radical intermediate being present on the reaction coordinate.

The reaction can be successfully extended to the common substituted phenylhydrazines, as demonstrated in Table 1.[15] In all cases the deuterium incorporation was high. With the reaction conditions developed, there was no alteration in the reaction outcome when the corresponding hydrochlorides or acetylated derivatives were studied, also resulting in the formation of hydrocarbons and methyl acetate (in the case of acetylated derivatives) when MeOH was used as a solvent. For comparison, our previous experiences demonstrate that when 1,4-diarylsemicarbazides are oxidised by CAN in MeOH solution, the oxidation is stopped at the stage of diazenecarboxamides and there is no further cleavage of the N–Ar bond since diazenecarboxamides are isolated in excellent yields.[16] Aryldiazenes are moderately unstable and are best prepared immediately prior to use by the base hydrolysis of aryldiazenecarboxylate esters.[17] To test whether the diazenecarboxamide oxo analogues, diazenecarboxylates, some of which are useful radical chain initiators,[18] can be approached using the above discussed reaction conditions, ethyl arylhydrazinecarboxylates **4a–c** were synthesised.[19] Thus, the addition of the substrate **4** to a CAN solution (2.1 equiv) in MeOH at room temperature provided a good yield of aryl- and heteroaryldiazenecarboxylates **5a**,[20] **5b**, and **5c**,[21] as outlined in Scheme 3. It is worth to mention that their mass spectra showed more abundant $[M + 2]^+$ signal than the expected $[M^+]$ molecular peak. The above described procedure is an alternative to the known two-phase Dimroth method.[22]

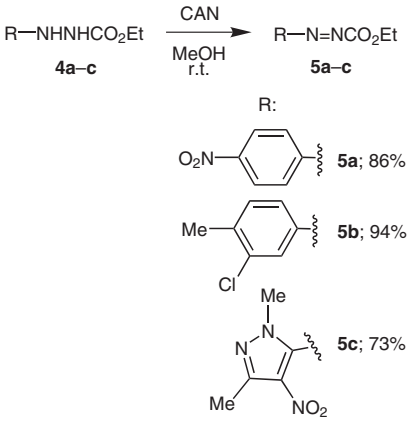


Scheme 2

Table 1 CAN-Mediated Oxidation of **1a–i**

Starting material			Yield of deuterated product[a] (%D)[b]	
	Ar		from **1**, R = H	from **1**, R = Ac
1a	2,4-di$NO_2C_6H_3$	**2a**	86 (100)	89 (100)
1b	2-CN-4-$NO_2C_6H_3$	**2b**	86 (100)	91 (100)
1c	4-$NO_2C_6H_4$	**2c**	73 (90)	65 (91)
1d	4-CNC_6H_4	**2d**	86 (92)	64 (94)
1e	2,4-diClC_6H_3	**2e**	93 (93)	80 (95)
1f	4-$CO_2HC_6H_4$	**2f**	98 (90)	90 (97)
1g		**2g**[12]	82 (96)	74 (95)
1h		**2h**[13]	76 (94)	80 (93)
1i		**2i**[14]	79 (91)	79 (89)

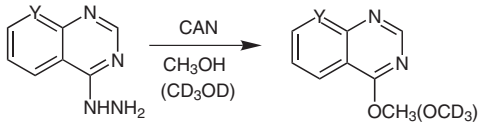
[a] Isolated yields.
[b] Deuterium incorporation was determined using MS analysis.



Scheme 3

Among the substituted phenylhydrazines presented in Table 1, we were also interested in the oxidation of heterocyclic hydrazines. Indeed, the method was successfully applied to the heterocyclic hydrazines, in the case of **1g–i** yielding dehydrazinated products (Table 1). Nevertheless, when we applied our oxidative conditions to 4-hydrazinoquinazoline (**6a**) and 4-hydrazinopyrido[2,3-*d*]pyrimidine (**6b**), surprisingly, methoxy derivatives **7a**,**b**[23] were isolated in good yields (Scheme 4). Similar results have been described in the literature when thallium(III) nitrate trihydrate is used for the oxidation of the heterocyclic hydrazines.[24]

Additionally, the reaction of **6a**,**b** with CAN was run in MeCN as a reaction medium, resulting in a significant slowing down of the reaction, and after the workup, pro-

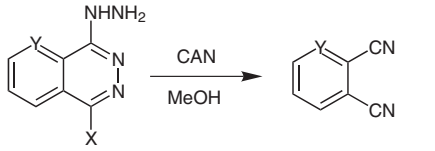


6a: Y = CH
6b: Y = N

7a: Y = CH; 76%; (99% CD_3)
7b: Y = N; 81%; (98% CD_3)

Scheme 4

viding an unidentified mixture of products. The formation of the methoxy products or their deuterated analogues **7a**,**b** can be explained by the presence of the polar intermediate on the reaction coordinate, which is subsequently trapped by the MeOH (or CD_3OD) as a nucleophile, followed by deprotonation. To further test the scope of CAN-promoted oxidations of hydrazines, we next studied the oxidations of hydrazinophthalazine **6c** and hydrazinopyrido[2,3-*d*]pyridazine **6d**. The reaction performed in MeOH resulted in the formation of nitrilo derivatives, phthalonitrile (**8a**) and its pyridine analogue **8b**, in good yields (Scheme 5). It is to be expected that the transformation of **6c** and **6d** to **8a** and **8b**, respectively, takes place via the same polar intermediate as discussed above, although in this case it results in the cleavage of the pyridazine N–N bond, yielding nitrile functionality.



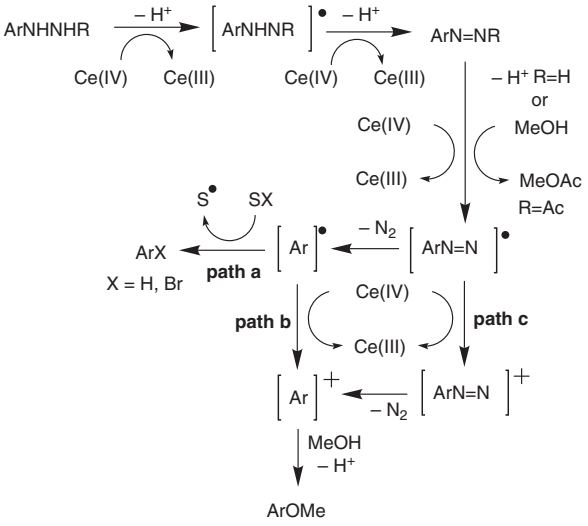
6c: Y = CH, X = H
6d: Y = N, X = Cl

8a: Y = CH; 87%
8b: Y = N; 70%

Scheme 5

On the basis of our experimental results we suggest the reaction-pathway rationalisation proposed in Scheme 6. In the first step the single-electron transfer and deprotonation steps lead to the formation of diimide, which rapidly undergoes a further single-electron transfer process, followed by deprotonation or, in the case of acetyl derivatives, a MeOH-assisted deacetylation process, leading to the formation of the diimide radical. The next step is the homolytic cleavage of the C–N bond, resulting in the formation of an aryl radical, which immediately undergoes hydrogen abstraction from the solvent or, in the case of adjacent α-nitrogen, further oxidation (Scheme 6, path b), producing the polar intermediate (assuming carbocation formation stabilised by neighbouring nitrogen, the stabilisation assistance reported by Eberlin et al.[25]) that is trapped by the nucleophilic solvent. Although all attempts to trap the eventual diazonium cation were unsuccessful, on the basis of the experimental results, path c (Scheme 6) cannot be completely excluded.

In conclusion, we have described a high-yielding CAN-mediated oxidative dehydrazination reaction of aryl- and heteroarylhydrazines. In addition, we found that the reaction mechanism depends strongly on the nature of the substrates, resulting in the formation of hydrocarbons or alkoxy derivatives. In the case of CAN oxidation of arylhydrazinecarboxylates, diazenecarboxylates are derived. Alternatively, this transformation clearly offers the opportunity to cleave aryl compounds from polymeric supports, leaving only an Ar–H (Ar–D) bond behind, or provides the option for regiospecific deuterium labelling. Additionally, further investigations concerning the reaction mechanism and its scope and limitations are currently underway.



Scheme 6 Proposed reaction pathway of CAN-mediated oxidations of hydrazines and hydrazides

Acknowledgment

The authors thank Dr. B. Kralj and Dr. D. Žigon (Mass Spectrometry Center, Jožef Stefan Institute, Ljubljana, Slovenia) for the mass spectrometry measurements. The Ministry of Higher Education, Science and Technology of the Republic of Slovenia (P0–0503–0103) is gratefully acknowledged for its financial support, and N. Brezavšček and J. Delibašić are thanked for their technical support.

References and Notes

(1) Marrocco, M.; Brilmyer, G. *J. Org. Chem.* **1983**, *48*, 1487.
(2) For reviews, see: (a) Nair, V.; Deepthi, A. *Chem. Rev.* **2007**, *107*, 1862. (b) Tse-Loh, H. In *Handbook of Reagents for Organic Synthesis, Oxidizing and Reducing Agents*; Burke, S. D.; Danheiser, R. L., Eds.; John Wiley & Sons: Chichester, **2005**, 77–80.
(3) Štefane, B.; Kočevar, M.; Polanc, S. *Tetrahedron Lett.* **1999**, *40*, 4429.
(4) For reviews, see: (a) Maulide, N.; Vanherck, J.-C.; Gautier, A.; Markó, I. E. *Acc. Chem. Res.* **2007**, *40*, 381. (b) Nair, V.; Panicker, S. B.; Nair, L. G.; George, T. G.; Augustine, A. *Synlett* **2003**, 156.
(5) Hoffman, R. V.; Kumar, A. *J. Org. Chem.* **1984**, *49*, 4014.
(6) Itoh, T.; Matsuya, Y.; Nagata, K.; Ohsawa, A. *Tetrahedron Lett.* **1997**, *38*, 4177.
(7) (a) Doyle, M. P.; Siegfried, B.; Fobare, W. F. *Tetrahedron Lett.* **1977**, 2655. (b) Varea, T.; González-Núñez, M. E.; Rodrigo-Chiner, J. *Tetrahedron* **1989**, *30*, 4708.

(8) (a) Millington, C. R.; Quarrell, R.; Lowe, G. *Tetrahedron* **1998**, *39*, 7201. (b) Stieber, F.; Grether, U.; Waldmann, H. *Angew. Chem. Int. Ed.* **1999**, *38*, 1073. (c) Müller, G. H.; Waldmann, H. *Tetrahedron Lett.* **1999**, *40*, 3549. (d) Stieber, F.; Grether, U.; Waldmann, H. *Chem. Eur. J.* **2003**, *9*, 3270. (e) Stieber, F.; Grether, U.; Mazitschek, R.; Soric, N.; Giannis, A.; Waldmann, H. *Chem. Eur. J.* **2003**, *9*, 3282.

(9) The products were analysed using MS spectrometry.

(10) Baciocchi, E.; Mei, S.; Rol, C. *J. Org. Chem.* **1978**, *43*, 2919.

(11) **Typical Procedure**: To a solution of CAN (2.193 g, 4 mmol) and 1,2-dibromotetrachloroethane (1.302 g, 4 mmol) in MeOH (5 mL) was added 2,4-dinitrophenylhydrazine (198 mg, 1 mmol) in one portion. The reaction mixture was stirred at r.t. for an additional 5 min, evaporated to dryness below 40 °C, treated with H_2O (10 mL) and extracted with CH_2Cl_2 (5 × 10 mL). The organic phase was dried over anhyd Na_2SO_4 and concentrated under reduced pressure to give a mixture of products (**2a**:**3Br**:**3Cl** = 50:7.5:1). The mixture was purified by column chromatography (SiO_2, EtOAc–light petroleum, 1:10). **2a**: orange solid (134 mg, 80%); R_f (light petroleum–EtOAc, 3:1) 0.34. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.87 (t, *J* = 8.0 Hz, 1 H), 8.60 (dd, *J* = 2.0, 8.0 Hz, 2 H), 9.08 (t, *J* = 2.0 Hz, 1 H). **3Br**: yellow oil (24 mg, 10%); R_f (light petroleum–EtOAc, 3:1) 0.44. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 9.0 Hz, 1 H), 8.32 (dd, *J* = 2.5, 9.0 Hz, 1 H), 8.70 (d, *J* = 2.5 Hz, 1 H). **3Cl**: yellow oil (2 mg, 1%); R_f (light petroleum–EtOAc, 3:1) 0.64. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 9.0 Hz, 1 H), 8.43 (dd, *J* = 5.5, 9.0 Hz, 1 H), 8.76 (d, *J* = 2.5 Hz, 1 H).

(12) Bernard, M. K.; Makosza, M.; Szafran, B.; Wrzeciono, U. *Liebigs Ann. Chem.* **1989**, 545.

(13) Kobe, J.; Stanovnik, B.; Tiler, M. *Tetrahedron* **1968**, *24*, 239.

(14) Wentrup, C.; Crow, W. D. *Tetrahedron* **1970**, *26*, 4915.

(15) **General Procedure for the Oxidation of Hydrazines and Hydrazides**: The hydrazine or hydrazide (1 mmol) was added at r.t. within a period of 10–15 min to a solution of CAN (4 mmol) in MeOH (5 mL). The reaction mixture was stirred at r.t. for an additional 10–40 min, evaporated to dryness below 40 °C, treated with H_2O (10 mL) and neutralised with $NaHCO_3$ (pH ca. 7). After extraction with CH_2Cl_2 (5 × 10 mL), the organic phase was dried over anhyd Na_2SO_4 and concentrated under reduced pressure to give dehydrazinated products **2**. If necessary the products were purified by column chromatography on SiO_2. Products **2a–f**, **8a** and **8b** were compared with the authentic samples. **2g**: yellow solid; R_f (light petroleum–EtOAc, 5:3) 0.43; mp 69–72 °C (MeCN). IR (KBr): 3119, 1543, 1517, 1471, 1442, 1371, 1341, 1167, 1066, 1004, 849, 836, 762, 606, 566 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.53 (s, 3 H), 3.87 (s, 3 H), 8.08 (s, 1 H). **2h**: white solid; R_f (CH_2Cl_2–MeOH, 10:1) 0.39; mp 47–50 °C (light petroleum–EtOAc). IR (KBr): 3121, 3105, 1619, 1531, 1475, 1345, 1298, 1271, 1144, 1024, 928, 872, 797, 756, 635, 571 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.02 (dd, *J* = 4.0, 9.0 Hz, 1 H), 7.78 (d, *J* = 1.0 Hz, 1 H), 7.96 (dd, *J* = 1.0, 9.0 Hz, 1 H), 7.98–7.99 (m, 1 H), 8.30 (dd, *J* = 1.0, 9.0 Hz, 1 H). **2i**: white solid; R_f (CH_2Cl_2–MeOH, 10:1) 0.40; mp 98–102 °C (light petroleum–EtOAc). IR (KBr): 3096, 1614, 1541, 1419, 1370, 1348, 1327, 1255, 1130, 1087, 1011, 810, 764 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.57 (dd, *J* = 4.0, 9.5 Hz, 1 H), 8.46 (dd, *J* = 1.5, 9.5 Hz, 1 H), 8.72 (dd, 1 H). **7a**: yellow oil; R_f (light petroleum–EtOAc, 5:3) 0.25. IR (KBr): 2949, 1618, 1574, 1500, 1447, 1371, 1098, 976, 875, 771 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.17 (s, 3 H), 7.54 (ddd, *J* = 1.0, 7.0, 8.0 Hz, 1 H), 7.81 (ddd, *J* = 1.5, 7.0, 8.5 Hz, 1 H), 7.92 (ddd, *J* = 1.0, 1.0, 8.5 Hz, 1 H), 8.14 (ddd, *J* = 1.0, 1.5, 8.0 Hz, 1 H), 8.80 (s, 1 H). MS (CI): *m*/*z* (%) = 160 (100) [M$^+$], 131 (40), 103 (95). **7b**: yellow oil; R_f (CH_2Cl_2–MeOH, 10:1) 0.40. IR (KBr): 2946, 1561, 1493, 1462, 1367, 1122, 832 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.29 (s, 3 H), 7.78 (dd, *J* = 4.0, 8.5 Hz, 1 H), 8.28 (dd, *J* = 1.5, 8.5 Hz, 1 H), 8.87 (s, 1 H), 8.99 (dd, *J* = 1.5, 4.0 Hz, 1 H). MS (EI, 70 eV): *m*/*z* (%) = 161 (100) [M$^+$], 104 (98), 77 (40). HRMS (EI): *m*/*z* calcd for $C_8H_7N_3O$: 161.0589; found: 161.0590.

(16) Košmrlj, J.; Kočevar, M.; Polanc, S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3917.

(17) Huang, P. C.; Kosower, E. M. *J. Am. Chem. Soc.* **1968**, *90*, 2354.

(18) Nonhebel, D. C.; Walton, J. C. *Free Radical Chemistry*; Cambridge University Press: Cambridge, **1974**, 25.

(19) (a) Tschirret-Guth, R. A.; Ortiz de Montellano, P. R. *J. Org. Chem.* **1998**, *63*, 9711. (b) Bergmann, H.; Strumpf, T.; Lyr, H. *Pestic. Sci.* **1988**, *23*, 141.

(20) Forchiassin, M.; Risalti, A.; Russo, C. *Tetrahedron* **1981**, *37*, 2921.

(21) **Representative Procedure for the Oxidation of Aryl Hydrazinecarboxylates 4a–c**: An aryl hydrazinecarboxylate (1 mmol) was added at r.t. in one portion to a solution of CAN (2.1 mmol) in MeOH (5 mL). The reaction mixture was stirred at r.t. for an additional 5 min, evaporated to dryness below 40 °C, treated with H_2O (10 mL) and extracted with CH_2Cl_2 (5 × 10 mL). The organic phase was dried over anhyd Na_2SO_4 and concentrated under reduced pressure to give the pure products **5a–c**. **5a**: ref. 19. **5b**: orange oil (213 mg, 94%); R_f (light petroleum–EtOAc, 3:1) 0.59. IR (NaCl): 2985, 1758, 1572, 1503, 1389, 1368, 1296, 1245, 1211, 1165, 1029, 977, 889, 863, 826, 748 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.48 (t, *J* = 7.0 Hz, 3 H), 2.48 (s, 3 H), 4.53 (q, *J* = 7.0 Hz, 2 H), 7.41 (d, *J* = 8.0 Hz, 1 H), 7.79 (dd, *J* = 2.0, 8.0 Hz, 1 H), 7.93 (d, *J* = 2.0 Hz, 1 H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.0, 20.2, 64.3, 122.90, 122.95, 131.3, 135.3, 142.3, 150.4, 161.8. MS (CI): *m*/*z* (%) = 225 (85) [M + 2]$^+$, 178 (50), 150 (55), 122 (100). HRMS (EI): *m*/*z* calcd for $C_9H_{11}N_3O_4$: 225.0750; found: 225.0759. **5c**: orange oil (176 mg, 73%); R_f (light petroleum–EtOAc, 5:1) 0.14. IR (NaCl): 2938, 1762, 1544, 1514, 1446, 1359, 1235 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.49 (t, *J* = 7.0 Hz, 3 H), 2.54 (s, 3 H), 4.05 (s, 3 H), 4.55 (q, *J* = 7.0 Hz, 2 H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 13.2, 14.1, 38.8, 65.3, 144.1, 146.2, 160.7, 171.1. MS (CI): *m*/*z* (%) = 243 (8) [M + 2]$^+$, 125 (14), 67 (100). HRMS (EI): *m*/*z* calcd for $C_8H_{13}N_5O_4$: 243.0968; found: 243.00968.

(22) Dimroth, K.; Tüncher, W. *Synthesis* **1977**, 339.

(23) (a) Mencarelli, P.; Stegel, F. *J. Org. Chem.* **1985**, *50*, 5415. (b) Higashino, T.; Uchida, M.; Hayashi, E. *Chem. Pharm. Bull.* **1972**, *20*, 772.

(24) Kočevar, M.; Mihorko, P.; Polanc, S. *J. Org. Chem.* **1995**, *60*, 1466.

(25) Gozzo, F. C.; Eberlin, M. N. *J. Org. Chem.* **1999**, *64*, 2188.